Researching the Autism Spectrum
Contemporary Perspectives

This selection of contemporary studies provides up-to-date perspectives from leading investigators who are at the cutting edge of research into Autism Spectrum Disorders. The book allows readers to grasp new approaches to understanding the autism spectrum. Key areas of theory and research are covered, from classification and diagnosis, genetics, neurology and biochemistry, to socio-cognitive, developmental and educational perspectives, essential to a broader understanding of the autism spectrum. In addition, it introduces new emphases on MEG, epilepsy and memory. In highlighting both biomedical and psychological perspectives, this book reflects the multi-level focus of contemporary thinking about autism. By addressing key unanswered questions, Researching the Autism Spectrum acts as a guidepost for future research and provides an authoritative and multi-disciplinary perspective.

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Contents

Preface page xi
Foreword xiii
List of Contributors xiv

Introduction 1
Ilona Roth and Payam Rezaie

Part I Classification and Diagnosis 17

1 Early assessment and diagnosis of children 19
Ann Le Couteur

1.1 Definition 20
1.2 Epidemiology 24
1.3 Assessment and diagnosis 25
1.4 Best Estimate Clinical Diagnosis (BECD) and research diagnosis 33
1.5 Conclusions and challenges for the early assessment and diagnosis of ASD 38
1.6 References 39

Part II Genetics, Neurology and Biochemistry 51

2 Unravelling the genetics of autism spectrum disorders 53
Inês de Sousa, Richard Holt, Alistair Pagnamenta and Anthony Monaco

2.1 Evidence for genetic liability and the multifactorial model for autism 53
2.2 Linkage studies 57
2.3 Association studies 61
2.4 Rare single gene mutations in autism 74
## Contents

2.5 Epigenetics 78  
2.6 Copy number variation (CNV) associated with ASD 81  
2.7 Final remarks 91  
2.8 References 93  

### 3 Brain imaging and the neuroanatomical correlates of autism 112  
**Michael Spencer, Andrew Stanfield and Eve Johnstone**  
3.1 Background 112  
3.2 Important considerations relating to autism spectrum literature 114  
3.3 Qualitative MRI findings 117  
3.4 Quantitative structural MRI image analysis techniques 119  
3.5 Quantitative structural MRI imaging findings, grouped by brain region 124  
3.6 Diffusion tensor imaging studies 137  
3.7 Neuroanatomical findings in females with ASD 138  
3.8 ‘Low-functioning’ autism, ‘high-functioning’ autism, Asperger syndrome and non-specific pervasive developmental disorders 138  
3.9 Conclusions and future directions 140  
3.10 Final remarks 142  
3.11 Acknowledgements 142  
3.12 References 142  

### 4 Magnetoencephalography (MEG) as a tool to investigate the neurophysiology of autism 156  
**Sven Braeutigam, Stephen Swithenby and Anthony Bailey**  
4.1 Instrumentation and measurements 156  
4.2 Analytical approaches 159  
4.3 MEG studies of autism spectrum disorders (ASD) 161  
4.4 Discussion 170  
4.5 References 172  

### 5 Autism and epilepsy 176  
**Christopher Gillberg and Brian Neville**  
5.1 Introduction 176  
5.2 Prevalence aspects 177  
5.3 Gender aspects 178  
5.4 Diagnostic/differential diagnostic aspects including EEG 179  
5.5 Autistic regression and epilepsy 179  
5.6 Types of seizures 180  
5.7 Early onset epilepsy syndromes with developmental regression 182
5.8 The phenotype of ASD with epilepsy 184
5.9 Investigation and management 185
5.10 Place of EEG in the investigation of autism 185
5.11 Pathogenesis of autistic regression in epilepsy 186
5.12 References 186

6  Biochemistry of autism: changes in serotonin, reelin and oxytocin 190
Elizabeta B. Mukaetova-Ladinska, Jodie Westwood and Elaine Perry
6.1 Introduction 190
6.2 Serotonin neurochemistry in autism 191
6.3 Reelin 200
6.4 Oxytocin neurochemistry in autism 203
6.5 Conclusions 207
6.6 Acknowledgement 208
6.7 References 208

Part III  Cognition, Development and Education 217

7  Psychological models of autism: an overview 219
Elizabeth Pellicano
7.1 Introduction 219
7.2 Criteria for explanatory accounts of autism 222
7.3 The Theory of Mind Hypothesis 222
7.4 The Executive Dysfunction Hypothesis 228
7.5 Central Coherence Theory 236
7.6 Beyond single-deficit models of autism 243
7.7 References 249

8  Cognitive flexibility in autism: a social-developmental account 266
Peter Hobson and Jessica Hobson
8.1 Introduction 266
8.2 Frameworks of understanding 268
8.3 A social-developmental account of flexible, creative symbolic thinking 271
8.4 Studies in autism: flexibility in attitude and stance 273
8.5 Symbolic thinking in autism 276
8.6 The case of congenital blindness 277
8.7 Executive dysfunction reconsidered 278
8.8 Acknowledgement 280
8.9 References 280
9 Language in autism spectrum disorders  284
   JILL BOUCHER
   9.1 Introduction  284
   9.2 Patterns of language abilities and impairments across the spectrum  285
   9.3 Causes of language impairment across the spectrum  299
   9.4 Summary  307
   9.5 References  307

10 Memory in autism: binding, self and brain  316
    DERMOT BOWLER, SEBASTIAN GAIGG AND SOPHIE LIND
    10.1 Preliminary remarks  316
    10.2 Empirical findings  319
    10.3 Wider conceptual themes  327
    10.4 Memory and the brain  334
    10.5 Conclusions  338
    10.6 Acknowledgements  338
    10.7 References  339

11 Measuring executive function in children with high-functioning autism spectrum disorders: what is ecologically valid?  347
    AYLÀ HUMPHREY, OFER GOLAN, BARBARA WILSON AND SARA SOPENA
    11.1 Introduction  348
    11.2 Participants  350
    11.3 Materials  351
    11.4 Procedure  354
    11.5 Results  354
    11.6 Limitations of study  358
    11.7 Discussion  358
    11.8 References  361

12 Autism spectrum disorders in current educational provision  364
    RITA JORDAN
    12.1 The role of education  364
    12.2 The particular challenges of the autism spectrum  365
    12.3 Core issues in learning in ASD  366
    12.4 Features of learning style  376
    12.5 Access to the curriculum  378
    12.6 Parental support, homework and the ‘24 hour’ curriculum  381
    12.7 Anxiety and stress  382
    12.8 Relationships with peers  383
    12.9 Information and communication technologies (ICT)  383
The colour plates are to be found between 208 and 209.
Preface

There is widespread concern about the apparently growing prevalence of autism, although this increase may be due, in large part, to factors such as changes in diagnostic criteria and ascertainment practices. Public and scientific interest in the causes and fundamental nature of autism has never been stronger. Research in this field has grown exponentially in the last twenty years, with significant financial support in this area provided by Governments, Research Councils and private charities. Studies spanning a whole range of disciplines share the goals of elucidating the core phenomena and underlying aetiology, thereby informing therapeutic interventions, as well as offering valuable insights into normal functioning. Research by individuals and groups in the UK has played a leading role in addressing key unanswered questions about autism, including its causes and psychological substrates, the underlying brain mechanisms, and the most effective ways to work with and support people with autism and their families.

A major conference which we were privileged to organise in 2007, entitled: ‘Autism Research UK: from diagnosis to intervention’ hosted by the Open University and sponsored by the Medical Research Council, Wellcome Trust, Autism Speaks and a number of other organisations, provided an effective backdrop to this book. At this first national meeting of this scope, internationally renowned speakers and chairpersons convened with representatives from the Medical Research Council, the Wellcome Trust, Economic and Social Research Council, National Autistic Society and Autism Speaks for two days of discussion and debate aimed at elucidating ways forward in understanding the autism spectrum and helping affected individuals and their families. A series of themed scientific sessions charted the way UK-based investigations have shaped and developed our understanding of the autism spectrum over recent years. This provided a strong rationale for an edited volume which would present a selection of ‘cutting edge’ contributions to theory and practice in this important, rapidly moving field.
This book, encompassing three main sections, presents an authoritative and multi-disciplinary perspective on autism from leading UK-based investigators who are active at the forefront of research in this field. A selection of key areas of research and theory covering classification and diagnosis, genetics, neurology and biochemistry, through to socio-cognitive, developmental and educational perspectives, including new emphases (MEG, autism and epilepsy, memory in autism) are highlighted, and provide the fundamental basis for a broader understanding of the autism spectrum. We are confident that this collection of works will serve as a balanced, authoritative and contemporary reference that will inform current understanding of the science of autism and act as a guidepost for research over the next few years. We expect that this book will appeal to, and inform a wide readership from clinical and academic professionals, to educators, healthcare providers, and policy makers. It will also be of interest to the substantial and growing body of parents and family members of those who are affected by autism.

We are deeply indebted to our colleagues and especially to the authors and contributors for their encouragement, their support and their commitment. We hope that you will find the contents stimulating and informative.

Ilona Roth
Payam Rezaie
The editors of this volume, Ilona Roth and Payam Rezaie, have assembled a valuable collection of chapters providing an excellent overview of a wide range of areas relevant to autism research. The book tackles the challenge of early detection; the complex biology of autism, including genetics (from linkage, to association, to CNVs), the autistic brain (from the perspectives of MRI, DTI, MEG, neuroanatomy and epilepsy) and molecular aspects of autism (from serotonin to oxytocin); the complex psychology of autism (from cognitive models, language, memory and executive function); and the challenge of education in autism.

Autism research is currently enjoying considerable growth, with hundreds of researchers joining in the hunt to understand this important set of conditions. This book showcases some of the best autism scientists in the UK who are contributing to this international effort. The editors are to be congratulated on pulling this collection together, since this will inspire a new generation of autism scientists among contemporary students. The hope is that an anthology of this kind will be produced every few years, so we can track this fast-changing field. This multi-disciplinary book nicely illustrates how autism is a multi-level phenomenon that will need integration across levels. This book exemplifies how each level must be represented and contributes to the bigger picture.

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The term ‘Autism Spectrum’ currently embraces a cluster of conditions known as Autism Spectrum Disorders or ‘ASD’, that are characterised by impairments in social functioning, verbal and non-verbal communication, together with repetitive and stereotypical patterns of behaviour and interests. Impairments within each of these ‘core’ clinical domains can range in severity from mild to profound, and intellectual disability may be present in more severe cases. The classification of ASD broadly includes classic autism (childhood autism; autistic disorder), Asperger syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) (Levy et al. 2009). Classic autism is frequently diagnosed around the age of 3 (and may be diagnosed as early as 2 years of age) (Baird et al. 2003; Landa, 2008). Asperger syndrome often presents with more subtle symptoms, and is usually diagnosed later on in childhood (frequently around 11 years of age), and occasionally in adults (Howlin and Asgharian 1999; Toth and King 2008).

While the precise causes of autism remain a mystery, prevalence estimates have risen almost exponentially within the last six decades, making autism a major global concern. Initially considered rare, current estimates suggest that as many as 1% of children under the age of 8 years may have an autism spectrum diagnosis (Baird et al. 2006), with boys being diagnosed up to four times more than girls. More than half a million people are thought to be living with autism in the UK alone (National Autistic Society, 2007), and in the US autism is considerably more common today than it was in the 1980s (Yeargin-Allsopp et al. 2003).

Terminology relating to the autism spectrum is markedly inconsistent between formal and informal contexts, and between different expert groups. The term ‘autism’ is often used colloquially as an umbrella term for the entire autism
Researching the Autism Spectrum

spectrum, as well as more specifically for the classic or prototypical form of autism spectrum disorder. Some researchers and autism advocates favour the term ‘Autism Spectrum Conditions’ (ASC), rather than Autism Spectrum Disorders or ASD, one rationale being that the first phrase avoids the connotation of autism as a disorder or disability, and is thus less discriminatory than the second. The terms ‘high-functioning’ and ‘low-functioning’ autism reflect a classification employed by many researchers, alongside the diagnostic distinctions, to distinguish those with normal or above normal intellectual abilities from those who are intellectually disabled. The question of whether high-functioning autism and Asperger syndrome denote the same, overlapping or different groups of individuals remains unresolved.

The two major classification systems, DSM-IV (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1993), also employ subtly different terms for the sub-groups within the spectrum. The forthcoming version of DSM (DSM-V due to be released in 2013) aims to reduce some of the complexity, and address unreliability in the diagnostic differentiation of sub-groups (American Psychiatric Association, 2010). The Neurodevelopmental Disorders Workgroup have publicised their intention to remove the diagnostic sub-types (autistic disorder, Asperger disorder and PDD-NOS) from the classification, replacing them with a single clinical entity ‘Autism Spectrum Disorder’, within which individual symptom patterns will be differentiated by a severity score (Swedo, 2008; 2009). Yet, despite its worthy aims, the proposal has stimulated considerable debate, underlining the wide range of views that still prevail in this area. Issues surrounding terminology, classification and diagnosis are discussed further in Chapter 1. In the remainder of this introduction, we will use the terms ‘ASD’ and ‘autism’ interchangeably to refer to the spectrum as a whole. In the remaining chapters of this volume we have left authors to adopt the terminology with which they feel most comfortable.

**Autism: an evolving concept**

Leo Kanner (1943) viewed autism as a syndrome, a specific developmental disorder with a characteristic set of symptoms, likely to have a single underlying cause. Evidence for a different and more nuanced interpretation existed in the contemporary work of Hans Asperger (1944), but it was 40 years before Asperger’s work came to wider attention through the work of Lorna Wing (1981). Asperger’s work, later translated into English and reprinted by Uta Frith (1991), provided the stimulus for Wing to make two radical proposals: firstly, the notion of autism as a spectrum, rather than a syndrome, and secondly, the idea of Asperger syndrome as a separable sub-type of autism.

The ramifications of these new ideas were profound, including revisions to the diagnostic criteria to include Asperger syndrome as a separate diagnostic
entity, diagnosis of many individuals who would not have been recognised as autistic by Kanner, recognition of the complex and possibly incidental relationship between intellectual disability and autism, increasing prevalence estimates and so on.

Three decades on from Wing’s pioneering contributions, the concept of the autism spectrum is still evolving: further major changes are being considered with the growing appreciation that the autism spectrum may be best characterised as a continuum rather than as a cluster of sub-types (hence the radical proposals for DSM-V); the concept that autistic traits are graded from those individuals with full expression, to family members with ‘shadow traits’ constituting the Broader Autism Phenotype, to the existence of some autistic-like characteristics even in the ‘neurotypical’ population.

The implication of this still moving trajectory is that the characterisation and explanation of autism is far more complex than either Kanner or Asperger could have realised. Despite much progress in research, theory and clinical practice in this field over the last seven decades, autism remains a conundrum, a disorder, or group of disorders, which is compelling and yet elusive, and for which medical remediation (e.g. Coury, 2010) is as yet extremely limited. Moreover the status of autism as a ‘disorder’ rather than a difference has been contested: there is a substantial diversity of views on whether all forms of autism, and especially Asperger syndrome, require remediation.

What are the reasons for the persisting obscurity surrounding this spectrum or cluster of conditions?

Heterogeneity across the autism spectrum

There is consensus on the substantial variability of autism. The expression and severity of symptoms vary significantly from one affected individual to another, and furthermore, autism may present with or without: (i) full expression of the diagnostic triad of symptoms; (ii) intellectual disability; (iii) marked delay/impairment of language; and (iv) a range of different co-morbid conditions (most notably epilepsy). In addition, autism may affect a solitary member of a family, or occur in multiple family members. From this picture, and from a substantial body of scientific studies, it has become clear that the causal factors involved in autism are likely to be multiple, complex, and quite possibly variable from one individual case and one major symptom group to another, even if different influences can be said to converge towards a ‘final common pathway’ (Frith et al. 1991; Darby and Clark, 1992; Geschwind, 2008). Earlier notions that it might be possible to identify specific biological markers for autism, or even a single gene, as in cystic fibrosis for example, have foundered (see Happé et al. 2006; Geschwind, 2008).
Researching the Autism Spectrum

Known single gene mutations account for less than 1% of all ASD cases, confirming the aetiological heterogeneity of autism (Geschwind, 2009).

Heterogeneity at both aetiological and behavioural levels has, in turn, led to methodological and interpretative difficulties in research. For instance, in psychological studies, there is limited consensus about the appropriate way of matching experimental and control participants (see for example the Journal of Autism and Developmental Disorders: Special Issue on Research Methodology-Matching, Jacob, 2004), and experimental groups may be heterogeneous in terms of sub-diagnosis and the presence or absence of co-morbid conditions. Experimental studies are also constrained by the difficulty of testing low-functioning individuals, with the result that insights tend to be confined to those at the high-functioning end of the spectrum. Neurobiological research is beset by related methodological difficulties. For instance, in neuropathological and neurochemical studies, samples may be small, clinically heterogeneous, often with co-existing/co-morbid conditions, and difficult to match with suitable controls (Palmen et al. 2004; Lam et al. 2006; Casanova, 2007). Brain tissue donors may also be at the low-functioning end of the spectrum. These limitations pose difficulties for cross-referencing and integrating psychological and neurobiological findings.

Blind alleys in autism research

As in many clinical fields where there is a pressing need for explanations leading to therapeutic interventions, some superficially appealing hypotheses have attracted undue interest, led nowhere and in the process, substantially undermined the progress of research and clinical practice. In the case of autism an early blind alley was Bruno Bettelheim’s hypothesis that the causes of autism lay in emotional detachment and faulty parenting by mothers of those on the autism spectrum (Bettelheim, 1967). This erroneous interpretation of what may in some cases have been genetically mediated ‘shadow traits’ led to the stigmatisation of several generations of parents, and distress in children from whom they were separated for ‘therapeutic’ reasons. Bettelheim’s theoretical and therapeutic approach to autism, now refuted, resonated strongly with psychoanalytical accounts of child development, which were extremely influential at the time (i.e. during the 1960s and 1970s).

An equally if not more damaging hypothesis put forward by Andrew Wakefield and his collaborators (Wakefield et al. 1998), subsequently retracted (Murch et al. 2004), identified the MMR vaccine as a possible cause of autism in children. Extensive research in this area, carried out over a number of subsequent years, has provided no evidence linking the MMR vaccine to autism. Such a link is unlikely to exist and cannot be considered a reason for the increase in incidence of autism.
that has been seen in recent years (see Honda et al. 2005). Moreover, while the pattern of inheritance in autism strongly suggests that genetic factors interact with environmental influences to produce susceptibility (Pardo and Eberhart, 2007), the negative publicity that environmental hypotheses have attracted through the work of both Bettelheim and Wakefield has also engendered a greater apparent reluctance amongst researchers to identify significant environmental risk factors.

**Neglected topics in autism research**

Just as some beguiling avenues of enquiry proved to yield little or no benefit, other potentially important but less seductive topics have been relatively neglected. One of these is the precise relationship of epilepsy to autism. In 1960 one of the first reports linking autism to epilepsy was published (Schain and Yannet, 1960). This was rapidly followed by others (e.g. Gubbay, 1970; Kolvin et al. 1971) which indicated that up to one-third of those with autism spectrum diagnoses may have epilepsy, while a review of studies published since 2000 has found that a much higher percentage (up to 60%) have atypical/epileptiform EEG activity (Hughes and Melyn, 2005; Spence and Schneider, 2009). Yet despite the steady accretion of evidence linking epilepsy and autism (see Hughes and Melyn, 2005; Levisohn, 2007; Spence and Schneider, 2009), and further work linking seizures to the sleep disturbances often reported in autism (Malow, 2004), the precise role that seizures play in the aetiology, developmental trajectory and long term outcomes of autism has been sparsely examined. This limitation has impacted further on our understanding of the differentiation of sub-groups within the spectrum. The disproportionate occurrence of epilepsy in those with autism and low IQ, and in females with autism (Amiet et al. 2008) highlights yet again the need for caution in generalising about this markedly heterogeneous condition.

There have been important omissions also at the psychological level of enquiry. The major foci of research on the psychology of autism, as well as the target areas for quite a number of interventions, have been the ‘triad’ of symptoms and characteristics included in the diagnostic criteria for autism. While the precise delineation of these three symptom groups has changed since separate criteria for autism were first included in the DSM-III diagnostic classification in 1980, they still centre upon three main areas of impaired functioning: communication, social interaction, and the rigid and repetitive quality of activities and interests (American Psychiatric Association, 2000; World Health Organisation, 1993). Both Kanner and Asperger documented other difficulties, notably sensory and perceptual problems, atypical memory, and special skills. Pioneering experimental research on memory, sensory and perceptual atypicalities was carried out by Hermelin and O’Connor in the 1960s (Hermelin and O’Connor, 1964; 1970), but due focus on
these topics in relatively recent. A recent review by Geschwind (2009) estimates that sensory atypicalities are observed in more than 90% of those with autism spectrum diagnoses. This resonates with the view of many parents and teachers of children on the autism spectrum, as well as individuals themselves, that sensory and perceptual difficulties are of paramount concern (Bogdashina, 2003). However, Rogers and Ozonoff (2005) argue that the evidence that such difficulties are more especially associated with autism than with other developmental disorders is unclear. Consequently, there is understandable reservation among experts about the explanatory status of sensory problems in relation to the autism spectrum, though at least one recent psychological account of autism has proposed atypical modulation of sensory and perceptual processes as a possible key to explanation (Mottron et al. 2006).

Other areas comparatively overlooked in research, but highlighted by Geschwind (2009) include the onset and development of motor signs, estimated to affect 60–80% of those on the spectrum, gastrointestinal problems (up to 50% of those on the spectrum) and co-morbid psychiatric diagnoses, in particular the presence of mood/conduct disorders, aggression and ADHD (between 25 and 70% of children on the spectrum). While it may be argued that the relationship of these symptoms to the autism spectrum is non-specific, and therefore their potential as ‘core deficits’ limited, their frequency of occurrence does emphasise the complex heterogeneity of the spectrum, which explanations need to encompass.

During much of three decades in which psychological theories have abounded, the major focus has been on explaining the deficits: it is only in more recent work that special skills have begun to attract more interest (see for instance Baron-Cohen et al. 2002; Happé, 1999). A constraint here has been a lack of clarity about what constitutes a special skill. Prodigious savant talents, as displayed, for instance, by the artist Stephen Wiltshire, are extremely rare, suggesting, once again, that this facet of autism should not be a central focus of explanation. However, according to recent estimates (Howlin et al. 2009) a much larger group of individuals on the spectrum (around 30%) have some measure of special skill. This then presents yet another phenomenon which, while not universal, characterises a major sub-population of the spectrum, meriting consideration in what will be almost certainly (given the heterogeneity of the phenomena) a fractionated account of the whole field.

Finally, at both biological and psychological levels of enquiry, the developmental trajectory of autism, from infancy to adulthood, has been comparatively neglected. Many studies have characterised atypical functioning within a relatively narrow window of time, paying scant attention to the cumulative effects of early biological and psychological deficits in engendering these outcomes. A notable exception to this trend is theoretical work by Hobson (see for instance Hobson 1993; Hobson, 2002) seeking to explain how impaired capacity to engage
emotionally and socially with other humans from birth onwards, could funda-
mentally alter a child’s developmental trajectory, resulting in both the cognitive
and social deficits seen in autistic conditions. Baron-Cohen (1995) has also offered
theoretical proposals for early developmental precursors of later theory of mind
deficits. The value of the ‘trajectory approach’ to developmental disorders is eleg-
gantly demonstrated by Thomas et al. (2009), while recent studies of the develop-
mental trajectory of behavioural symptoms (Richler et al. 2010) and neurobiology
(Schumann et al. 2010) represent an encouraging shift of emphasis.

Positive trends in biology, psychology and practice

Findings gathered over the last four to five decades have resulted in a
substantial contemporary framework of understanding about the causes and key
phenomena of autism. From initial sources such as the influential monograph by
Bernard Rimland (1964) and the pioneering concordance study by Folstein and
Rutter (1977; see also Folstein and Rutter, 1978) came persuasive evidence for bio-
logical and genetic factors in the causation of autism. The 1970s and 1980s brought
a steady stream of further findings concerning biological aspects of autism. This
field has taken significant leaps forward since the 1990s, thanks to revolutionary
advances in the fields of brain imaging (Minshew and Keller, 2010; Verhoeven et al.
2010) and molecular genetics (Abrahams and Geschwind, 2008; Geschwind, 2008;
Weiss, 2009). In relation to the neurobiology of autism there is now little doubt
that there are subtle atypicalities in the structure and functioning of the brain and
neural pathways in people on the autism spectrum (Amaral et al. 2006; DiCicco-
Bloom et al. 2006; Pardo and Eberhart, 2007). Current opinion views autism as
a disorder of functional ‘connectivity’ between cortical networks (Minshew and
Williams, 2007), in which key brain areas involved in verbal and non-verbal com-
munication, social interaction, planning and flexibility, as well as networks that
govern emotional responses (including fear and anxiety), facial recognition, and
the ability to conceptualise mental states in self and others (theory of mind) are
affected to varying degrees. Although a unifying pathology has not been identified,
and is perhaps even unlikely to be identified for autism, given the heterogeneity
in clinical and behavioural presentation of the spectrum, changes that affect early
brain development (evidenced by early brain overgrowth during the post-natal
period) are indicated in a significant proportion of children with autism (Courch-
esne et al. 2007). Developmental involvement of the frontal and temporal lobes
and the amygdala are strongly implicated (see Geschwind, 2009).

Neurochemical investigations have focused on several transmitter systems in
autism, including serotonin, dopamine, noradrenaline, acetylcholine, glutamate,
gamma-aminobutyric acid (GABA) and oxytocin (McDougle et al. 2005; Lam et al.
2006). Overall it has been difficult to draw firm conclusions from these studies
mainly due to the limitations highlighted earlier (i.e. heterogeneity of the spec-
trum, co-morbidities, sample sizes and matching to controls). Although a central
role for altered serotonergic function in autism has gained the most empirical evi-
dence, this still requires further investigation and validation. Promising new areas
of research include the possibility that oxytocin (the so-called ‘social hormone’)
signalling is perturbed in autism.

Concerning genetic factors, the heritability of autism is now well established.
The main focus of interest is in identifying candidate genes and their mode of
action on the developmental trajectory in autism (Abrahams and Geschwind,
2008; Geschwind, 2008; Weiss, 2009).

Psychological findings have also played an important role in theory and
research on autism from an early stage. Besides offering detailed descriptions
of the phenomena of autism, psychological approaches have offered a number
of theoretical models seeking to identify the core psychological processes under-
lying the observed phenomena. A significant breakthrough in the field of theo-
retical models came with the work of Baron-Cohen, Frith and Leslie (Baron-
Cohen et al. 1985) initiating two and a half decades of important research on
theory of mind deficits in people with autism. An additional impact of this model
has been to stimulate the development of a number of rival models, each origi-
ally presented as an account of the single ‘core deficit’ which could explain
the full range of symptoms and characteristics in autism. Recently this era of
model building has entered a new phase with the realisation that underlying pro-
cesses proposed within mutually exclusive accounts may in fact constitute parallel
factors which operate together to produce the observed pattern of symptoms in
autism.

Progress in the field of interventions for autism has been somewhat slower.
Some of the most widely used psychological interventions for autism remain those
such as the TEACCH framework (Treatment and Education of Autistic and related
Communication-handicapped Children) and the behavioural approach pioneered
by Ivar Lovaas (Pasco and Roth, 2010). Both originated several decades ago and
though reasonably effective in ameliorating certain symptoms of autism, and pro-
moting scope for education, cannot be considered as treatments. Progress in the
development of effective pharmacological interventions remains extremely lim-
ited. However, some encouraging trends are evident in recent work. For instance,
a growing number of interventions seek to address core psychological problems
in autism, such as theory of mind or mind-reading deficits (see for example, Golan
et al. 2010). Moreover, advances in the design and implementation of critical eval-
uations have greatly enhanced the evidence base for a whole range of treatments,
thus limiting the scope for practitioners to make unfounded claims about ‘cures’
(Pasco and Roth, 2010).
Moving forward – contemporary issues in autism, from diagnosis to development and education

As we have outlined, progress in understanding the autism spectrum combines encouraging progress in some areas with a history of conceptual and methodological difficulties, false trails and puzzling omissions. One important goal of this volume is to redress this uneven and patchy coverage. The selected topics combine contemporary developments in areas widely accepted as fundamental for understanding autism, with new work representing some less widely researched themes and approaches. A recurring theme throughout the volume is the need to develop a suitably nuanced account of autism, fully informed by the heterogeneity and complexity of the phenomena which it presents. All chapters in this compendium are by leading contributors at the forefront in the field of autism theory, research and practice. Their wide-ranging contributions embrace classification and diagnosis, genetics, neurology and biochemistry through to socio-cognitive, developmental and educational perspectives, reflecting the multi-level emphasis of current thinking. This volume aims to promote a broader, more balanced and contemporary understanding of the autism spectrum.

The first section of the book examines classification and diagnosis. In the opening chapter on ‘Early assessment and diagnosis of children’, Professor Ann Le Couteur from the Institute of Health and Society at Newcastle University first addresses the challenge of dissecting and clarifying the difficult terminology of the autism spectrum, offering an invaluable framework for the volume as a whole. The remainder of this chapter focuses on key aspects of assessment and current diagnostic procedures, including the use of the best estimate clinical diagnosis for clinical and research practice. Difficulties and challenges surrounding diagnosis of childhood autism and ASD are explained and discussed in depth. These are placed in context for the reader with reference to landmark and ongoing studies.

The next section (Chapters 2–6) deals with genetics, neurology and biochemistry. In Chapter 2, ‘Unravelling the genetics of autism spectrum disorders’, a team of investigators from the Wellcome Trust Centre for Human Genetics at Oxford University led by Professor Anthony Monaco, an integral part of the International Molecular Genetic Study of Autism Consortium (IMGSAC), provide an exceptional insight into this crucial topic. They review and evaluate the extensive body of evidence from linkage and association studies (including genome-wide association), focusing on candidate genes, single gene mutations, epigenetics and copy number variations. They emphasise that the complex aetiology of ASD, which is likely to involve multiple interacting genes and pathways, calls for several different strategies of enquiry, and show how this field of research may move forward, with
larger-scale sequencing efforts required to unravel the causal variants involved in ASD.

Dr Michael Spencer at the Cambridge Autism Research Centre and colleagues from the Centre for Clinical Brain Sciences, Royal Edinburgh Hospital Department of Psychiatry consider ‘Brain imaging and the neuroanatomical correlates of autism’ in Chapter 3. They provide a detailed overview of structural alterations within neural circuits and brain areas involved with social functions, and restricted and repetitive behaviours in autism. Importantly, they discuss key factors that impact on the interpretation of brain imaging studies which, besides the established heterogeneity of the spectrum, include the gender and intellectual ability of individuals, the developmental trajectory of autism, as well as differences in analytical and technical approaches. They conclude that longitudinal studies exploring the developmental trajectory in ASD, and interdisciplinary efforts to combine neuroimaging with genomic techniques, relating these to neuropsychological findings, represent a productive route to further important insights into the neurobiology of autism.

In the chapter which follows, ‘Magnetoencephalography (MEG) as a tool to investigate the neurophysiology of autism’ (Chapter 4), Dr Sven Braeutigam from the Oxford Centre for Human Brain Activity (OHBA) and colleagues introduce this modern functional neuroimaging method, describing its application to investigating dynamic brain activity and neural processing in autism. The technical and analytical approaches are outlined before the authors move on to the ‘functional systems’, focusing on key aspects of neural processing which may be affected in autism–auditory processing, semantic processing, face processing and theory of mind-associated with activity within the so-called ‘mirror neuron’ network. An important feature of MEG highlighted in this chapter is the scope it offers to define and further characterise subclinical epilepsy and epileptiform activity (seizures) that may remain otherwise undetected in a significant proportion of individuals on the spectrum. The authors emphasise that while MEG is a relatively new tool, the few studies conducted to date broadly support the notion that autism involves altered cognitive strategies as opposed to cognitive impairments or ‘deficits’ per se. The technique is presented as holding significant promise for advancing understanding of the neural basis of autism.

In the next chapter ‘Autism and epilepsy’ (Chapter 5), this critically important and often understated relationship is the focus of discussion by Professors Gillberg and Neville, from the University College London Institute of Child Health and the University of Gothenburg in Sweden. They discuss prevalence, gender and differential diagnostic aspects, before examining autistic regression and epilepsy and taking a closer look at the various types of seizures that may be associated/co-exist with autism, as well as early-onset epilepsy syndromes. The authors consider
investigation and management, emphasising the need for an integrated approach to epilepsy and psychiatric problems, and for neurological investigations to include MRI scanning and biochemical investigation, and discuss the place of EEG in investigating autism and the pathogenesis of autistic regression in epilepsy.

Dr Mukaetova-Ladinska and colleagues from Newcastle University shift the focus to the 'Biochemistry of autism: changes in serotonin, reelin and oxytocin' in Chapter 6. They review the field and present evidence to support the notion that disruption in one or more of these systems, which may be interlinked, is associated with aspects of the clinical phenotype in autism. Currently available pharmacological interventions targeting these systems are evaluated and discussed in the context of these findings. The authors conclude by highlighting some important limitations in these studies and the need for more concerted efforts and validation.

The next section (Chapters 7–12) deals with cognition, development and education. In the opening chapter of this section, ‘Psychological models of autism: an overview’, Dr Elizabeth Pellicano from the Centre for Research in Autism and Education at the London Institute of Education, sets the scene with an overview of three theoretical accounts of autism which have played a major role in psychological explanation of autism in recent decades (the theory of mind hypothesis, the executive dysfunction hypothesis and the weak central coherence theory). She analyses some of the reasons why the status of these approaches as ‘single-deficit’ accounts has been challenged, not least that there may be different substrates for the three major symptom groups in autism, leading to the more recent reconfiguration of these proposals within ‘multiple-deficit’ models. She concludes by stressing the all-important issue of situating explanatory approaches within a developmental context. In relation to cognitive functioning in autism, this chapter uses ‘deficit’ and associated terminology only where historically appropriate. The author’s preference for alternative terms such as ‘atypicality’ reflects an important and growing trend in the discussion of autism.

In the chapter on ‘Cognitive flexibility in autism: a social-developmental account’ (Chapter 8), Professor Peter Hobson and Dr Jessica Hobson from the Behavioural and Brain Science Unit at the UCL Institute of Child Health in London offer a theoretical extension of the social-developmental approach to autism. A theory prioritising the impaired capacity of infants later diagnosed with autism to form social and emotional relationships might seem ill-equipped to explain the narrow and repetitive activities and interests that form the third symptom cluster of the triad. However, the authors present an elegant account of how a child’s social-developmental endowments could also determine their cognitive capacity for flexible and context-sensitive thinking and engagement with the world. The claim that these may be affected in individuals with autism, leading to specific forms of cognitive restriction and rigidity, provides an interesting counterpoint
to the theoretical fractionation of the three symptom clusters, set out in the preceding chapter.

Professor Jill Boucher of the Autism Research Group at the Department of Psychology, City University London, addresses one of the most complex and puzzling patterns of deficit in those on the autism spectrum; in her chapter on ‘Language in autism spectrum disorders’ (Chapter 9). As she points out, language capacities across the spectrum vary widely across sub-groups and from low- to high-functioning individuals. Among those who have problems with structural language (as opposed to more subtle problems with communication), there is also a range from marked difficulties with grammar, syntax and phonology, to difficulties in processing meaning. Her chapter reviews the possible role of theory of mind and associated impairments, as well as that of co-morbid specific language impairment in generating this complex pattern. She concludes with a hypothesis suggesting a selective but pervasive impairment in the declarative aspects of memory.

In Chapter 10, ‘Memory in autism: binding, self and brain’, Professor Dermot Bowler and colleagues, also from the Autism Research Group at the Department of Psychology, City University London, continue with the theme of memory difficulties. They provide convincing arguments for the importance of this often-neglected area of impairment in ASD, showing how memory impairment may impact on fundamental aspects of human functioning, including the binding of experience and sense of self, and may also relate closely to known neuropsychological atypicalities.

Dr Ayla Humphrey and colleagues from the Cambridge Autism Research Centre, Developmental Psychiatry Section, and MRC Cognition and Brain Sciences Unit consider the crucial interface between psychological theory and its application in clinical and educational settings in their chapter ‘Measuring executive function in children with high-functioning autism spectrum disorders: what is ecologically valid?’ (Chapter 11). In so doing, they highlight how the nuanced consideration of differences in symptoms and capacities, which has surfaced repeatedly in this volume, must extend not only to sub-groups, but also to the level of the individual child. Their study suggests that there is in fact no best measure of executive function, and that information from several sources should be considered when evaluating this (and perhaps other neuropsychological functions), in this group of children. Their work provides further important insight into how expectations of parents and teachers of children with ASD influence their views and reporting of a child’s abilities and disabilities.

In the concluding chapter, ‘Autism Spectrum Disorders in Current Education Provision’ (Chapter 12), Professor Rita Jordan of the School of Education at Birmingham University provides a stimulating analysis of the crucial issue of educational provision for children on the spectrum. She examines the evidence base for learning styles in ASD, in particular how psychological characteristics and
cognitive style impact on the child’s capacity to learn, and on their ability to access key areas of the curriculum. The role of stress and the importance of parental support are further emphasised. The value of different kinds of educational placement, the issue of inclusion, and the need for further research in these and other associated areas are identified in these discussions.

It has been a great privilege and a pleasure to assemble and shape the material in this volume. We hope that readers will enjoy engaging with the content as much as we have enjoyed preparing it.

References


Early assessment and diagnosis of children

Ann Le Couteur

Autism is an organic neurodevelopmental disorder, the prototypical disorder of the group of conditions known as the pervasive developmental disorders. Genetic findings and general population studies indicate that these types of disorders (commonly referred to as Autism Spectrum Disorders (ASD) or more recently Autism Spectrum Conditions (ASC)), probably occur along a broad continuum of severity. This spectrum of presentations include those individuals with a definable disorder and clear evidence of social impairment and incapacity, qualitatively similar behavioural characteristics in other family members (described as the broader autism phenotype), and a range of more subtle social, communicative and repetitive behaviours in the general population. ASD are no longer considered rare, with a replicated reported prevalence of approximately 1 in 100. With increasing public and professional awareness and an emphasis on the importance of both early recognition and access to so-called ‘early interventions’, there is an expectation of early identification, assessment and diagnosis. This chapter will review the evidence for ASD, the epidemiology and prevalence of these disorders and consider (using the framework of the National Autism Plan for Children) a range of assessment and diagnostic procedures including the use of the best estimate clinical diagnosis for clinical and research practice. Inevitably, the purpose of assessment informs the format and content of the diagnostic process. The chapter will conclude by considering some current diagnostic challenges. Although the focus of this chapter is the diagnosis of ASD in children, there is an increasing awareness that the needs of adults from across the autism spectrum must be recognised. For some individuals this will include access to assessment and
diagnosis during adult life to inform the development of a personalised package of support.

1.1 Definition

Autism Spectrum Disorders are lifelong severe neurodevelopmental disorders with a considerable functional and financial impact on both the individual and their family. In recognition of this broader spectrum of difficulties the terms ASD and ASC have gained wider acceptability over the last twenty years or so (Frith, 1991; Johnson et al. 2007; Volkmar et al. 2004; Wing, 1978; Wing and Gould, 1979). The terms ASD and ASC have become widely used in lay, clinical and research contexts to include autism, Asperger syndrome, atypical autism and pervasive developmental disorders not otherwise specified (PDD-NOS) (Frith, 1991; Volkmar et al. 2004; Wing and Gould, 1979). ASD/ASC is used as a pragmatic category, both for purposes of clinical and research diagnosis and for the identification of special needs in relation to the provision of appropriate support services. Throughout this chapter the term 'Autism Spectrum Disorder' will be used interchangeably to mean autism spectrum disorders/autism spectrum conditions and Pervasive Developmental Disorders (PDD).

Autism is the prototypical disorder of this broad spectrum of disorders. All individuals share a common triad of impairments in social interactions, atypical and often delayed verbal and non-verbal communication together with a repertoire of repetitive and unusual behaviours, interests and play. Studies have shown a wide variation in rates of cognitive impairment. Historically autism was frequently recognised in individuals with severe impairment and learning disability (Rutter, 2005). Estimates suggested learning disabilities (IQ less than 70) affected 70 to 80% of individuals with ASD (Baird et al. 2003; Johnson et al. 2007). In recent years the inclusion of higher functioning individuals has led to an apparent decrease in the rates of cognitive impairment (Baird et al. 2006; Johnson et al. 2007). Those higher functioning individuals with autism spectrum disorder may show good verbal skills in contrast to those with autism or PDD-NOS who may perform better in non-verbal measures. However, this ‘higher’ degree of intelligibility on performance tasks cannot be assumed to reflect their social skills which may be significantly impaired (Carrona et al. 2008; Le Couteur, 2003).

Another unique feature of these disorders is the characteristic patchy pattern of deficits and areas of relative strength. Indeed approximately ten percent of individuals with core autism have been shown to possess a skill that is significantly better than would be predicated by their global intellectual ability (Frith, 2003). Howlin (2003) has also reported that adults with high functioning autism can show giftedness in one or more areas of functioning. Frith and her colleagues have proposed that early atypical processing biases may play a role in the development
of these so-called splinter skills (Frith, 2003). These skills include perfect pitch, artistic, musical and mathematical ability.

Most authors agree that the spectrum of neurodevelopmental disorders extends beyond ASD to include other specific developmental disorders such as specific language impairment (SLI), specific academic difficulties (such as dyslexia) and other disorders such as attention deficit hyperactivity disorder (ADHD) (Rutter, 2006). Rutter (2006) wrote ‘For all these disorders persistence into adult life involves a mixture of the expected and unexpected and substantial challenges remain in the identification of key mediating variables’. These disorders have many features in common including: early onset life long disorders; delay/deviance in maturationally influenced psychological features; a general tendency for impairments to lessen with age; and some degree of accompanying general or specific cognitive impairment. Much of the behavioural symptomology of these disorders shows considerable overlap. These disorders also have in common a genetic liability and marked male preponderance.

One of the first clinical descriptions of Autism was made by Kanner in 1943. He identified an underlying ‘innate inability to form the usual biologically provided affective contact with people’ (Kanner, 1943). The following year Asperger (1944) reported a number of clinical cases using the term ‘autistic psychopathy’ and wrote that this ‘disturbance results in severe and characteristic difficulties in social integration’ (Frith, 1991).

It was not until 1980 that the American Psychiatric Association coined the term pervasive developmental disorders (PDD) highlighting the significant impact on everyday life that these complex neurodevelopmental disorders have across all aspects of functioning. The currently agreed international diagnostic criteria (ICD-10 and DSM IV-TR) define these disorders in relation to particular developmental history profiles and current behavioural characteristics. The subcategories are similar across the two classification systems (American Psychiatric Association, 2000; World Health Organization, 1993) (Table 1.1).

The diagnostic criteria include: qualitative impairments in social interaction; qualitative impairments in social communication; the presence of a repertoire of restricted, repetitive (often non-adaptive) interests, behaviours and activities; together with evidence of delay or deviance in development within the first 3 years of life. There is clear evidence that the diagnosis of autism is valid and can be made reliably from 2 years of age (Charman et al. 2004; Lord, 1995; Lord et al. 2006; Moore and Goodson, 2003). Studies also show that despite individual variations in presentation and patterns of developmental progress, the diagnosis remains valid at follow-up (up to the age of 9 years) (Baird et al. 2006; Lord et al. 2006; Volkmar et al. 2004). Turner et al. (2006) reported that 88% of children who received a diagnosis of autism/autism spectrum disorder at 2 years remained on the autism spectrum at the age of 9 years.
Table 1.1 *International diagnostic sub-categories for Pervasive Developmental Disorders*

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<th>Pervasive Developmental Disorders (ICD-10)</th>
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<tr>
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<td>• F84.0 Childhood autism</td>
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<td>• F84.1 Atypical autism</td>
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<td>• F84.2 Rett’s syndrome</td>
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<td>• F84.3 Other childhood disintegrative disorder</td>
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<td>• F84.4 Overactive disorder associated with mental retardation and stereotyped movements</td>
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<td>• F84.5 Asperger syndrome</td>
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<td>• F84.9 Pervasive Developmental Disorder, unspecified</td>
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<th>Pervasive Developmental Disorders (DSM-IV-TR)</th>
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<td>(American Psychiatric Association, 2000)</td>
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<tr>
<td>• Autistic Disorder</td>
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<td>• Rett’s syndrome</td>
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<td>• Childhood Disintegrative Disorder</td>
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<td>• Asperger Syndrome</td>
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<tr>
<td>• Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)</td>
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The nosological validity of the other sub-groups within the pervasive developmental disorder classification is less certain and the use of these diagnoses in early childhood shows more variability and is less reliable (Charman and Baird, 2002; Cox et al. 1999; Lord et al. 2006; Turner et al. 2006).

Taking one specific subcategory, Asperger syndrome (AS), several international clinical and research teams have developed specific sets of diagnostic criteria for Asperger syndrome (Attwood, 2006; Leekam et al. 2000; Wing, 1981). These clinical research criteria show areas of both overlap and separation but most include more detailed requirements than the ICD 10/DSM IV-TR descriptions and definitions for Asperger syndrome. Further, a number of studies have highlighted the difficulties replicating the internationally agreed diagnostic criteria (ICD; DSM). This has led to conflicting findings (Gilchrist et al. 2001; Howlin, 2003; McConachie et al. 2005; McIntosh and Dissanayake, 2004; Szatmari et al. 2003). McConachie et al. (2005) explored the rates of Asperger syndrome in a cohort of 104 pre-school children recruited in the north-east of England, all of whom had received detailed diagnostic assessments. Only three children met the current ICD-10 criteria. These authors reported that repetitive behaviours seemed to be important for the diagnosis of AS but were more likely to be reported in older children as they enter school age. Several authors have also observed that with age (i.e. into adolescence and adulthood) individuals with an early childhood diagnosis of AS showed similar clinical behavioural characteristics to those with a diagnosis of autism, albeit high functioning autism (Gilchrist et al. 2001; Howlin, 2003).
Moving beyond the diagnoses of autism and Asperger syndrome, published reports of both clinical and general population samples identify a spectrum of developmental difficulties and behaviours in individuals presenting with milder clinical traits and evidence of social impairment/incapacity. These types of developmental and functional difficulties meet the internationally agreed diagnostic criteria for atypical autism, Pervasive Developmental Disorder unspecified (ICD-10)/Pervasive Developmental Disorder not otherwise specified (PDD-NOS) (DSM-IV-TR) and would be included within the terminology of Autism Spectrum Disorders. These categories (PDD-NOS) are defined by exclusion (Volkmar, 1998). Volkmar also noted the striking paradox that individuals with PDD-NOS are much less frequently studied but are much more common than other recognised diagnostic Pervasive Developmental Disorder diagnostic categories.

However, the spectrum probably extends even further beyond those individuals with an ASD defined by some degree of impairment in social functioning. Genetic studies of families recruited through individuals with core autism indicate that some affected individuals experience milder variants known as the broader autism phenotype (Bailey et al. 1998; Bailey and Parr, 2003; Bolton et al. 1994; Le Couteur et al. 1996; Parr et al. 2006; Pickles et al. 2000; Piven et al. 1997; Rutter, 2006). Furthermore the study of several other recognised disorders, such as tuberous sclerosis, neuromuscular disorders, Fragile X, cerebral palsy, congenital blindness, congenital rubella and ADHD, has shown autistic-like behavioural characteristics and patterns of development (Brown et al. 1997; Chess, 1977; Darke et al. 2006; Kerr, 2002; Reiersen et al. 2007). The association of known medical conditions is much stronger for the prototypical disorder of autism (childhood autism (ICD-10); autistic disorder (DSM-IV-TR)) than the more broadly defined ASD (Fombonne, 2003).

Finally, several studies using various different measures including study specific self report rating scales and checklists through to ASD screening and diagnostic tools have reported a range of so-called Autism Spectrum Disorder type social-communication and repetitive behavioural traits in general population samples (Constantino and Todd, 2003; Leekam et al. 2007; Ronald et al. 2006). These findings need replication with valid and reliable measures. However, the conceptual implications of a categorical or continuous dimensional approach to ASD and the implications of a symptom model, factor solution or the continued acceptance of the triad of impairment for defining autism/Autism Spectrum Disorder will significantly influence our future understanding of the aetiology and the investigation of the underpinning constructs of these disorders. Yet it may not be possible to resolve these controversies until there is finally a better understanding of the aetiology of the autism spectrum.

In summary, over recent decades, there have been major changes in both the diagnostic terminology and our conceptual understanding of Autism Spectrum
Disorders across a broad spectrum of presentations from specific diagnoses to so-called dimensional traits in the general population.

1.2 Epidemiology

The most recent UK epidemiological study was conducted by Baird et al. (2006) and reported an overall prevalence rate for ASD of approximately 1 in 100 in school aged children (38.9 per 10 000 for autism and 77.2 per 10 000 for other ASD). This study included the direct assessment of a proportion of all the children within the identified study community. These rates are in keeping with other UK and US studies (Chakrabarti and Fombonne, 2005; Newschaffer et al. 2007) but in sharp contrast to the reports of the first epidemiological study when autism was defined as a rare disorder with a population prevalence of 4–5 per 10 000 (Lotter, 1966). There are likely to be several factors contributing to this increase. First there is a greater knowledge and awareness about Autism/ASD amongst both the general population and relevant professional groups working with children leading to improved case recognition. Second there is a greater preparedness to extend the diagnostic criteria to include more able individuals rather than to restrict diagnosis to a narrow definition of autism with accompanying significant and severe learning difficulties. Third, there is some evidence to suggest diagnostic substitution for example from learning disabilities to autism/ASD. Finally it is possible that recent studies using systematic standardised screenings of total populations or birth cohorts are likely to have missed fewer children with ASD than in earlier studies (Rutter, 2005). Whether or not these most recently reported prevalence rates for autism/ASD are accurate or an underestimate it is clear that these are common disorders of childhood (Baird et al. 2006; Filipek et al. 1999). Further a recent report from the Adult Psychiatric Morbidity survey (2007) has indicated that 1% of adults living in the English general population had ASD. The authors highlight that it is the first time that such data have been collected in adults in any country (Brugha et al. 2009).

Although the genetic underpinnings of autism/ASD are indisputable (see Chapter 2) there have been a number of hypotheses about possible environmental aetiologies. Some of these hypotheses have received a great deal of media coverage. The published large epidemiological studies have not supported these postulated causal factors (Atladottir et al. 2007; Honda et al. 2005). If environmental risk factors are relevant they are likely to be operating either in the prenatal period or in the early years of life (Rutter, 2005). New studies of high risk siblings and large scale longitudinal studies may shed light on these controversial areas.
1.3 Assessment and diagnosis

Assessment and diagnosis can be challenging as affected individuals can not only show a wide variation in the degree of both intellectual ability and behavioural severity across the key developmental domains (see above), but their behavioural profiles will inevitably change with age. Any developmental concerns highlighted by parents/carers or identified during routine developmental surveillance require further assessment. However, a lack of concern from parents about their child’s early development does not necessarily imply a normal developmental history. Many parents express concerns as early as 15 to 18 months of age and some as early as 11 months (Chawarska et al. 2007) but it is often difficult to differentiate clearly when developmental difficulties began (Baird et al. 2003). These early symptoms may include: lack of joint attention (Charman et al. 1997; Charman, 2003); failure to develop spoken language (McConachie et al. 2005); failure to respond to name (Baranek, 2004); and showing decreased imitation of facial expressions, vocal imitations and object-orientated imitation (Bryson et al. 2007). Despite these findings the usual age of early pre-school diagnosis in the UK is not before 4 to 5 years of age (Carrona et al. 2008; Charman and Baird, 2002, Dumont-Mathieu and Fein, 2005).

At the time of initial presentation in early childhood it can be difficult to determine the significance of behavioural abnormalities with respect to the onset of ASD. For instance there may be uncertainty about the differentiation of developmental impairment/delay from developmental deviance or impaired social reciprocity from social anxiety or withdrawal. The child may have experienced a lack of opportunities to learn to play rather than displaying specific abnormalities in play skills or unusual interests. Other factors such as the presence of sensory deficits and/or the presence of other potentially co-morbid problems such as poor attention, poor concentration and levels of hyperactivity add to the complexity of defining the boundaries of the ASD spectrum. Certainly there are many children, especially at the more intellectually able end of the ASD spectrum, who are unlikely to be identified during the pre-school period. On the other hand there is emerging evidence that early intervention targeted on skills development leads to better outcome (Bryson et al. 2003).

Although a number of early general developmental and ASD screening tools have been developed and used in both clinical practice and research, universal use has not been recommended (Bryson et al. 2003; Le Couteur, 2003; Robins et al. 2001; Rutter 2005; Scottish Intercollegiate Guidelines Network (SIGN), 2007; Stone et al. 1999; Swinkels et al. 2006). There is a recent optimism regarding the potential for earlier identification and diagnosis of ASD (Johnson et al. 2007; see Autism: the
The age of clinical diagnosis depends on a combination of factors that include parental and professional recognition of presenting concerns, variability of behavioural symptoms and assessment procedures. For example speech delay in pre-school children may activate a referral whereas a child who is high functioning and has adequate language skills may present later with behavioural difficulties or problems with peer relationships as academic and social demands increase. Gilchrist et al. (2001), using the Autism Diagnostic Interview (ADI) to obtain retrospective accounts from parents of adolescents with AS, reported that although 70% of parents were aware of some abnormality in their child’s behaviour and development before the age of 3, only 35% of those parents sought professional help. In contrast, 92% of parents of young adults with high functioning autism (in the same study) were reportedly aware of problems before the age of 3, and 77% sought help at that early stage. When assessing a particular individual it may be hard to separate the features of ASD, co-morbid condition(s) and any environmental factors; or indeed the diagnosis may include a combination of all three.

1.3.1 Assessment process

It is equally important to diagnose, and not diagnose, accurately (SIGN, 2007)

The purpose of clinical or research assessment in ASD is to make a diagnosis where applicable. The assessment is based on an account of the developmental history, specific individual behavioural assessments and investigations, observation in several settings and the consideration of an appropriate differential diagnosis. The resulting diagnosis should be based on clinical judgement and the expertise of the multi-disciplinary/multi-agency assessments (Levy et al. 2009).

Standardised instruments (including diagnostic assessment tools) can enhance or facilitate diagnosis, may not be essential for every clinical assessment, but are required for most published peer reviewed research studies. Diagnostic assessment tools should not be used in isolation and most currently published instruments are less reliable in children under 2 years of age (Charman and Baird, 2002). The multi-disciplinary/multi-agency assessment should also include the identification of the individual’s and family’s profile of developmental skills and deficits, together with any associated developmental problems and co-morbidities that might impact on the functioning for the individual with ASD and their family.

The National Autism Plan for Children (Le Couteur, 2003) and the Scottish Intercollegiate Guidelines Network clinical guideline number 98 (SIGN, 2007)
Table 1.2 Components for a Multi-agency Assessment

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<th>Multi-agency Assessment (MAA) (NAP-C, 2003)</th>
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<td>1. Collate existing information</td>
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<td>2. ASD specific developmental history (ADI-R; DISCO; 3di)</td>
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<td>3. Observational assessments (incl ADOS)</td>
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<td>4. Cognitive assessment</td>
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<td>5. Communication assessment</td>
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<td>6. Behaviour &amp; mental health assessment</td>
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<td>7. Family assessment</td>
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<td>8. Physical examination</td>
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<td>9. Medical investigations</td>
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<tr>
<td>10. Other investigations (such as Occupational therapy and/or Physiotherapy)</td>
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provide a framework for early recognition, assessment and diagnosis and early intervention for young children/children and adolescents respectively. The stages for assessment include:

- **Stage 1:** General Developmental Assessment (GDA) for any child with a possible developmental problem.
- **Stage 2:** Multi-agency Assessment (MAA) including the ‘essential’ components for a complete ASD diagnostic assessment and differential diagnosis

The components for a multi-agency (MA) assessment are listed in Table 1.2.

1.3.2 ASD-specific developmental history

Standardised instruments, such as the Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al. 2003; Lord et al. 1994), the Diagnostic Interview for Social and Communications Disorders (DISCO) (Leekam et al. 2002; Wing et al. 2002) and the Developmental Diagnostic and Dimensional Interview (3di) (Skuse et al. 2004), provide frameworks for the specific developmental history required for a differential diagnosis of ASD/PDD. Although a criticism of such semi-structured interviews is that they can be time consuming, the detailed developmental history framework may provide relevant information that is not available from assessments of current functioning (Royal College of Psychiatrists (2006) Council Report CR 136).

**Autism Diagnostic Interview-Revised (ADI-R)** (Le Couteur et al. 2003; Lord et al. 1994; Rutter et al. 2003). The ADI-R is a semi-structured investigator-based interview undertaken with the parents/main caregiver. The format of the interview is designed to provide a framework for a lifetime differential diagnosis of PDD/ASD defined within the internationally accepted diagnostic systems (DSM-IV-TR and ICD-10). The interview emphasises the need to record descriptions of specific
behaviours in the three key domains necessary for a diagnosis of autism/ASD (with sections focusing on regression and special skills) and some other relevant clinical behaviours. The interview can be used for individuals of the mental age of 2 years and above. It takes around two to three hours to administer and training is required. The published algorithm provides a threshold for autism/non-autism only. With increasing awareness of the autism spectrum the original authors and a number of other ASD research groups are reanalysing ADI-R datasets to propose new diagnostic algorithm(s) threshold cut-off scores for autism and ASD (Buitelaar et al. 1999; Le Couteur et al. unpublished data). The interview does not, however, cover the more subtle and milder symptoms of the broader autism phenotype.

The ADI-R format records information about current behaviours (defined as the last three months), lifetime and early childhood ratings. Individual items show high reliability and high diagnostic validity (Rutter et al. 2003). However, it is the multiplicity of items across the three domains of enquiry that allows the separation of ASD from general developmental delay/learning disability and other neurodevelopmental disorders (Rutter et al. 2003). Further studies by other research groups have reported both good psychometric properties (de Bildt et al. 2004; Lecavalier et al. 2006) and the usefulness of the ADI-R in research studies (South et al. 2005). However, studies have also reported high sensitivity (83–91%) but lower specificity for autism (56–72%) in different age groups and populations. For instance Charman et al. (2004) reported that in a sample of 2-year-olds the diagnoses based on ADI-R alone were less stable when the children were followed up at 3 years of age. These findings support the importance of not relying on a single diagnostic measure and that algorithm threshold cut-off scores should not be used as the sole diagnostic criterion (Baird et al. 2006; de Bildt et al. 2004; Ventola et al. 2006). The interview is now available in seventeen languages.

The Diagnostic Interview for Social and Communication Disorders (DISCO) (Leekam et al. 2002; Wing et al. 2002). The DISCO is a clinical interview schedule based on Wing and Gould’s original theoretical proposal that autism is a spectrum of conditions with a particular emphasis on the triad of impairments. It was designed to collect information on development and behaviour for individuals of all ages and levels of ability. The interview evolved from the earlier Handicaps, Behaviours and Skills schedule (HBS) (Wing and Gould, 1978; 1979) and is used to elicit information relevant for the broader autism spectrum, other associated developmental disorders and co-morbid conditions. A set of algorithms and information on developmental skills and atypical behaviours can be derived from the interview but these are not clinical diagnoses (Leekam et al. 2002; Wing et al. 2002). The semi-structured interview is undertaken with parents/main caregivers. It takes approximately 3 hours to administer and specific training is required. The authors report good to excellent inter-rater reliability on 90% of items. The
instrument shows good agreement with the ADI-R. For both the ADI-R and the DISCO, informants (parents/carers) usually report that the experience of taking part in this type of detailed interview is reassuringly thorough and comprehensive.

The Developmental Diagnostic and Dimensional Interview (3di) (Skuse et al. 2004). This is a computerised interview assessment procedure that is designed to be administered by a trained interviewer with a parent informant using a laptop computer. A structured computer-generated report is available at the end of the interview, together with algorithms using a dimensional framework of symptom and diagnostic profiles for autism and common non-autistic co-morbidities. The focus is on current functioning. Parents can be sent a pre-interview package of questionnaires to complete. This information can be entered onto the computer and allows an abbreviated face-to-face interview lasting forty-five minutes, compared with ninety minutes for the full interview. The interview was devised to assess autistic traits, social impairment and co-morbidity in children of normal ability and is not recommended for use on pre-school children. The authors report good test inter-rater reliability (Skuse et al. 2004).

Vineland Adaptive Behaviour Scale (VABS). An additional structured interview undertaken with the parent/main caregiver that is completed in some studies (clinical and research) immediately after the ASD specific developmental history is the VABS (Sparrow et al. 1984). Carter et al. (1998) have published supplementary norms for individuals with autism. This interview provides information about the individual’s developmental level in four domains of everyday adaptive self help and independence skills (motor behaviours; communication; social interactions; maladaptive behaviours). This information complements direct testing (see below).

1.3.3 Observation and individual assessments

For children and individuals with ASD and other developmental and neurodevelopmental disorders, behaviour can vary considerably in different settings. Direct observations can be undertaken in a range of settings such as home, educational settings (including playgroup, nursery, school or college), health-based settings, other local authority and social services settings. Observations of behaviour in different settings will allow assessment of both the individual’s functioning in different contexts but also how they interact with peers and adults in their usual social settings. It also provides the opportunity to assess the level of adaptability to predictable and less predictable events.

ASD-specific standardised observational assessments give complementary information that allows comparisons between individuals over time and between different clinical/research centres and samples.
**Autism Diagnostic Observational Schedule (ADOS)** (Lord *et al.* 2000). This assessment was first developed together with the ADI as a package of instruments for research diagnosis (Bailey *et al.* 1995; Bolton *et al.* 1994). The ADOS is a widely used semi-structured, standardised play and activities-based assessment focusing on the three behavioural domains necessary for a differential diagnosis of ASD and/or other neurodevelopmental disorders namely:

1. communication
2. social interaction
3. play/imaginative use of materials and repetitive behaviours

These observations complement the information gained from other assessment procedures such as the developmental history and direct observations. It takes 30–45 minutes to administer. Training in the use of pre-determined social contexts is required and once trained regular reliability checks are necessary (de Bildt *et al.* 2004; Lord *et al.* 2001). There are four modules for use with individuals ranging from pre-school children without useful speech through to verbally able adults (Lord *et al.* 1989; 2000; 2001). The module choice controls for levels of expressive language. The ADOS publications report high levels of reliability of items across modules. The exception is coding of items such as repetitive behaviours and sensory abnormalities which may occur less frequently during a live individual assessment.

Diagnostic algorithms summarise the ratings for social behaviour and communication in relation to DSM-IV and ICD-10 diagnostic criteria with separate thresholds for autism and ASD. Until recently restricted and repetitive behaviours were not included in these diagnostic algorithms (Gotham *et al.* 2007; 2008). The ADOS is available in several languages, but further work may well be required to consider particular social and cultural factors. This assessment provides useful clinical and research information that can inform intervention planning. Although the instrument was originally developed as a diagnostic tool, it has also been used as an outcome measure (Aldred *et al.* 2004; McConachie *et al.* 2003). A new severity metric has been reported which may prove useful for evaluating the effectiveness of interventions (Gotham *et al.* 2009).

### 1.3.4 Assessment of individual profile of skills and deficits

For some individuals with ASD, co-operating with direct testing can pose particular challenges. However, since those with neurodevelopmental disorders such as ASD are likely to have unique profiles of skills and deficits (see Table 1.2), direct assessment will usually be needed. This information is important for both clinical and research purposes to inform, for example, planning of appropriate interventions for an individual, to investigate specific research hypotheses and to compare research findings across studies. Successful direct assessment inevitably
requires specialist skills and experience working with people with ASD. Individual profiling of intellectual ability, neuropsychological functioning, communication, motor and sensory skills and adaptive functioning have been recommended (Johnson et al. 2007; Le Couteur, 2003; Ministries of Health and Education, 2008; SIGN, 2007).

1.3.5 Neuro-cognitive assessment

Some neuropsychological impairments may not be specific to ASD but may be more severe in individuals with ASD and the degree of impairment is likely to be influenced by several factors such as levels of communicative skills and verbal mental age. Although standardised IQ tests are considered reliable measures of functioning, direct testing of those with ASD across the age range can be challenging. For instance using the example of the assessment of verbal and non-verbal skills, this usually requires separate testing and since the age range for many tests is limited, different tests/measures are likely to be used for different age groups. This in turn means that the measures used may be different over time and indeed different centres may choose to use different measures. All these factors are likely to lead to problems with interpretation of any findings such as change in scores. This is a particular concern when evaluating the impact of an intervention for an individual and in larger scale intervention evaluation studies. Further, although many published cognitive assessment tests provide scoring protocols and norms for typically developing children, norms for different cultural groups and for individuals with ASD may not be available. Several authors have provided summaries of available tests (Howlin, 1998; The National Autism Plan for Children (Le Couteur, 2003)).

1.3.6 Communication, speech and language assessment

A comprehensive assessment of an individual profile of verbal and non-verbal communication skills will include a combination of targeted observations in different settings and direct assessment work. Again the choice of assessment measure(s) will depend on several factors including: the purpose of the assessment; the individual characteristics of the child/individual; other potential co-morbidities; and/or the focus of the research study (Bishop and Norbury, 2008; Botting and Conti-Ramsden, 2003; Charman et al. 2003; Cohen et al. 2003; see National Autism Plan for Children for summary of assessment tools for use with young children (Le Couteur, 2003)).

1.3.7 Behavioural and mental health assessment

Disturbances of behaviour, attention, activity, thought and emotion are common in individuals/children with ASD (de Bruin et al. 2007; Leyfer et al. 2006; Simonoff et al. 2008). Individuals with ASD can experience the same
developmental, medical and mental health conditions as individuals without ASD (SIGN, 2007). Disordered sleep and food selectivity are well recognised (Bowers, 2002; Couturier et al. 2005; Keen, 2007; Mills and Wing, 2005; Ministries of Health and Education, 2008; Polimeni et al. 2005; Wigg and Stores, 2004). Problematic emotional reactions and behaviours can occur in response to a range of potentially modifiable factors such as medical conditions (for example earache) or a change in their environment. These behaviours can include self-injurious behaviour, disruptive behaviours, aggressiveness, temper tantrums, emotional lability, irritability, anxiety and a range of co-morbid mental health disorders. Co-morbidities with ASD are well recognised and have been reported to affect up to 72% of cases (de Bruin et al. 2007; Gillott et al. 2001; Green et al. 2000; Hutton et al. 2008; Leyfer et al. 2006; Mills and Wing, 2005; Simonoff et al. 2008; Witwer and Lecavalier, 2005). There is a limited evidence base for using currently available mental health diagnostic assessment tools. New instruments for individuals with ASD have been reported (Bolton and Rutter, 1994; Brereton et al. 2006; Hutton et al. 2008; Leyfer et al. 2006). These instruments need further testing in independent samples.

1.3.8 Family assessment

It has long been acknowledged that the continuity of care and attention that individuals with ASD receive has an important impact on their outcome and ability to achieve their individual potential (National Research Council, Committee on Interventions for Children with Autism Report, 2001; Schopler and Reichler, 1971; Schopler et al. 1982). However, the impact of caring for individuals with ASD is significant for the whole family (parents, siblings and grandparents) (Bromley et al. 2002; Gold, 1993; Gray, 2002; Hastings and Johnson, 2001; Margetts et al. 2006; Mills and Wing, 2005; National Autistic Society Report entitled ‘The impact of autism on the family’, 2005). Family studies have confirmed an increased genetic risk for both ASD and a broader range of qualitatively similar social, cognitive and communication traits and behaviours in relatives of individuals with autism/ASD (Bailey et al. 1998; Bolton et al. 1994; Parr et al. 2006; Szatmari et al. 1998). Studies have also reported increased rates of other psychiatric disorders (Bolton et al. 1998; Daniels et al. 2008; Murphy et al. 2000). Recently published clinical guidelines and practice parameter documents highlight the importance of assessing the profile of family skills and difficulties to inform both a family care plan and the individual education and therapeutic plan for the young person with ASD (Le Couteur, 2003; Ministries of Health and Education, 2008; Scottish Intercollegiate Guidelines Network, 2007; Yates and Le Couteur, 2009).

1.3.9 Physical examination, medical investigations and other needs

An initial general developmental assessment should be performed for all individuals when there is a concern about developmental progress. This will
include a careful medical and family history and a full neurological examination. Hearing and visual impairments should be ruled out by performing appropriate assessment(s). When the differential diagnosis includes possible ASD, this medical assessment should include looking for neurocutaneous stigmata, dysmorphisms and a Wood’s light examination especially in the presence of learning disability (Baird et al. 2003; Johnson et al. 2007; Scottish Intercollegiate Guidelines Network, 2007; Yates and Le Couteur, 2009). Approximately 10–15% of children with ASD have a currently recognised medical condition such as tuberous sclerosis (Barton and Volkmar, 1998; Fombonne et al. 1997; Kielinen et al. 2004; Rutter et al. 1994). Some disorders (for example epilepsy) are common in individuals with ASD (Billstedt et al. 2005; Kagan-Kushnir et al. 2005; Tuchman and Rapin, 2002) and at least a fifth to a third of pre-school children have a history of regression (Baird et al. 2008; Lord et al. 2004; Meilleur and Fombonne, 2009; Tuchman and Rapin 1997; Werner and Dawson, 2005). Karyotyping and DNA-specific testing for Fragile X is recommended in all individuals with other investigations guided by clinical presentation, family history and where there are specific management, treatment or genetic implications (Johnson et al. 2007; Ministries of Health and Education, 2008; Scottish Intercollegiate Guidelines Network, 2007; Yates and Le Couteur, 2009). Investigative yield is generally low, quoted as between 8% and 37% depending on the population studied (Challman et al. 2003). The yield of positive investigations is increased if there is lower IQ and dysmorphic features (Cass et al. 2006; Challman et al. 2003; Johnson et al. 2007).

Neuroimaging and EEGs should only be performed if there is a clinical indication, or if part of the research paradigm. Similarly evaluation of gastrointestinal tract should be guided by clinical presentation. Increasing emphasis on, and awareness of, the rates of motor, sensory and perceptual difficulties has led to specific assessments of sensory profiles and perception difficulties but this is only indicated in response to clinical and research indications (Dover and Le Couteur, 2007; Dunn 1999; Ministries of Health and Education, 2008; Scottish Intercollegiate Guidelines Network, 2007).

1.4 Best Estimate Clinical Diagnosis (BECD) and research diagnosis

Structured ASD diagnostic interviews and observational methods are often used in combination in both clinical and research practice. However, the systematic collection of information does not replace clinical judgement and further, such standardised procedures will not always resolve the problems of discrepancies between sources of information (Goodman et al. 1996). In most research and clinical studies all sources of information are combined to produce the ‘Best Estimate’ Clinical Diagnosis (BECD). This procedure is often defined as the gold standard
in research and clinical guidelines (Dunn, 2000; Dover and Le Couteur, 2007; Le Couteur, 2003).

1.4.1 ASD research diagnostic procedures

For all research, protocols should include a detailed description of the diagnostic paradigm for ASD (see Table 1.3). This will usually comprise a developmental interview, a range of observational measures and an indication about whether or not clinical information is available to be included within a BECD procedure.

The following examples of baseline ASD assessments illustrate the use of a combination of measures (together with inclusion and exclusion criteria) to provide the details of participant characteristics required to address specific research hypotheses. The details of the specific sample recruitment, selection and study procedures are reported elsewhere.

The International Molecular Genetic Study of Autism Consortium (IMGSAC, 1998; 2001). For this multi-centre molecular genetic study, the inclusion criteria for probands with autism were very specific with the aim of minimising genetic heterogeneity. Probands had to have a clinical diagnosis of autism before the age of 12 years together with specified algorithm threshold criteria for ADI-R and ADOS; physical examination; karyotyping and specific DNA testing to exclude Fragile X; and cognitive tests. The study exclusion criteria were:

1. Age less than 4 years at time of recruitment
2. IQ < 35 (using specified assessments)
3. Presence of other known medical conditions (e.g. tuberous sclerosis, Fragile X chromosomal anomaly, neurological disorders)
4. Neonatal brain damage or incomplete obstetric information
5. Adoptive, foster or institutional upbringing during the first 4 years (or other potential contributing circumstances, e.g. severe nutritional or psychological deprivation)
6. Any other observational data that cast doubt on the diagnosis
Families and Communication: Training and Support (FACTS trial) (McConachie et al. 2003). The aim of this study was the evaluation of an early intervention group training programme for parents of pre-school children with complex social communication disorders (including suspected autism/ASD). The children did not, however, need a definite diagnosis of autism to be considered for inclusion in the parent group training programme. The main inclusion criterion was evidence of language and social or behaviour problems. The best estimate clinical diagnoses (autism, ASD and other (including those children with a speech and language disorder)) were derived from a combination of assessments (clinical accounts, ADI-R; ADOS, VABS and cognitive assessment using the Mullen Scale of Early Learning (Mullen, 1995)) (see Figure 1.1). In this study the ADOS was also used as an outcome measure.

Pre-School Children Communication Trial (PACT) (Green et al. 2010). This is a recently completed UK-based three-site randomised controlled trial of a parent-mediated communication-focused intervention for pre-school children with ASD added to their treatment as usual (TAU) against TAU alone. For this study all
subjects have a definite clinical diagnosis of autism (using the ADI-R and ADOS algorithm thresholds) and greater than twelve months age equivalent level in non-verbal development. The exclusion criteria are severe epilepsy and twins.

Figure 1.1 illustrates the model of measurement for diagnosis and the evaluation of outcomes of the children, used over the course of the FACT study.

**The Special Needs and Autism Project (SNAP)** (Baird *et al.* 2006). This community-based project assessed a cohort of 1733 children in South Thames with identified special education needs and a further 255 cases known to local services, drawn from the population of just under 57,000 children born between July 1990 and December 1991. All assessed children were given a research diagnosis based on the findings from the standardised research assessment tools including ADI-R and ADOS. Each case was then reviewed by the study clinical principal investigators. Using all available information from ADI-R, ADOS, clinical vignette, IQ and language assessment and teacher reports and ICD-10 criteria, a decision was made on current presentation. This method resulted in a reported prevalence rate of 116 per 10,000. By contrast the reported prevalence rate was 143 per 10,000 using just a single diagnostic instrument such as the ADI-R: a considerable over-estimate using information derived from a single source.

These examples illustrate the significant dedicated resources needed to undertake the research procedures for assessment and diagnosis of ASD. Each study has included a combination of published standardised ASD assessments together with other measures to characterise individual functioning.

Over the last 20 years this type of combination of research instruments has been recommended for autism research although little systematic attempt has been made to evaluate how information from such instruments should be combined (Risi *et al.* 2006). In recent years more emphasis has been placed on the need to investigate the stability of ASD as well as autism (Lord *et al.* 2006; Tanguay, 2000).

Some studies have investigated the relationships both between diagnostic instruments and in combination with a BECD procedure. In 2006, Risi *et al.* proposed criteria for the combined use of ADI-R and ADOS to diagnose autism and the broader category of ASD and compared the resultant algorithms with BECD in four US and Canadian samples (Risi *et al.* 2006). Sensitivities and specificities of 75–80% and higher were obtained for autism, depending on the sample. Specificity was significantly lower using a single instrument and poor in individuals with profound intellectual disability. De Bildt *et al.* (2004) in a study of 184 children and adolescents with intellectual disability (aged 5–20 years) showed that both instruments measured autism and PDD reliably with ‘fair’ agreement between the instruments (63.5%). The authors had devised an ADI-R algorithm for PDD for this study. Agreement was higher for the younger children (aged 5–8 years) and most difficult for
the broader diagnosis of PDD/ASD, especially in the very low-functioning individuals. The authors concluded that diagnostic instrument algorithm cut-off scores should not be used as the sole criterion and noted the additional limitation that both instruments were resource-intensive. Lord et al. (2006) in a follow-up study of 172 children referred for evaluation of possible autism before 36 months of age showed that both the ADI-R and PL-ADOS (pre-linguistic ADOS) had similar rates of research diagnosis of ASD but were more inclusive than clinical judgement. In this study both these instruments had been modified for use in young children under the age of 3 years. Further in a simple additive logistic regression for best estimate autism diagnosis at age 9 years, all three diagnostic measures (ADI-R, PL-ADOS and clinical judgement) made an independent contribution to the accurate prediction of an ASD diagnosis.

Other studies from different research centres have reported fair to good concordance between the ADI-R and ADOS and made some specific recommendations for the use of the instruments in particular samples (Gray et al. 2008; Mazefsky and Oswald, 2006; Papanikolaou et al. 2009; Wiggins and Robins, 2008). The Special Needs and Autism Project (Baird et al. 2006) identified the limitations of using the ADI-R in isolation and the consequent impact on reported prevalence for autism if this instrument was the only source of information (Baird et al. 2006). Tomanik et al. (2007) recommended that including a measure of adaptive functioning improved classification.

Several studies using the ADI-R and ADOS in young pre-school children have noted that repetitive behaviours are reported and observed less frequently than in older age groups. These observations have implications for the validity of the existing ICD/DSM-TR diagnostic criteria for autism/ASD/PDD in this age group (Charman and Baird, 2002; Ventola et al. 2006; Wiggins and Robins, 2008). One recently published study (Le Couteur et al. 2008) has reported the utility of ADI-R and ADOS in a cohort of 101 pre-school children. In line with other studies it showed good (67%) concordance with ADI-R, ADOS and BECD for autism and less good agreement for ASD. The authors also noted that for those children where there were discrepancies between research instrument diagnoses and clinical judgement both for autism and ASD, the differences in scores were only marginal. Often the scores were just below the algorithm cut-off and yet the recorded data using the research measures were entirely consistent with the clinical evidence of difficulties across a range of settings and over time. These findings add weight to the previously reported observation that published algorithm cut-off scores should not be used in isolation. Further the authors noted that for those young children who did show evidence of repetitive behaviours during the ADOS play-based assessment, these behaviours appeared to be of diagnostic significance.
1.5 Conclusions and challenges for the early assessment and diagnosis of ASD

To progress our understanding of ASD it is essential that case definition is consistent and adequate across specialist clinical academic centres and research studies. Yet the reliable and valid diagnosis of autism/ASD has always presented a challenge both for research and clinical practice, not only in terms of the breadth of the spectrum of clinical presentation but also because of the inevitable developmental change in symptom profile for each affected individual over time. However, it is now generally agreed that the ASD spectrum extends beyond currently defined disorder(s) to a broader autism phenotype (as identified in the relatives of individuals with autism) and probably beyond even there, to qualitatively similar traits in the general population (Bailey et al. 1998; Bolton et al. 1994; Brugha, 2002; Melzer et al. 2002; Szatmari et al. 1998).

New measures have been developed such as the Social Responsiveness Scale (SRS), a parent completed postal questionnaire (Constantino et al. 2003), to investigate the relationship between the so-called social domain including social and communication traits and non-social domain namely rigidity, obsessive and repetitive behaviours, detail-focused behaviours and strong interests domains or characteristics of autism in different general population or at risk samples. This questionnaire has been used with a US population-based twin sample collected as part of an epidemiological study of ADHD, to assess the rates of autistic traits. The study has shown increased rates of autistic traits in children with ADHD (Reiersen et al. 2007). Some studies such as the Avon Longitudinal Study for Parents and Children (ALSPAC) have used existing brief ASD screening tools to record rates of autistic type behaviours; while others have devised study specific measures, for instance the 16-item parent and teacher postal/telephone questionnaire (Ronald et al. 2006), to investigate the genetic relationship between individual differences in the proposed social and non-social behaviours in the UK Twins Early Development Study (TEDS). Our own ASD research group in the north-east of England has focused on the repetitive behavioural domain, using the 20-item parent postal Repetitive Behaviour Questionnaire (RBQ-2) to investigate the rates of repetitive behaviours in a general population cohort of typically developing children (Leekam et al. 2007).

Further work is needed both to assess the validity and reliability of these various measures and to replicate the findings in independent samples. As yet we do not know whether these studies are indeed identifying components of autism in the general population. However, these findings raise important questions about the characterisation of the autism behavioural phenotype and whether or not the three domains of autistic symptomatology are more separate than the currently accepted diagnostic criteria imply. Diagnostic boundaries will inevitably be revised.
as our understanding of causal mechanisms for neurodevelopmental and other mental health disorders increases. In the meantime, diagnosis depends on the identification of specific behavioural characteristics in the affected individual and the skills of the professionals involved in the multidisciplinary assessment procedures.

There is an increasing awareness of autism/ASD amongst the general public, affected families and the professionals working to support them. The emphasis is for early identification, assessment and diagnosis of autism and the broader autism phenotype. Methodological constraints include the limitations of our current understanding of the underlying aetiology of these lifelong neurodevelopmental disorders and the more subtle and possibly less socially impairing manifestations of the broader autism phenotype. This awareness of the limitations of currently accepted diagnostic criteria emphasises the need for the systematic recording of clinically relevant information to contribute to the best estimate clinical diagnosis and the refinement of appropriate standardised diagnostic assessment instruments and measures to evaluate outcomes and change in presentation in the most severely affected individuals. Alongside this work with the most severely affected individuals, new epidemiological methods are needed to investigate the relevance of possible underlying component domains/factors identified in the general population that might advance knowledge of these lifelong neurodevelopmental characteristics.

1.6 References


Early assessment and diagnosis of children


Researching the Autism Spectrum


Researching the Autism Spectrum


PART II  GENETICS, NEUROLOGY AND BIOCHEMISTRY
2

Unravelling the genetics of autism spectrum disorders

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Since autism was first described in 1943, it has become evident that the condition is one of the most heritable of all the childhood onset neurodevelopmental disorders. In this chapter we chart the progress of researchers’ attempts to understand the genetic components of autism spectrum disorders and how these studies have tracked the advances in technology and knowledge in the field of genetics in general. We start by describing the evidence that autism spectrum disorders have such a strong genetic component. We then consider approaches to identify susceptibility genes such as linkage, candidate gene studies and association analysis. Various epigenetic mechanisms of potential relevance to autism as well as the expanding area of copy number variations are also highlighted. Some of the theoretical background to each of these approaches is given and findings from each approach are summarized and discussed. In addition, several specific examples are given for each method to demonstrate in detail the way in which they have been employed to yield key successes within the field of autism genetics. Finally, we look towards the future and suggest possible further avenues of investigation, as well as newly arising challenges, in this difficult, yet exciting field of study.

2.1 Evidence for genetic liability and the multifactorial model for autism

In 1943, Leo Kanner, an Austrian psychiatrist, was the first to describe a condition observed in a group of eleven children with developmental abnormalities, a disorder that today is known as autism (Kanner, 1943). Autism (OMIM 209850) is a severe complex neurodevelopmental disorder, characterised by impairments in (1) reciprocal social interaction and (2) communication, and (3)
restricted and stereotyped patterns of interests and behaviours (Lord et al. 2000). It is an extremely heterogeneous condition, predominantly affecting males (with a sex ratio of about 4:1), and the severity of symptoms and intellectual ability varies greatly in a continuum along these three main areas (Fombonne, 2005; Santangelo and Tsatsanis, 2005). Family and twin studies have demonstrated over the years that genetic factors are the major cause of idiopathic autism, broadening our understanding of the disorder, although the major causative variants/genes and their mode of transmission remain elusive even today.

Family studies are commonly used to assess familial clustering and thus the genetic component of a certain trait. The latter can be quantified by comparing the disease frequency in family members of one proband (the first person in the family to be brought to medical attention) in relation to the observed frequency in the general population. The prevalence of autism and other pervasive developmental disorders (PDDs) in siblings of autistic individuals was estimated to be approximately 2.2% and 3.6% respectively (Bailey et al. 1998; Maestrini et al. 1998; Szatmari et al. 1998). However, this prevalence could be an underestimate since some parents may decide not to have any more children after their first autistic child is born (the stoppage effect) (Szatmari et al. 1998; 1999). To overcome this constraint and avoid its effects, the siblings recurrence risk ($\lambda_s$, also called the Dahlberg’s later-sib method) can be calculated (Maestrini et al. 1998). The recurrence risk estimates the likelihood that each sibling born after an autistic child will develop autism and is far higher among siblings of individuals with autism (2–8%) than the general population prevalence (0.5% for autism spectrum disorders (ASD) (Rutter, 2005)); however, it is much lower than for monogenic diseases (Fombonne, 2005; Muhle et al. 2004; Rutter, 2005). Nevertheless, for complex diseases, such as autism, having an elevated $\lambda_s$ in a certain population does not necessarily mean that the identification of genetic factors is a straightforward task, since this value can be the result of several genetic factors of weak effect, rather than a single gene of major effect.

A marked reduction has been observed in autism prevalence in second and third degree family members compared to first degree relatives. The risk for autism in these family members decreases by nearly half as degrees of genetic relatedness become more distant, pointing to the involvement of multiple interacting genes in autism aetiology (Maestrini et al. 1998; Szatmari et al. 1998). Autistic related traits, such as obsessive-compulsive disorder, communication disorders and social phobias, are more frequently found in non-autistic parents and family members of the patients than in the general population (Bailey et al. 1996; 1998; Folstein and Rosen-Sheidley, 2001). These individuals show milder behaviour/personality characteristics from the traditional triad of autistic symptoms (social interaction, communication and/or stereotyped and repetitive behaviours), showing a broader
unravelling the genetics of autism spectrum disorders

phenotypic spectrum even when a common genetic background is present (Bailey et al. 1998).

The high degree of familial aggregation in autism can reflect common environmental factors, but especially suggests the involvement of genetic factors (Maestrini et al. 1998). One powerful tool to estimate the relative contribution of genetic and environmental factors is to compare the concordance rate of autism in monozygotic twins (MZ, that are genetically identical) with dizygotic twins (DZ, that share approximately half of the genome identical by descent), measuring the percentage of cases where both twins present with autism. Several studies in idiopathic cases of ASD have shown that the concordance rate for MZ twins is much higher than for DZ pairs (Bailey et al. 1995; Folstein and Rutter, 1977; Rutter, 2005; Steffenburg et al. 1989). The first study for autism carried out in the UK reported a 36% concordance in MZ twins compared to 0% in DZ twins, providing further evidence for a key role of genetic factors (Folstein et al. 1977). A following study conducted in the UK showed a concordance rate of 60% and 0% for MZ and DZ twins, respectively (Bailey et al. 1995). However, when concordance is examined for a broader phenotype that includes not only autism but also milder ASD impairments, 82–92% of MZ twins compared to 10% of DZ pairs are concordant (Bailey et al. 1995; Folstein and Rosen-Sheidley, 2001). This higher concordance rate indicates that genetic factors have a prominent role in increasing the susceptibility to autism and ASD when compared to environmental factors, since both MZ and DZ twins tend to share common environments (MacGregor et al. 2000). These studies also show, based on the different concordance rates, that the heritability estimates are especially high (approximately 90%), showing autism is one of the most heritable of all neuropsychiatric disorders (Bailey et al. 1995; Rutter, 2000). Heritability is strongly related with familial correlations and corresponds in the broad sense to the proportion of the total phenotypic variance that can be explained by genetic factors (Folstein and Rosen-Sheidley, 2001; Yashin and Iachine, 1995).

The transmission mode of autism seems to be non-Mendelian since the concordance between MZ twins is below 100% if full penetrance (which is the the conditional probability that an individual with a given genotype expresses a specific phenotype) is assumed, even accounting for twin pairs affected with other PDDs. Also, both the lower concordance rates of DZ compared to MZ twins and the recurrence risk estimates being lower than expected for single gene diseases are not consistent with an autosomal dominant or recessive mode of transmission. Therefore, autism is classified as a complex disorder, because it is a genetic condition whose mode of inheritance does not follow any of the simple Mendelian laws. Furthermore, studies report a higher recurrence risk for siblings of female probands than for siblings of male probands (Ritvo et al. 1989) and, as mentioned earlier, autism is more frequent in males than females (Fombonne, 2005). This
Researching the Autism Spectrum

suggests different genetic or epigenetic factors in male and female patients, with a higher penetrance or genetic susceptibility in males. One possible explanation would be the involvement of genes on the sex chromosomes, as males only have one copy of the X chromosome. The contribution of weak effect X-linked mutations and rare variants are possible. However, a mode of inheritance linked to the X chromosome has been ruled out by the analysis of extended pedigrees and evidence of male-to-male transmission in a number of family studies (Hallmayer et al. 1996a; 1996b). This gender bias could also be explained by epigenetic factors (which modify expression of the genome and gene function, without changing the DNA sequence; see Section 2.5) (Knickmeyer and Baron-Cohen, 2006).

Several alternatives have been suggested over the years as possible models for the genetic aetiology of autism. Among others, reduced penetrance, variable expression (different outcomes for the same genotype), locus and allele heterogeneity (variations in different genes, or different variations within the same gene, respectively producing the same characteristic) or the combined action of several genes have been suggested (Cook et al. 1997a; O’Roak and State, 2008). These genes could act epistatically (epistasis generally being defined as the interaction between different genes), and even maternal effects and gestation complications could interact with some of these genes affecting their expression (Cook et al. 1997a; Szatmari et al. 1998). In an analysis of twin (Bailey et al. 1995) and family data (Bolton et al. 1994), Pickles et al. (1995) suggested a multilocus model involving two to ten epistatic loci. Other results are explained by different models that include more than twenty different loci, each with a minor effect (Maestrini et al. 1998; Risch, 1990; Stoltenberg and Burmeister, 2000). Thus, depending on the set of variants/genes present and their variable expression, each individual could develop either the full autistic phenotype or just part of the spectrum of impairments. It is currently believed that multiple interacting genes of weak effect are likely involved, in which alterations in one gene may not be necessary or sufficient to cause disease (Maestrini et al. 1998; Szatmari et al. 1998). There is still little agreement regarding several questions about the aetiology of this disorder, such as the number of genes involved or whether we are looking for relevant common (common disease – common variant hypothesis) or rare (rare variant – common disease hypothesis) risk variants/genes. It is likely that both hypotheses will be relevant and that gene contributions may alter in different families. Genetic susceptibility may result from the combined action of several common genetic variants, or it may arise from rare mutations in single genes, such as the recently identified mutations in neuroligins (NLGN3 and NLGN4), neurexin 1 (NRXN1) and SHANK3 (Durand et al. 2007; Feng et al. 2006; Jamain et al. 2003).

It has also recently been suggested that we are addressing genetically different classes with distinct underlying aetiologies. The first hypothesis is that autism in singleton families is more likely to be due to de novo spontaneous mutations, and
multiplex families have a higher chance of containing common inherited genetic predisposing factors (O’Roak and State, 2008; Risch, 2001; Sebat et al. 2007). Zhao et al. (2007) propose another model for multiplex families, in which high risk families (where male offspring have an approximate risk of nearly 50% for developing autism) originate from offspring that carry and transmit a new causative mutation in a dominant way. In contrast, sporadic autism in low-risk families would mainly be caused by spontaneous mutations with high penetrance in males and relatively poor penetrance in females (Zhao et al. 2007). Both models account for the importance of common and rare factors contributing in different manners to disease susceptibility, confirming once more that autism is an extremely genetically heterogeneous disorder.

2.2 Linkage studies

Linkage was first observed in the early 1900s by Bateson and Punnet (Darden, 2005). It can be described as the tendency of genes or other DNA segments at a specific locus to be inherited together on the same chromosome, as a consequence of their physical proximity. The further apart two loci are, the higher the probability of recombination events (crossing-over, a process by which pre-existing genetic variation is reshuffled) occurring during meiosis. Therefore, the closer two loci are, the smaller the frequency of recombination will be, and the larger the probability of co-segregation compared to independent assortment. Thus, linked loci are inherited together as a ‘block’. Linkage studies are designed to test for co-segregation between a well characterised polymorphic genetic marker and an unknown locus influencing the disease susceptibility, using affected sibling pairs (ASPs) or extended families (Lewis, 2007; Maestrini et al. 2000; Strachan and Read, 1996).

Genetic linkage methods can be model-based (parametric) or model-free (non-parametric), the former of which requires knowledge of the mode of inheritance of the trait and relevant initial parameters (such as number of alleles at each locus, allele frequencies and genotype penetrances, among others). While the traditional model-based tests are very powerful tools for monogenic disorders, model-free tests, based on allele-sharing methods, are more useful for complex traits in which the mode of inheritance is not known (O’Roak and State, 2008). Model-free linkage methods aim at the identification of genomic regions that are shared more often by affected siblings or affected relative pairs, or less often in discordant family members, than expected by chance, that is, where alleles at different loci are inherited together. In contrast to parametric methods, this approach does not require such large numbers of extended families with multiple affected members across several generations; however, a greater number of affected relative pairs is required. Furthermore, for both methods identification of the locus of interest is not precise; it
could be a broad region in the order of megabases. Therefore, the identified area has to be subsequently refined by fine-mapping approaches for the identification of the gene(s) of interest (Elston and Thompson, 2000; Maestrini et al. 2000).

Genome-wide linkage screens were frequently the first choice adopted by most studies to locate unknown susceptibility genes in ASD. Typically, this approach would involve hundreds of evenly spaced polymorphic satellite markers screened across the genome in multiple families (Klauck, 2006). This information is used to calculate a logarithm (base 10) of the odds score (LOD score) for each marker and to estimate the multipoint maximum LOD score (MLS), constructing a profile across all chromosomes. The profile peaks correspond to regions of increased sharing between ASPs and subsequently can identify possible locations for susceptibility variants or genes (Maestrini et al. 2000).

The LOD score, introduced by Morton in 1955, is then a useful measure of linkage that represents the ratio between the likelihood of linkage for a certain recombination fraction and the expected likelihood of no linkage, in the families under study. Conventionally, a LOD score of 3.3 or greater can be interpreted as significant evidence for linkage, meaning that the observed data are 1000 times more likely to have occurred if the variants/genes are in physical proximity, than by chance (Lander and Kruglyak, 1995). In contrast, if it is less than −2 the hypothesis of linkage can be rejected. LOD scores between −2 and 3 are generally inconclusive (Strachan and Read, 1996). Linkage studies are powerful and specific for the discovery of genes of main effect on the phenotype, although genes of weak effect may not be detected. So, when studying complex diseases, where several genes are probably involved, a modest maximum LOD score is expected and should not be disregarded (Elston and Thompson, 2000; Lewis, 2007; Maestrini et al. 1998; Strachan and Read, 1996).

In the case of ASD the mode of inheritance is uncertain. Therefore parametric linkage studies are rarely reported in the literature, compared to non-parametric studies (O’Roak and State, 2008). Since the first published genome-wide linkage screen in 1998 (carried out by the IMGSAC [International Molecular Genetic Study of Autism Consortium]) several independent studies for autism and many follow-ups have been conducted. However, suggestive evidence for linkage has been found on almost all chromosomes, with little concordance between studies (Figure 2.1). This supports the hypothesis that autism aetiology contains extensive genetic heterogeneity, possibly with the involvement of a few genes of major effect and/or the interaction of multiple genes of weak effect. The interpretation of the results obtained can become more difficult due to lack of consistency of the data, which in turn can be the result of a combination of factors such as sample size, inclusion–exclusion criteria, the statistical approach taken and markers genotyped by each group (Bacchelli and Maestrini, 2006).
The most consistently replicated loci, with greatest evidence of linkage, are on chromosomes 2q, 7q and 17q (see Figure 2.1). These overlapping regions likely contain autism susceptibility variants or genes.

The Autism Susceptibility Locus 1 (AUTS1), identified by the IMGSAC on chromosome 7q with an MLS of 2.53 in 99 families from the UK (IMGSAC, 1998), was further established in two following studies conducted by the IMGSAC using additional families and markers (IMGSAC, 2001; Lamb et al. 2005). It has also shown more consistent positive results, with evidence of increased haplotype sharing seen in several studies (Alarcón et al. 2002; Arking et al. 2008; Ashley-Koch et al. 1999;
Auranen et al. 2002; Barrett et al. 1999; Molloy et al. 2005; Philippe et al. 1999; Risch et al. 1999; Shao et al. 2002a). However, the linkage significance and location of the peak varies between studies. Thus the peak of linkage in this area remains broad, spanning more than 40 Mb and containing over two hundred mapped genes.

Another region that shows frequent overlap is located on chromosome 2q (Buxbaum et al. 2001; IMGSAC, 2001; Lamb et al. 2005; Philippe et al. 1999; Shao et al. 2002a).

It is a similar story for the chromosome 17q region, where a linkage peak at 17q11–17q21 with an MLS of 2.04 was found in 345 AGRE (Autism Genetic Resource Exchange) consortium families (Yonan et al. 2003), and afterwards reported in other studies (Cantor et al. 2005; Lamb et al. 2005; McCauley et al. 2005; Stone et al. 2004).

Another approach taken in parallel to resolve discrepancies between studies is to conduct a statistical analysis that integrates the available results of several independent analyses, called a meta-analysis. To date, there have been two meta-analyses performed for autism. The first, a regional meta-analysis, combined the reported results from the first four autism genome scans (from the IMGSAC, Stanford group, PARIS [Paris Autism Research International Sibpair Study] group and CLSA [Collaborative Linkage Study of Autism]), the 7q locus being the most significant finding and replicating the individual evidence reported previously for the region (Badner and Gershon, 2002). The second meta-analysis used data from six independent genome-wide screens and confirmed evidence for linkage at 7q22–q32 (containing the AUTS1 locus). Moreover, suggestive linkage was also met for the regions 17p11.2–q12 and 10p12–q11.1 in weighted analyses (Trikalinos et al. 2006).

Decreasing sample heterogeneity, for instance by studying specific trait components or phenotypic subsets associated with disease that tend to be shared by family members, increases the probability of gene identification. These traits (endophenotypes) are then commonly used to refine specific linkage regions. However, with this type of analysis, statistical power is reduced because of the smaller sample size in each subgroup, so this must be taken into account when designing this sort of study (Bacchelli and Maestrini, 2006; Veenstra-VanderWeele and Cook, 2004). Genome screens that restricted the analysis to autistic families with phrase-speech delay (onset of phrase speech later than 3 years of age) or other language problems found increased evidence for linkage to 7q (Alarcon et al. 2002; Bradford et al. 2001), 2q (Buxbaum et al. 2001; Shao et al. 2002b), 3q and two regions on chromosome 17 (17p13–q21 and 17q23–q25) (Alarcon et al. 2005). Other reports employed repetitive and stereotyped behaviours as a covariate to partition their sample sets (Hauser et al. 2004). Thus families sharing high scores of ‘insistence on sameness’ were used and resulted in increased evidence for linkage to autism at 15q11–q13 (Shao et al. 2003) (a region of common cytogenetic abnormalities). Evidence for linkage to regions 7q and 21q was found for autism using a
subset of autistic families presenting a history of developmental regression (loss of pre-existing communication skills) (Molloy et al. 2005). Moreover, support for linkage on chromosome 1q (Buxbaum et al. 2004) was found using affected relative pairs with more severe obsessive-compulsive behaviours as a criterion for linkage analysis. This suggests that restricting the original sample may create more genetically homogeneous population sets and lead to the identification of genes that are closely related to these specific traits.

Sex-specific linkage analysis, separating the sample according to the sex of the affected individuals (male only versus female containing groups) was another criterion used to reduce genetic heterogeneity. Since autism is more frequent in males, some genetic susceptibility factors could possibly be different between males and females. A male-specific effect has been identified for the locus on 17q11, where linkage was greatly increased compared to the original signal identified in the whole AGRE cohort (Stone et al. 2004; Yonan et al. 2003). Likewise, in the IMGSAC sample, male ASPs largely contribute to the linkage evidence found on chromosomes 7q and 16p, whereas the linkage on 15q derived from the female-containing ASPs (Lamb et al. 2005). The latter study also looked at parent-of-origin effects and discovered what seem to be two different peaks at the 7q region, with paternal and maternal contributions, respectively. This could possibly implicate an imprinted gene(s) underlying the susceptibility in these locations (Lamb et al. 2005).

The 2007 linkage scan by the Autism Genome Project Consortium (AGP, www.autismgenome.org) found significant linkage to a novel region on chromosome 11p12 (LOD score of 3.57), using 1181 multiplex families and 10 000 markers (Szatmari et al. 2007). Despite the high power of this study, attained by collaboration between over fifty different research groups, there was an absence of a major locus for autism, confirming the heterogeneity within the disorder.

### 2.3 Association studies

An alternative method to identify ASD susceptibility genes is genetic association studies. These attempt to identify alleles of polymorphisms that are present in affected individuals more often than would be expected by chance based on the frequency of the polymorphism in the general population. Such polymorphisms are said to be associated with the disorder. Currently the most commonly used polymorphisms for such studies are single nucleotide polymorphisms (SNPs) that consist of a single base change in the DNA. One of the main advantages of association studies over linkage studies is that they allow finer mapping of disease genes (Hirschhorn and Daly, 2005).

Association studies are typically performed by genotyping SNPs in groups of affected (case) and typical (control) individuals, although other classes of polymorphism, such as insertion/deletions, may also be used. Such case–control
association study designs are able to detect more subtle effects than family-based
cohorts of similar size. However, if the controls used are not well matched to
the cases for variables such as sex, age, geographical location and ethnicity, the
study can suffer from population substructure (differences between the genotypes
of the case and control populations for reasons other than affection status). This
can then lead to an increased incidence of false-positive results. However, statisti-
cal methods are now available to address this possible source of error (Hirschhorn
and Daly, 2005; Ober and Hoffjan, 2006). Alternatively, family-based study designs
can be used, based on the frequency of transmission of alleles to affected children.
Under the null hypothesis (i.e. if the alleles under study are not associated with
disease), then they will have an equal probability of transmission (50%). Signifi-
cantly elevated transmission rates may suggest the allele in question is indexing a
susceptibility gene. One of the most widely used family-based tests is the transmis-
sion disequilibrium test (TDT), as implemented by Spielman (Spielman et al. 1993).
These types of association tests offer the advantage of immunity to population sub-
structure, controlling for environmental effects and allowing the identification of
parent-of-origin effects (Hirschhorn and Daly, 2005).

Typically, polymorphisms are chosen for association studies by one of four
methods. The first is by the identification of polymorphisms within the region
of interest, such as by the sequencing of the locus in several affected individuals.
This has the advantage of identifying polymorphisms that may be of direct rele-
vance to the disorder in the population being studied. However, sequencing can
be costly and time consuming. Alternatively, polymorphisms may be obtained by
interrogation of databases, such as the freely available dbSNP on the NCBI website
(http://www.ncbi.nlm.nih.gov/) (Hirschhorn and Daly, 2005). This is cheaper and
quicker, but care is required to choose verified polymorphisms. Third, the phe-
nomenon of linkage disequilibrium (LD) may be used. LD is when the alleles of two
or more polymorphisms occur together more frequently than expected by chance
due to their physical proximity in the genome (Hirschhorn and Daly, 2005). If the
level of LD between two polymorphisms is high, then by genotyping one polymor-
phism, the genotype of the other can be predicted with a high degree of certainty
(The International HapMap Project, 2003). Therefore, by knowing the pattern of LD
across the region it is possible to capture the variation by genotyping fewer poly-
morphisms (Hirschhorn and Daly, 2005; The International HapMap Project, 2003),
with consequent savings in time, cost, and quantity of DNA required per sam-
ple. The human HapMap project (http://www.hapmap.org/) (2003) has identified
such blocks of SNPs in regions of high LD, thus allowing researchers to tactically
choose SNPs for genotyping that capture all or most of the variation in their target
region. These so called ‘tagging’ approaches again reduce costs and time, but may
fail to capture the whole variation in the region if the LD is not strong enough
(The International HapMap Project, 2003). Finally, companies such as Illumina®
and Affymetrix® currently produce standard panels of SNPs for use with high throughput genotyping technologies. While providing good cost efficiency, such panels of SNPs are most appropriate for genome-wide investigations rather than targeted association studies of candidate genes.

If a polymorphism is associated with the disorder, it can be for one of three reasons. First, the result may be a false positive. Therefore, care must be taken in designing the experiment to ensure it is as statistically powerful as possible, and to correct results for the effect of seeking association with multiple polymorphisms or multiple subphenotypes (Hirschhorn and Daly, 2005; Risch and Merikangas, 1996). Second, the polymorphism may be associated because it is a direct cause of susceptibility to the disorder. However, the third possibility is that the polymorphism is not itself causing susceptibility, but rather is in LD with the true susceptibility variant. Therefore, it is important to know both the extent of LD within a region showing association, so as to localise the area in which to search for a true susceptibility allele, and to perform extensive functional experiments to verify that such an allele is truly responsible for increasing susceptibility to the disorder (Hirschhorn and Daly, 2005).

Association studies have typically been performed on candidate genes, due to technological and financial limitations on the number of polymorphisms which could be genotyped (Risch and Merikangas, 1996). However, with the rise of cost-effective high throughput genotyping methods, genome-wide association studies have become a reality (Seng and Seng, 2008). Such projects are currently being employed for ASD.

A large amount of effort has been spent carrying out association studies for candidate genes for ASD susceptibility. Such genes are chosen due to an implied role in ASD, either on account of their putative function or location in a region previously implicated in ASD susceptibility. A literature search between 1995 and late 2009 revealed that more than 200 genes have been investigated for association with ASD, with approximately 100 reported as showing a positive result (Table 2.1). However, there is a large amount of variability in terms of the power of the studies, strength of association and the amount of positive replication that has been observed. It is beyond the scope of this chapter to cover in detail each of these genes, but instead three of the ASD candidate genes most highly studied using association, RELN, SLC6A4 and GABRB3, will be described, together with a gene more recently identified as a strong candidate, CNTNAP2.

2.3.1 RELN

The first study to show association between RELN and autism was performed by Persico et al. (2001). RELN was chosen as a candidate due to three lines of evidence indicating its possible involvement in autism susceptibility.
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<th>Chromosome</th>
<th>Genes*</th>
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<td>1</td>
<td><strong>DISC1</strong> (disrupted in schizophrenia 1)</td>
<td>Kilpinen et al. 2008</td>
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<td></td>
<td><strong>GSTM1</strong> (glutathione S-transferase M1)</td>
<td>Buyske et al. 2006</td>
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<td></td>
<td><strong>MARK1</strong> (MAP/microtubule affinity-regulating kinase 1)</td>
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<td><strong>MTF1</strong> (metal-regulatory transcription factor 1)</td>
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<td><strong>PTGS2</strong> (prostaglandin-endoperoxide synthase 1)</td>
<td>Yoo et al. 2008</td>
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<td><strong>DLX1</strong> (distal-less homeobox 1)</td>
<td>Liu et al. 2009</td>
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<td><strong>DLX2</strong> (distal-less homeobox 2)</td>
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<td><strong>INPP1</strong> (inositol polyphosphate-1-phosphatase)</td>
<td>Serajee et al. 2003b</td>
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<td><strong>NPAS2</strong> (neuronal PAS domain protein 2)</td>
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<td><strong>NRP2</strong> (neuropilin 2)</td>
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<td><strong>NRXN1</strong> (neurexin 1)</td>
<td>Feng et al. 2006; Szatmari et al. 2007</td>
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<td><strong>SLC25A12</strong> (solute carrier family 25 (mitochondrial carrier, Aralar), member 12)</td>
<td>Segurado et al. 2005; Ramoz et al. 2008; Turunen et al. 2008</td>
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<td><strong>STK39</strong> (serine threonine kinase 39)</td>
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<td>3</td>
<td><strong>DRD3</strong> (dopamine receptor D3)</td>
<td>de Krom et al. 2009</td>
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<td><strong>HTR3C</strong> (5-hydroxytryptamine (serotonin receptor 3, family member C)</td>
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<td><strong>GPX1</strong> (glutathione peroxidise 1)</td>
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<td><strong>OXTR</strong> (oxytocin receptor)</td>
<td>Jacob et al. 2007; Lerer et al. 2008; Wu et al. 2005b; Yrigollen et al. 2008</td>
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<td>4</td>
<td><strong>EGF</strong> (epidermal growth factor (beta-urogastrone))</td>
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<td><strong>GABRA2</strong> (gamma-aminobutyric acid (GABA) A receptor, alpha 2)</td>
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<td><strong>GABRA4</strong> (gamma-aminobutyric acid (GABA) A receptor, alpha 4)</td>
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<td><strong>TDO2</strong> (tryptophan 2,3-dioxygenase)</td>
<td>Nabi et al. 2004</td>
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<td><strong>ADRB2</strong> (adrenergic, beta-2, receptor, surface)</td>
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<td><strong>APC</strong> (adenomatous polyposis coli)</td>
<td>Zhou et al. 2007</td>
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<td><strong>DHFR</strong> (dihydrofolate reductase)</td>
<td>Adams et al. 2007</td>
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<td>6</td>
<td>DRD1 (dopamine receptor D1)</td>
<td>Hettinger et al. 2008a</td>
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<td>PITX1 (paired-like homeodomain 1)</td>
<td>Philippi et al. 2007</td>
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<td>PRLR (prolactin receptor)</td>
<td>Yrigollen et al. 2008</td>
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<td>AHI1 (Abelson helper integration site 1)</td>
<td>Alvarez Retuerto et al. 2008</td>
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<td>C4B (complement component 4B (Childo blood group))</td>
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<td>GLO1 (glyoxalase I)</td>
<td>Junaid et al. 2004</td>
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<td>GRIK2 (glutamate receptor, ionotropic, kainate 2)</td>
<td>Jamain et al. 2002; Kim et al. 2007; Shuang et al. 2004</td>
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<td>HLA-A (major histocompatibility complex, class I, A)</td>
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<td>HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)</td>
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<td>MHC (major histocompatibility complex) genes</td>
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<td>6</td>
<td>PRL (prolactin)</td>
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<td>DOCK4 (dedicator of cytokinesis 4)</td>
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<td>EN2 (engrailed homeobox 2)</td>
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<td>FOXP2 (forkhead box P2)</td>
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<td>GRM8 (glutamate receptor, metabotropic 8)</td>
<td>Serajee et al. 2003a</td>
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<td>HTR5A (5-hydroxytryptamine (serotonin) receptor 5A)</td>
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<td>LAMB1 (laminin, beta 1)</td>
<td>Bonora et al. 2005; Hutcheson et al. 2004</td>
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<td>NRCAM (neuronal cell adhesion molecule)</td>
<td>Bonora et al. 2005; Marui et al. 2009b</td>
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<td>PIK3CG (phosphoinositide-3-kinase, catalytic, gamma polypeptide)</td>
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<td>PON1 (paraoxonase 1)</td>
<td>D’Amelio et al. 2005</td>
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<td>RELN (reelin)</td>
<td>Dutta et al. 2007; Persico et al. 2001; Skaar et al. 2005; Serajee et al. 2006; Zhang et al. 2002</td>
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<td>Campbell <em>et al.</em> 2008</td>
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<td>Nakamura <em>et al.</em> 2008</td>
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<td>11</td>
<td><em>UBE2H</em> (ubiquitin-conjugating enzyme E2H (UBC8 homologue, yeast))</td>
<td>Vourc’h <em>et al.</em> 2003</td>
</tr>
<tr>
<td>8</td>
<td><em>WNT2</em> (wingless-type MMTV integration site family member 2)</td>
<td>Marui <em>et al.</em> 2009a; Wassink <em>et al.</em> 2001</td>
</tr>
<tr>
<td>7</td>
<td><em>CNTNAP2</em> (contactin associated protein-like 2)</td>
<td>Alarcon <em>et al.</em> 2008; Arking <em>et al.</em> 2008</td>
</tr>
<tr>
<td>9</td>
<td><em>DBH</em> (dopamine beta-hydroxylase, plasma)</td>
<td>Robinson <em>et al.</em> 2001</td>
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<tr>
<td>10</td>
<td><em>PTEN</em> (phosphatase and tensin homologue (mutated in multiple advanced cancers 1))</td>
<td>Butler <em>et al.</em> 2005</td>
</tr>
<tr>
<td>11</td>
<td><em>BDNF</em> (brain-derived neurotrophic factor)</td>
<td>Cheng <em>et al.</em> 2009; Nishimura <em>et al.</em> 2007</td>
</tr>
<tr>
<td>12</td>
<td><em>HRAS</em> (v-Ha-ras Harvey rat sarcoma viral oncogene homologue)</td>
<td>Herault <em>et al.</em> 1995</td>
</tr>
<tr>
<td>13</td>
<td><em>HTR3A</em> (5-hydroxytryptamine (serotonin) receptor 3A)</td>
<td>Anderson <em>et al.</em> 2009</td>
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<td>14</td>
<td><em>ROBO3</em> (roundabout, axon guidance receptor, homologue 3)</td>
<td>Anitha <em>et al.</em> 2008</td>
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<td>15</td>
<td><em>ROBO4</em> (roundabout homologue 4, magic roundabout)</td>
<td>Anitha <em>et al.</em> 2008</td>
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<tr>
<td>12</td>
<td><em>AVPR1A</em> (arginine vasopressin receptor 1A)</td>
<td>Kim <em>et al.</em> 2002; Wassink <em>et al.</em> 2004; Yirmiya <em>et al.</em> 2006</td>
</tr>
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<td>13</td>
<td><em>DAO</em> (D-amino-acid oxidase)</td>
<td>Chung <em>et al.</em> 2007</td>
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<td>14</td>
<td><em>NOS1</em> (nitric oxide synthase 1 (neuronal))</td>
<td>Kim <em>et al.</em> 2009</td>
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<tr>
<td>15</td>
<td><em>TPH2</em> (tryptophan hydroxylase 2)</td>
<td>Coon <em>et al.</em> 2005</td>
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<tr>
<td>13</td>
<td><em>HTR2A</em> (5-hydroxytryptamine (serotonin) receptor 2A)</td>
<td>Cho <em>et al.</em> 2007</td>
</tr>
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<td>15</td>
<td><em>ATP10A</em> (ATPase, class V, type 10A)</td>
<td>Nurmi <em>et al.</em> 2003</td>
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<tr>
<td>15</td>
<td><em>ATP10C</em> (ATPase, class V, type 10C)</td>
<td>Kato <em>et al.</em> 2008</td>
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<td>12</td>
<td><em>GABRA5</em> (gamma-aminobutyric acid (GABA) A receptor, alpha 5)</td>
<td>Kim <em>et al.</em> 2008a; McCauley <em>et al.</em> 2004b</td>
</tr>
<tr>
<td>12</td>
<td><em>GABRB3</em> (gamma-aminobutyric acid (GABA) A receptor, beta 3)</td>
<td>Buxbaum <em>et al.</em> 2002; Cook <em>et al.</em> 1998; Curran <em>et al.</em> 2006; Kim <em>et al.</em> 2008a; McCauley <em>et al.</em> 2004b; Yoo <em>et al.</em> 2009b</td>
</tr>
<tr>
<td>13</td>
<td><em>GABRG3</em> (gamma-aminobutyric acid (GABA) A receptor, gamma 3)</td>
<td>Kim <em>et al.</em> 2008a; Menold <em>et al.</em> 2001</td>
</tr>
<tr>
<td>14</td>
<td><em>SNRPN</em> (small nuclear ribonucleoprotein polypeptide N)</td>
<td>Kato <em>et al.</em> 2008</td>
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</table>
Table 2.1 (cont.)

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Genes*</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>16</td>
<td>A2BP1 (ataxin 2-binding protein 1)</td>
<td>Martin et al. 2007</td>
</tr>
<tr>
<td></td>
<td>CACNA1H (calcium channel, voltage-dependent, T type, alpha 1H subunit)</td>
<td>Splawski et al. 2006</td>
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<td></td>
<td>GRIN2A (glutamate receptor, ionotropic, N-methyl D-aspartate 2A)</td>
<td>Barnby et al. 2005</td>
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<td></td>
<td>PRKCB1 (protein kinase C, beta 1)</td>
<td>Lintas et al. 2009; Philippi et al. 2005</td>
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<tr>
<td></td>
<td>TSC2 (tuberous sclerosis 2)</td>
<td>Serajee et al. 2003b</td>
</tr>
<tr>
<td>17</td>
<td>ACCN1 (amiloride-sensitive cation channel 1, neuronal (degenerin))</td>
<td>Stone et al. 2007</td>
</tr>
<tr>
<td></td>
<td>CACNA1G (calcium channel, voltage-dependent, T type, alpha 1G subunit)</td>
<td>Strom et al. 2009</td>
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<tr>
<td></td>
<td>DHRS7B (dehydrogenase/reductase (SDR family) member 7B)</td>
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<td></td>
<td>DKF204340047</td>
<td>Stone et al. 2007</td>
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<tr>
<td></td>
<td>ITGB3 (integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61))</td>
<td>Coutinho et al. 2007; Ma et al. 2009</td>
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<td></td>
<td>LASP1 (LIM and SH3 protein 1)</td>
<td>Stone et al. 2007</td>
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<td></td>
<td>LOC440421</td>
<td>Stone et al. 2007</td>
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<td>LOC440422</td>
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<td></td>
<td>LOC636202</td>
<td>Stone et al. 2007</td>
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<td>LOC645435</td>
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<td></td>
<td>LOC646157</td>
<td>Stone et al. 2007</td>
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<tr>
<td></td>
<td>MGC333894</td>
<td>Stone et al. 2007</td>
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<td></td>
<td>MYO1D (myosin ID)</td>
<td>Stone et al. 2007</td>
</tr>
<tr>
<td></td>
<td>NA (protein kinase, lysine-deficient 4)</td>
<td>Stone et al. 2007</td>
</tr>
<tr>
<td></td>
<td>NF1 (neurofibromatosis, Type 1)</td>
<td>Marui et al. 2004</td>
</tr>
<tr>
<td></td>
<td>NOS-II (nitric oxide synthase 2, inducible)</td>
<td>Kim et al. 2009</td>
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<tr>
<td></td>
<td>PER1 (period homologue 1 (Drosophila))</td>
<td>Nicholas et al. 2007</td>
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<td></td>
<td>PIPOX (pipecolic acid oxidase)</td>
<td>Stone et al. 2007</td>
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<tr>
<td></td>
<td>PSMD11 (proteasome (prosome, macropain) 26S subunit, non-ATPase, 11)</td>
<td>Stone et al. 2007</td>
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<tr>
<td></td>
<td>SLC6A4 (solute carrier family 6 (neurotransmitter transporter, serotonin), member 4)</td>
<td>Cho et al. 2007; Coutinho et al. 2004; 2007; Guhathakurta et al. 2006; 2008; Ma et al. 2010; Mulder et al. 2005</td>
</tr>
<tr>
<td></td>
<td>TMEM98 (transmembrane protein 98)</td>
<td>Stone et al. 2007</td>
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(cont.)
First, the Reelin protein is involved in neuronal migration, functionally implying a possible role in autism (Persico et al. 2001). Second, regions of brain alteration in autistic individuals overlap those of male reeler mutant mice, who lack expression of the \textit{reln} gene. Finally, \textit{RELN} is located either close to or within the region of chromosome 7 that has repeatedly shown linkage to autism. These three lines of evidence made \textit{RELN} an attractive candidate gene to investigate using association studies. In their study, Persico et al. identified polymorphisms within \textit{RELN}, including a triplet repeat (GGC) in the 5’ untranslated region (UTR) of the gene. The identified polymorphisms were genotyped in 95 autistic participants and 186 matched non-autistic individuals for a case-control analysis. The results indicated that the frequency of long alleles (≥11 repeats) of the triplet repeat in individuals with autism was more than double that of controls \((P < 0.001)\). To confirm the result, genotyping was performed in a further 172 complete and 12 incomplete trios in a family-based test. This confirmed the preferential transmission of long alleles to autistic individuals \((P < 0.05)\). It was concluded that the GGC repeat polymorphism probably directly conferred susceptibility to autism, although the authors were unable to rule out

\begin{table}[h]
\centering
\caption{Genes and References \textit{(cont.)}}
\begin{tabular}{lll}
\hline
Chromosome & Genes & References \\
\hline
19 & \textit{APOE2} (apolipoprotein E like-2) & Persico et al. 2004 \\
& \textit{FOSB} (FBJ murine osteosarcoma viral oncogene homologue B) & Yrigollen et al. 2008 \\
& \textit{PLAUR} (plasminogen activator, urokinase receptor) & Campbell et al. 2008 \\
20 & \textit{ADA} (adenosine deaminase) & Hettinger et al. 2008b \\
& \textit{OXT} (oxytocin, prepro – (neurophysin I)) & Yrigollen et al. 2008 \\
22 & \textit{ADORA2A} (adenosine A2a receptor) & Freitag et al. 2010 \\
& \textit{MIF} (macrophage migration inhibitory factor) & Grigorenko et al. 2008 \\
X & \textit{AR} (androgen receptor) & Henningsson et al. 2009 \\
& \textit{FMR1} (fragile X mental retardation 1) & Vincent et al. 1996 \\
& \textit{HTR2C} (5-hydroxytryptamine (serotonin) receptor 2C) & Orabona et al. 2009 \\
& \textit{MAOA} (monoamine oxidase A) & Yoo et al. 2009a \\
& \textit{MECP2} (methyl CpG binding protein 2 (Rett syndrome)) & Loat et al. 2008; Shibayama et al. 2004 \\
& \textit{NLGN3} (neuroligin 3) & Ylisaukko-oja et al. 2005 \\
& \textit{NLGN4} (neuroligin 4, X-linked) & Ylisaukko-oja et al. 2005 \\
\hline
\end{tabular}
\end{table}

* Names were checked using the HUGO Gene Nomenclature Committee Database (http://www.genenames.org/index.html).

** \textit{ATP10A} – previously called \textit{ATP10C}.**
the possibility that it was in LD with an alternative susceptibility polymorphism (Persico et al. 2001).

Since the original study, a further ten association studies for RELN with ASD have been performed (Ashley-Koch et al. 2007; Bonora et al. 2003; Devlin et al. 2004; Dutta et al. 2007; 2008; Krebs et al. 2002; Li et al. 2004; Serajee et al. 2006; Skaar et al. 2005; Zhang et al. 2002). The success of these studies in replicating the initial finding has been mixed. Five of the studies failed to find association (Bonora et al. 2003; Devlin et al. 2004; Dutta et al. 2008; Krebs et al. 2002; Li et al. 2004). However, the remaining five did find evidence for the role of RELN in ASD susceptibility (Ashley-Koch et al. 2007; Dutta et al. 2007; Skaar et al. 2005; Serajee et al. 2006; Zhang et al. 2002). Therefore, RELN remains an intriguing candidate gene for ASD.

2.3.2 SLC6A4

The serotonin transporter gene SLC6A4 (also known as 5-HTT), located on chromosome 17, was initially chosen as a candidate gene solely based upon its function. It was known that mean whole blood serotonin levels are increased in autistic cohorts compared to the general population and serotonin transporter inhibitors had been shown to effectively reduce routines that are part of autistic behaviour (Anderson et al. 1987; Cook et al. 1997b). Some studies show that higher levels of serotonin are more significant in multiplex families (Piven et al. 1991), while other studies show a unimodal increase. Therefore, SLC6A4 was considered a very good functional candidate gene for autism. The first association study performed between the gene and autism was by Cook et al. (1997b). Two polymorphisms, a VNTR (variable number tandem repeat) in the second intron and an insertion/deletion polymorphism in the promoter region, were genotyped in 86 trios. A significant preferential transmission of the promoter deletion variant to autistic children was observed ($P = 0.03$), although the VNTR was non-significant. When both polymorphisms were analysed as a two-marker haplotype, a significant result was again obtained ($P = 0.018$). It was concluded that the research showed preliminary evidence for a role of SLC6A4 in autism, but that further study was required to replicate the finding and to determine whether the polymorphisms genotyped were themselves causal or acting as markers in LD with causal variants.

Later that year, a second association study was published by Klauck et al. (1997). The polymorphisms genotyped were again the promoter insertion/deletion and intron 2 VNTR, in an initial group of 52 trios and an extended set of 65 trios. A significant over-transmission of the long allele of the promoter variant was observed in the extended population ($P = 0.032$), opposite to the previous result of Cook et al. (1997b). Haplotype analysis also gave a weakly significant result in the extended population ($P = 0.049$). Therefore, although a significant result was obtained, it
is difficult to view these findings as a replication of those of Cook et al., due to
the opposite alleles of the same polymorphism being found to be significantly
associated. Klauck et al. considered reasons such as small sample size, differences
in geographical and ethnic background and differences in ascertainment of the
patients as possibly explaining the discrepancy in results (Klauck et al. 1997).

Since these initial two studies, a further 21 have been performed on SLC6A4 for
autism or ASD, of which twelve have found evidence for association (Cho et al. 2007;
2008; Ma et al. 2010; McCauley et al. 2004a; Mulder et al. 2005; Sutcliffe et al. 2005;
Tordjman et al. 2001; Yirmiya et al. 2001) while nine have not (Betancur et al. 2002;
Guhathakurta et al. 2006; Koishi et al. 2006; Longo et al. 2009; Maestrini et al. 1999;
Persico et al. 2002; Ramoz et al. 2006; Zhong et al. 1999; Wu et al. 2005a). This makes
SLC6A4 the most studied ASD candidate gene to date.

2.3.3 GABRB3

The first study reporting association between autism and GABRB3 was per-
fomed by Cook et al. Due to the repeated identification of 15q11–13 duplications
in autistic individuals, they used markers in this region to create a LD map for
autism in 138 families. This resulted in the marker 155CA-2 in GABRB3 showing
significant association \((P = 0.0014)\), with no evidence of parent-of-origin effects
(Cook et al. 1998).

As with the previously discussed genes, subsequent attempts to replicate the
association between GABRB3 and ASD have been mixed. The first four studies that
attempted to confirm Cook et al.’s result failed to do so (Maestrini et al. 1999;
Martin et al. 2000; Nurmi et al. 2001; Salmon et al. 1999). Since then, six studies
have presented data offering support for an association between GABRB3 and ASD
(Buxbaum et al. 2002; Curran et al. 2006; Kim et al. 2006; Kim et al. 2008a; McCauley
et al. 2004b; Yoo et al. 2009b), but an additional three negative results have also been
published (Ashley-Koch et al. 2006; Ma et al. 2005; Tochigi et al. 2007). In addition to
differences between populations used and the estimated powers of the studies, it
has been suggested that a possible reason for the difficulty to replicate the positive
result is the difference in statistical methods used (Buxbaum et al. 2002).

Despite this, GABRB3 remains a good ASD candidate gene for several reasons.
First, it is located in the 15q11–13 region, maternal duplications of which can lead
to ASD (Shao et al. 2003). Second, there is evidence that the GABA neurotransmitter
system is involved in ASD. This includes findings of reduced GABA\(_A\) ligand binding
in the brains of individuals with autism, together with reduced GABA\(_A\) receptors
and increased levels of circulating GABA and its precursor molecule in these
individuals (McCauley et al. 2004b). GABA\(_A\) receptor agonists have also been useful
for treating seizures and anxiety disorders found in a significant proportion of
individuals with autism (McCauley et al. 2004b). Finally, linkage to autism has also been shown in this region (Shao et al. 2003).

2.3.4 CNTNAP2

A recent gene to be implicated in ASD susceptibility is CNTNAP2, a neuronal cell adhesion molecule known to interact with Contactin 2 (Bakkaloglu et al. 2008), and a member of the neurexin gene family (Alarcón et al. 2008). Two studies (Alarcón et al. 2008; Arking et al. 2008) were published concurrently, both utilising, at least in part, association study designs to identify CNTNAP2 as an ASD susceptibility gene.

Alarcón et al. (2008) performed a two-stage association study in a 15 Mb region of 7q35, including a 10 Mb region thought to be a language related autism quantitative trait locus (QTL), and approximately 200 known genes. In the first stage of the study 172 trios were genotyped for 2758 SNPs across the region and association to age at first word sought. This identified four genes worthy of further study, KIAA1549, PRKAG2, FLJ42291 and CNTNAP2. In stage two, six tagging and two non-tagging SNPs across the four genes were genotyped in 304 independent trios, again seeking association to age at first word. The only significant result observed was with a tagging SNP in CNTNAP2, rs2710102, the association being driven by trios containing male probands. The authors concluded that CNTNAP2 was a good candidate for autism susceptibility and that common variants were important in language acquisition in autistic individuals. The authors further supported the role of CNTNAP2 functionally by demonstrating that its transcripts are restricted to regions of the brain thought to be important for verbal communication and language development (Alarcón et al. 2008).

Concurrently, Arking et al. (2008) published a two-stage study, also implicating CNTNAP2 in autism. The first stage of the study consisted of a joint genome-wide linkage and association screen genotyping 500 000 SNPs in 72 autism multiplex families. The affected individuals were required to be positive for autism using both the ADI-R and ADOS instruments, an inclusion criterion stricter than any previously reported study on the genetics of autism. This was designed to reduce phenotypic heterogeneity within the cohort. No genome-wide significant result was identified by the association analysis, but two regions of linkage were found, on 7q35 and 10p13–14. The SNP under the 7q35 linkage peak, rs7794745, showed association to autism, including after the result was corrected for the number of SNPs contained within the linkage peak, and lay within CNTNAP2. This SNP was then genotyped in a further 1295 more broadly defined autism trios, yielding a significant association, with parent-of-origin and gender effects. An additional ten SNPs flanking rs7794745 and tagging the LD block in which it lies were genotyped.
in all trios from stage one and two, but no increase in significance was obtained (Arking et al. 2008).

An issue raised by Arking et al. concerning the two studies was the occurrence of overlap of the samples used (70 of the 72 trios from stage one and one third of trios from stage two had been used by Alarcón et al.). Arking et al. do not think that this invalidates the results of either study due to the use of alternative phenotypes, different polymorphisms being implicated and the SNPs being located > 1 Mb apart with no evidence of LD between them. In addition, rs7794745 remained significant in the study by Arking et al. even with the removal of overlapping samples in stage two (Arking et al. 2008).

CNTNAP2 is a good candidate gene for autism and ASD due to the region of the genome in which it resides showing linkage to autism and also because of functional work which has been performed. CNTNAP2 is a neurexin, members of which have been implicated in autism (Feng et al. 2006; Kim et al. 2008b; Szatmari et al. 2007), and are known to interact with genes shown to be mutated in some instances of ASD. Mutations in CNTNAP2 have been identified in an Amish family with seizures, language regression and PDD (Alarcón et al. 2008). The gene also segregates with a seizure disorder that is itself associated with autism and language delay (Alarcón et al. 2008). Finally, CNTNAP2 has been shown to be expressed in regions of the brain believed to be relevant in autism (Bakkaloglu et al. 2008).

2.3.5 Genome-wide association studies

As molecular genetic genotyping technologies have advanced, they have increased throughput while simultaneously decreasing the cost per genotype and the quantity of DNA per sample needed for experiments. This has made genome-wide association studies for complex diseases a possibility, enabling the identification of common polymorphisms with small to moderate effects on disease susceptibility, such as for asthma (Moffatt et al. 2007). The resolution of genome-wide association studies is sufficient to enable fine-mapping of single genes, in contrast to linkage studies which are rarely capable of doing so.

To date, five genome-wide association studies examining ASD have been published. The first can be considered a bridge between earlier genome-wide linkage studies and the later SNP-based genome-wide association studies described below. It examined association across the genome in a case–control study using individuals from the Faroe islands genotyped for a total of 601 microsatellite markers. Evidence of association at six loci (2q, 3p, 6q, 15q, 16p, 18q) was found, with the strongest result being on 3p25.3. Therefore, the results provided support for loci identified by earlier linkage studies. However, the study suffered from limited sample size (12 cases, three with an uncertain diagnosis of ASD, and 44 controls) and marker density (Lauritsen et al. 2006).
Unravelling the genetics of autism spectrum disorders

Arking et al. genotyped approximately 500,000 SNPs, but in a small number of families, 72 in total (Arking et al. 2008). Despite the affected children having a strict diagnosis of autism, this was a very low number of families for such a study. Therefore, it was not surprising that no significant association results were identified, although other findings of interest were observed with the data using different analyses (Section 2.3.4).

Since then, studies involving larger numbers of individuals have been reported. Wang et al. (2009) identified a region of association on chromosome 5p14.1. Initially, 780 families were genotyped for 550,000 SNPs and a family-based association analysis performed. However, no significant results were obtained after taking into account the number of tests performed. Subsequently, a further 1453 cases and 7070 controls were genotyped for the same SNPs and a case–control analysis performed, but still no genome-wide significant results were identified. However, when the two data sets were combined a single SNP on chromosome 5p14.1 reached genome-wide significance, with another five SNPs at the locus reaching nominal significance. Two further cohorts were examined for association in order to replicate this result. The first consisted of 447 families genotyped for 1 million SNPs, while the second was 108 cases and 540 controls genotyped for 300,000 SNPs. Taking nominal significance as replication, the authors took the findings from their combined analysis to be confirmed. The associated region on 5p14.1 lies between two genes, \textit{CDH9} and \textit{CDH10}, in a region containing conserved elements, hinting at a possible regulatory role for the region. In addition to this major finding, several other interesting results were obtained, including multiple cell adhesion genes, already of interest in ASD genetics, being implicated (Wang et al. 2009). Concurrently, a genome-wide association paper was published by Ma et al. They also reported the presence of a risk locus on 5p14.1, but due to the considerable overlap of data with the study of Wang et al., this cannot be considered an independent replication of this risk locus (Ma et al. 2009).

The most recent genome-wide association study for ASD was published by Weiss et al. (2009). The initial analysis was comprised of a TDT analysis of association on 1031 families genotyped for \(\sim\)500,000 SNPs, but no genome-wide significant results were found. However, an excess of nominally significant results compared to that expected by chance was observed, indicating a lack of power to identify the associated variants. A case–control analysis using 90 additional cases and 1476 controls was performed for all the SNPs of interest from the original analysis and these data combined with that of the TDT. This resulted in the identification of seven regions of interest, one SNP at each of 4q13 between \textit{CENPC1} and \textit{EPHA5}, 5p15 between \textit{SEMA5A} and \textit{TAS2R1}, 6p23 in \textit{JARID2}, 9p24 between \textit{PTPRD} and \textit{JMJD2C}, 9q21 between \textit{ZCCHC6} and \textit{GAS1}, and 10q21 in \textit{CTNNA3}, and 2 SNPs on 11p14 in \textit{GAS2}. By including data from the Autism Genome Consortium (AGC, 318 trios),
Researching the Autism Spectrum

Autism Genome Project (AGP), Finland and Iran (1755 trios in total), they found an increased signal at the chromosome 5 locus. The associated region is \( \sim 80 \text{ kb} \) upstream of SEMA5A, a strong candidate for ASD as it is involved in axon guidance, is downregulated in autistic lymphoblastoid cell lines, has lower expression in the brains of individuals with autism than in controls and is in a pathway involving MET, a gene shown to have association with ASD in multiple studies (Campbell et al. 2006; Sousa et al. 2009; Weiss et al. 2009).

These studies demonstrate both the difficulties encountered in trying to identify common variants of moderate effect in ASD, the need for data from large cohorts, the importance of replication in independent samples and the benefit of pursuing results that do not necessarily meet strict criteria for genome-wide significance. They are also examples of co-operation between researchers in the field of ASD genetics, as the latter three studies used data generated by multiple consortia.

2.4 Rare single gene mutations in autism

In addition to common variants being associated with autism and ASD, there is a body of evidence indicating that in some cases the disorder can be due to rare mutations of large effect in single genes. These include the genes Neurexin 1 (NRXN1), SH3 and Multiple Repeat Domains 3 (SHANK3, also known as ProSAP2), Neuroligin 3 (NLGN3) and Neuroligin 4 (NLGN4).

Jamain et al. (2003) were the first to identify single mutations in neuroligin genes likely to be causal in individuals with ASD. They noted that two regions of the X chromosome likely to be associated with autism, Xp22.3 and Xq13, contained the neuroligin genes NLGN4 and NLGN3, respectively. They therefore decided to screen NLGN3, NLGN4X and NLGN4Y for mutations in 36 sibling pairs and 122 trios with autism or Asperger syndrome. In one Swedish family a mutation in NLGN4 resulting in a premature stop codon (a mutation that leads to a truncated protein) was observed in two brothers, one with autism and the second with Asperger syndrome. The mutation was shown to have occurred \textit{de novo} in the mother and was not present in an unaffected brother or 350 control individuals. In a second family, a C/T transition in NLGN3 was identified in two brothers, again one autistic and one with Asperger syndrome. This mutation was inherited from the mother, but was absent in 200 controls and predicted to affect a highly conserved amino acid which could result in altered binding to neurexins. Therefore, it was concluded that in these two families the alterations in the neuroligin genes were leading to the development of ASD (Jamain et al. 2003).

In a large French pedigree Laumonnier et al. identified a 2 bp deletion in exon 5 of NLGN4, resulting in a premature stop codon. This mutation was present in all male members of the pedigree affected by autism, intellectual disability or PDD, but absent in the healthy males of the family and 200 healthy male controls.
The authors stated that the deletion was therefore likely to be a rare causative mutation for cognitive disorders (Laumonnier et al. 2004). Other possible evidence for the role of missense mutations in NLGN4 (Yan et al. 2005) and alternative splice isoforms of NLGN3 and NLGN4 (Talebizadeh et al. 2006) as causative in individual cases of autism has been gathered. In addition, copy number variants (CNVs) (Section 2.6.1) affecting NLGN3 have been found in individuals with ASD (Glessner et al. 2009; Marshall et al. 2008). However, several studies have been unable to identify mutations within the neuroligin genes likely to play a causal role in autism development (Blasi et al. 2006; Gauthier et al. 2005; Talebizadeh et al. 2006; Vincent et al. 2004; Werther et al. 2008; Ylisaukko-oja et al. 2005), or association between these genes and autism or ASD (Werther et al. 2008; Ylisaukko-oja et al. 2005), reinforcing the view that these genes only rarely play a role in ASD development, estimated as 0.4% of cases (Ylisaukko-oja et al. 2005).

The neuroligin genes encode post-synaptic membrane cell-adhesion molecules which bind β-neurexins, which are themselves encoded by three neurexin genes NRXN1, NRXN2 and NRXN3. Each neurexin gene also encodes a longer α variant (Feng et al. 2006). Due to the interaction between NRXN1 and the neuroligins (Figure 2.2A), Feng et al. scanned the exons and splice junctions of the three neurexin genes for mutations in 72 Caucasian autistic individuals. No structural variants were identified in NRXN2 or NRXN3. However, two putative missense mutations in exon 1 of NRXN1 were observed which were not present in 535 non-autistic Caucasian controls ($P = 0.0056$). Further sequencing in both the Caucasian and an additional 194 African-American controls identified no further changes in exon 1. Feng et al. suggested that the variants may affect signalling function, thereby resulting in autism susceptibility, but that there might be incomplete penetrance based on family data (Feng et al. 2006). In a paper published by the AGP, a CNV which removed the paternal coding exons of NRXN1 was identified in two autistic children from one family. The CNV was not present in the parents, was likely inherited due to paternal gonadal mosaicism and might be a causative variant (Szatmari et al. 2007). In addition, Glessner et al. (2009) found deletions in 10 of 2195 ASD cases, but in none of 2519 controls, a statistically significant result of $P = 4.7 \times 10^{-4}$ ($P = 0.002$ after correcting for multiple testing). This striking result was also observed by Bucan et al. while analysing the same data, although they also noted the lack of perfect segregation of the CNVs with affected status. This indicates the lack of total penetrance of the deletions of this gene and the importance of other factors in ASD susceptibility (Bucan et al. 2009). Marshall et al. have also published a report implicating CNVs involving NRXN1 in ASD (Marshall et al. 2008). Recently, Kim et al. have identified two independent individuals with ASD and chromosomal aberration breakpoints at 2p16.3. In the first proband there is an 8.9 Mb non-reciprocal translocation involving chromosomes 2 and 16, with one breakpoint occurring in intron 5 of NRXN1. This mutation affects the transcription
Figure 2.2 Data from Search Tool for the Retrieval of Interacting Genes/Proteins (http://string.embl.de/). Spheres represent specific genes/proteins. Lines represent evidence for associations from experimental data (pink), text mining (green) or homology studies (blue). (A) Network of proteins that interact with NRXN1. (B) Network of proteins interacting with SHANK3 (von Mering et al. 2007). See plate section for colour version.
of $\alpha$-NRXN1, while $\beta$-NRXN1 is unaffected. The father also carries the polymorphism, but is unaffected, so that if the mutation is causal it is not fully penetrant. In the second proband a \textit{de novo} balanced translocation was identified with a breakpoint approximately 750 kb 5’ of exon 1 of $\alpha$-NRXN1 in a region containing no other known genes, but predicted to have strong regulatory potential. The translocation therefore has the potential to affect NRXN1 expression. Due to the identification of two independent subjects with the same phenotype and chromosomal aberrations potentially affecting the same gene, Kim \textit{et al.} concluded that NRXN1 is a causal gene in autism susceptibility in some individuals (Kim \textit{et al.} 2008b).

Finally, rare mutations in a third gene involved in the function of the synapse have been implicated in ASD susceptibility. One of the common chromosomal alterations found in autism involves 22q. Microdeletion of chromosome 22q12.3 leads to cognitive deficits with the minimal deleted region containing three genes, ACR, RABL2B and SHANK3. The latter is the strongest candidate to be involved in autism due to its encoding a scaffolding protein found in the synapse which can also bind to the neuroligin proteins (Figure 2.2B) (Durand \textit{et al.} 2007). Therefore, Durand \textit{et al.} used a combination of FISH (fluorescent \textit{in situ} hybridisation) and direct sequencing to search for alterations of SHANK3 in families containing children with ASD. This led to three SHANK3 alterations being observed. One family contained an autistic proband with absent language and moderate intellectual disability who had a \textit{de novo} 22q13 deletion containing SHANK3. A second family contained two autistic brothers, both of whom were heterozygous for a single base pair insertion in exon 21 of SHANK3 inherited on the mother’s haplotype. The insertion caused a frameshift leading to a truncated version of the protein. Both brothers had severely impaired speech and intellectual disability. No unaffected members of the family carried the mutation, including the mother, indicating that it was inherited due to maternal gonadal mosaicism. The third family contained a girl with autism and severe language delay who had a 22q deletion. Her brother suffered from Asperger syndrome, although with precocious language and fluent speech, and had a 22qter trisomy. Both aberrations were paternally inherited and affected SHANK3. Durand \textit{et al.} concluded that these three families demonstrated the importance of alterations in SHANK3 causing susceptibility to ASD (Durand \textit{et al.} 2007). A second study by Moessner \textit{et al.} (2007) looked at the frequency of CNVs in SHANK3 in 400 ASD subjects. They found a single \textit{de novo} non-synonymous mutation and two chromosomal deletions within their cohort. The non-synonymous mutation occurred in exon 8 of SHANK3 and was not observed in either the parents and unaffected siblings of the proband, or in controls. Of the chromosomal deletions, one resulted in the loss of approximately 277 kb of DNA, including SHANK3. The deletion was present in the proband, but not in the unaffected siblings or parents. The second deletion was of 3.2 Mb of 22q13.31–33
in a proband with autism from a second family (Moessner et al. 2007). In addition Moessner et al. characterised a deletion including \textit{SHANK3} in a family previously characterised by Szatmari et al. (2007). Within the family, a 4.4 Mb deletion of the maternal chromosome was present in an affected brother and sister, but not in either parent, indicating that it had been inherited due to gonadal mosaicism (Moessner et al. 2007). Moessner et al. failed to identify any CNVs in controls, indicating that those observed were autism specific. By combining the frequency of causal \textit{SHANK3} alterations observed by both themselves and Durand et al., Moessner et al. concluded that mutations in the gene accounted for approximately 1\% of autism cases (Moessner et al. 2007). A further study identified a missense and splice site mutation in \textit{SHANK3} not present in controls. However, seven other missense mutations were also identified which either occurred in cases and controls, or controls alone (Gauthier et al. 2009). Additional CNV studies have also been mixed, with one implicating CNVs in ASD (Marshall et al. 2008), whereas work by Sykes et al. failed to identify any in their cohort (Sykes et al. 2009). Therefore, as with other genes discussed, it appears that mutations involving \textit{SHANK3} may not be fully penetrant or sufficient to cause ASD in isolation.

In conclusion, it seems that in some rare cases, ASD is due to single gene changes of major effect. Also of interest is that the genes in the work presented are all involved in the function of the synapse, suggesting that this pathway is of importance in the development of ASD.

\section*{2.5 Epigenetics}

Epigenetics are heritable changes in gene expression that are not due to alterations in the sequence of the genome. Epigenetic changes have been implicated in a variety of complex diseases, including ASD. They can be caused by methylation of CpG dinucleotides, post-translational modification of histone proteins or by non-coding RNA (ncRNA) based gene silencing. These multiple types of epigenetics can interact and stabilise each other (van Vliet et al. 2007).

\subsection*{2.5.1 DNA methylation}

In mammalian genomes, approximately 80\% of CpG dinucleotides are methylated (van Vliet et al. 2007). Such alterations of the genome are associated with increased chromatin stability and gene silencing (van Vliet et al. 2007). Methylation may result in gene silencing by recruiting proteins such as MeCP2 to the region, which in turn interact with co-repressors and histone deacetylases resulting in repression of transcription (Persico and Bourgeron, 2006; Samaco et al. 2004; Schanen, 2006; van Vliet et al. 2007). MeCP2 has been implicated in ASD susceptibility. Decreased expression of its protein has been observed in the brains of autistic
individuals (Samaco et al. 2004). MeCP2 is also mutated in Rett syndrome, an ASD (Persico and Bourgeron, 2006; Schanen, 2006; van Vliet et al. 2007), and variants have been implicated as a rare cause of idiopathic autism (Lam et al. 2000). The resulting decrease in activity of MeCP2 causes derepression of specific promoters, including some for genes involved in brain development and plasticity, such as BDNF, DLX5, UBE3A and GABRB3 (Persico and Bourgeron, 2006), the latter of which has itself been well studied as an ASD candidate gene (Section 2.3.3). In addition, MeCP2 null mice lack normal expression patterns for imprinted genes, including UBE3A (Samaco et al. 2005).

Regions of the human genome that have shown linkage to autism overlap with, or are close to, areas that are also imprinted, i.e. regions where either the maternal or paternal allele is silenced by epigenetic mechanisms. These include chromosome 15q and two areas of chromosome 7q (Persico and Bourgeron, 2006; Schanen, 2006). The linkage region of chromosome 15 includes the gene UBE3A, which, in addition to its relationship with MeCP2, has itself been shown to have abnormal methylation in post-mortem brain tissue from individuals with autism (Jiang et al. 2004; van Vliet et al. 2007). Also, UBE3A shows decreased expression in autism, Asperger syndrome and Rett syndrome (Jiang et al. 2004; Samaco et al. 2005). Therefore, UBE3A misexpression may be of importance in ASD.

Other lines of evidence also indicate that epigenetic modification of the chromosome 7q and 15q loci may also be of importance in ASD. Maternally derived duplications of chromosome 15q11–13 are associated with increased ASD risk and regulation of the region is controlled by methylation and non-coding RNAs (nc-RNAs) (Schanen, 2006). Approximately 5% of cases of ASD have these duplications, which include the gene UBE3A (van Vliet et al. 2007). The region also contains paternally expressed genes which may be good candidates for autism, including NDN and MAGEL2. NDN is involved in controlling the expression of DLX5, a maternally expressed gene on chromosome 7 which is itself a possible autism susceptibility gene (Schanen, 2006). Specifically on chromosome 7, Lamb et al. have shown an excess of paternal allele sharing in individuals with autism near an imprinted gene cluster (Lamb et al. 2005; Schanen, 2006). This cluster includes the paternally expressed genes SGCE and PEG10, both of which are targets of MeCP2.

2.5.2 Histone modification

DNA is packaged by winding around nucleosomes, which consist of histone proteins. These histone proteins have a globular region and a tail, the latter of which can be modified in a variety of ways, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation and glycosylation. The combination of modifications of the histone tail forms a code which is recognised by proteins that modify the chromatin structure, such as HP1, and so
Figure 2.3 CNVs often arise by unequal crossing over during meiosis. Schematic diagram showing 3 genes in green, flanked by segmental duplications in orange. (A) Equal crossing over leads to gametes with a single copy of the three genes. (B) Unequal crossing over results in gametes with 0 or 2 copies of these genes. See plate section for colour version.
modify gene expression (van Vliet et al. 2007). Evidence has been presented showing that increased prenatal exposure to HDAC (a histone deacetylase) can increase susceptibility to autism, indicating a possible role for this type of epigenetic change in autism (van Vliet et al. 2007).

2.6 Copy number variation (CNV) associated with ASD

2.6.1 What are CNVs?

With the exception of genes localised on the sex chromosomes and multicopy genes such as the ribosomal RNAs, the vast majority of human genes are represented twice; once on each chromosome of a homologous pair. However, due to sporadic deletion or duplication events, two copies can become zero, one, three, four, or greater. These genetic regions are collectively termed CNVs. The size of the genetic fragment that is deleted or amplified typically ranges from a few thousand to many million base pairs.

CNVs can be inherited in a Mendelian fashion, arise during gametogenesis or as somatic mutations. The genetic regions that flank CNVs often contain segmental repeats, suggesting that the principal underlying mechanism is unequal crossing-over during meiosis (also known as non-allelic homologous recombination, Figure 2.3). The duplication architecture of the human genome can even be used to predict CNV hotspots and this method has been successfully employed to identify novel CNVs associated with intellectual disability (Sharp et al. 2006).

For many recessive genes, a single functional copy is enough to protect against a particular trait or disease. However, other genes can affect phenotype in a dosage-dependent manner. Therefore, the effect of any particular CNV depends on which dosage-sensitive genes are contained therein. Large CNVs are likely to contain more dosage-sensitive genes than smaller ones and thus tend to have a greater effect on phenotype. For example, trisomy 21 (Down’s syndrome) can be thought of as a CNV comprising the whole of chromosome 21 and causes a severe, multifaceted disorder. In contrast, a 64 kb segmental duplication CNV encompassing CCL3L1 and CCL4L1 has a smaller direct phenotypic effect relating solely to immune function (Burns et al. 2005; Mamtani et al. 2007; McKinney et al. 2008), such as influencing susceptibility to AIDS (Gonzalez et al. 2005).

2.6.2 Methods used to detect CNVs

Due to the role of chromosomal rearrangements in oncogenesis, plus the increasingly acknowledged impact of CNVs on human disease and normal phenotypic diversity, there has been a proliferation of methods developed for studying genomic imbalances.
The resolution of standard karyotyping is approximately 5 Mb (reviewed along with recent developments by de Ravel et al. (2007)), so this approach will pick up only the largest of CNVs. However, it does have an advantage over array-based approaches of being able to identify balanced translocations.

Another traditional approach used to detect CNVs is comparative genomic hybridisation (CGH). This involves differential labelling of test and reference DNA samples, for example with cyanine dyes Cy3/Cy5 or with FITC/Texas Red, and hybridising this DNA onto a normal human metaphase spread. Alternatively, for increased resolution, in array-based CGH (aCGH), the fluorescently labelled DNA is hybridised onto a microarray containing thousands of single-stranded DNA probes. Differences in the fluorescence ratio found between test and reference samples indicate regions of the genomes differing in copy number and can be confirmed by simple dye-swap experiments.

Commercial SNP arrays are now available which can target over a million polymorphic and potentially polymorphic sites in the human genome. As well as determining SNP genotypes for use in whole genome association studies (Section 2.3.5), regions of uniparental disomy and homozygosity-by-descent can be detected. In addition, by combining the B-allele frequency and log R ratio (Figure 2.4), data can be used to identify CNVs (Collela et al. 2007; Peiffer et al. 2006; Szatmari et al. 2007).

Representational oligonucleotide microarray analysis (ROMA) is another commonly used method for detecting copy number aberrations. This method is a form of CGH involving restriction digestion of sample and reference DNA. Adapters are then ligated to the resulting sticky-ended fragments. PCR is then used to amplify a selection of these fragments using primers complementary to the adapter sequence. Because only fragments of a certain size will amplify efficiently, this reduces the complexity of the resulting DNA and subsequently aids hybridisation to the custom microarray. PCR fragments from the two genomes are labelled with different fluorophores and, as with aCGH, differences in the fluorescence ratio at a specific feature on the microarray indicate copy number changes relative to the reference sample. Copy number changes can be verified using a different genomic representation, by using an alternative restriction enzyme for the procedure.

For verification of novel CNVs, or for large-scale screening of a particular gene for CNVs, other methods such as multiplex ligation-dependent probe amplification (MLPA) have been developed (Slater et al. 2003). In MLPA, a pair of oligonucleotide probes are designed that can bind immediately adjacent to each other on the same genomic template strand. Pairs of oligonucleotides can be multiplexed for analysis of 40 or more target sites (for example each exon in a large gene). Once annealed, the ends of these two oligonucleotides are close enough to be ligated. The amount of ligation is dependent on the number of oligonucleotide pairs to have annealed and hence on the amount of genomic template present for that
target sequence. The oligonucleotides have a universal primer sequence tail and a 'stuffer' fragment that allows size-based identification of fluorescently labelled PCR fragments. Following capillary electrophoresis, peak detection and normalisation of samples, CNV changes are identified by relative changes in peak heights.

Finally, fluorescence in situ hybridisation (FISH), where a specific fluorescently labelled DNA probe (usually a bacterial artificial chromosome [BAC], P1-derived artificial chromosome [PAC] or fosmid) is hybridised to interphase or metaphase chromosome spreads, is also another commonly used method to confirm CNVs.

2.6.3 Presence of CNVs in the general population

Sebat and colleagues used ROMA analysis of 20 unrelated individuals from a variety of geographical backgrounds to determine the extent of CNVs found in the normal population (Sebat et al. 2004). Using a BglIII representation with 35 kb resolution arrays, 71 unique CNVs were detected. Over 90% of these CNVs could be verified using another technique. In addition, many of these changes were
confirmed by running two of the DNA samples again with a HindIII genomic representation. Five additional unique copy number changes were detected using this alternative restriction enzyme. This non-redundant set of 76 CNVs had an average length of 465 kb and only 5 had been described previously. The average number of CNVs found between any two individuals was 11. Although CNVs were widely distributed through the genome, some hotspot regions, such as on chromosome 15q (near the Prader-Willi and Angelman locus), were overrepresented. The importance of these findings was highlighted by the fact that there are 70 genes contained within this set of CNVs.

A more comprehensive CNV study of the HapMap DNA samples from four human populations using both SNP arrays and clone-based aCGH suggested that as much as 12% of the genome (360 Mb) contains CNVs (Redon et al. 2006). Even though recent data suggest this figure is possibly an overestimate (Perry et al. 2008), these regions are still likely to comprise more nucleotide content per genome than do SNPs – for instance there were a total of 3.1 million SNPs in the 2007 release of HapMap (Frazer et al. 2007) – thus highlighting the importance of CNVs in genetic diversity and human evolution. The average combined length of CNV regions per genome was more than 20 million base pairs. Two-thirds of the 1447 CNV regions detected have been replicated, either on both CNV detection platforms, using a locus-specific platform, or by virtue of being present in more than one sample or in a previous study. Approximately 8% were estimated to be false positives. In more than half overlap genes, however, deletions were less likely to encompass genes than were duplications. CNVs were spread throughout the genome, with the proportion of any given chromosome being susceptible to CNV ranging from 6% to 19%. However, gaps in the human genome reference sequence (build 35) had an increased likelihood of being associated with CNVs. In addition, the paucity of HapMap phase I SNPs in regions surrounding CNVs meant that few could be efficiently tagged for potential analysis in genome-wide association studies. CNVs from the two studies described above are available as Structural Variation tracks on the UCSC genome browser (http://genome.ucsc.edu/), along with copy number data from seven other studies (Conrad et al. 2006; Hinds et al. 2006; Iafrate et al. 2004; Locke et al. 2006; McCarroll et al. 2006; Sharp et al. 2005; Tuzun et al. 2005). CNVs found in controls are also listed in the Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation/).

2.6.4 Whole genome CNV screens in ASD

Despite the unexpectedly high CNV rate found in controls, there has been much effort directed towards identifying autism-associated copy number changes that might confer susceptibility to this disorder. Seven notable whole genome CNV studies in autism cohorts are summarised below and in Table 2.2.
<table>
<thead>
<tr>
<th>Sample cohort</th>
<th>Method</th>
<th>Autism specific / de novo / clinically relevant CNVs detected</th>
<th>Total CNVs detected in probands</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 syndromic ASD cases</td>
<td>aCGH with 1M resolution BAC and PACs</td>
<td>7/29 de novo 1/29 inherited with skewed X inactivation in mother</td>
<td>33 200 kb to 16 Mb</td>
<td>Jacquemont et al. 2006</td>
</tr>
<tr>
<td>1168 multiplex ASD</td>
<td>Affymetrix 10K array</td>
<td>10 de novo 126 recurrent or overlapping 18 overlapped rearrangements found in the ACRD*</td>
<td>254 in 173 families, average size 3.4 Mb**</td>
<td>Szatmari et al. 2007</td>
</tr>
<tr>
<td>118 simplex ASD, 49 multiplex ASD and 99 controls</td>
<td>ROMA, 35 kb resolution</td>
<td>17 de novo CNVs in 16 individuals in 12/118 sporadic cases in 2/77 multiplex families in 2/196 controls</td>
<td>NA</td>
<td>Sebat et al. 2007</td>
</tr>
<tr>
<td>751 multiplex AGRE families, 2814 bipolar/control samples</td>
<td>Affymetrix 5.0 arrays for patients, 500K arrays for controls</td>
<td>32 loci found in 3 or more patients but variant in &lt;1% of parents, 8 of these regions had at least one de novo event**</td>
<td>NA</td>
<td>Weiss et al. 2008</td>
</tr>
<tr>
<td>237 simplex ASD, 189 multiplex ASD 500 controls</td>
<td>Affymetrix 500K array and karyotyping</td>
<td>277 autism-specific CNVs, 27 cases with de novo CNV, 13 recurrent loci</td>
<td>1315, average size 603 kb**</td>
<td>Marshall et al. 2008</td>
</tr>
<tr>
<td>397 ASD cases from AGRE and 372 controls</td>
<td>aCGH with 19K BACs, 200 kb resolution</td>
<td>51 autism specific CNVs in 46 patients 9 de novo</td>
<td>NA</td>
<td>Christian et al. 2008</td>
</tr>
<tr>
<td>859/1336 ASD cases and 1409/1110 controls</td>
<td>Illumina 550K SNP array</td>
<td>CNVs enriched in ubiquitin pathway (UBE3A, PARK2, RFWD2 and FBX040) and neuron development genes (NRXN1, CNTN4, ASTN2 and NLGN1)</td>
<td>78 490</td>
<td>Glessner et al. 2009</td>
</tr>
</tbody>
</table>


**Highest confidence data; NA – not available.
A French study of 29 cases of syndromic ASD used aCGH with a resolution of 1 Mb and identified clinically relevant CNVs in eight patients (Jacquemont et al. 2006). These rearrangements comprised six deletions and two duplications and ranged from 1.4 to 16 Mb in size. Seven of these CNVs were de novo and the eighth was a duplication of Xq25, inherited from a mother who exhibited skewed X-inactivation. Although none of these CNVs was recurrent in this small sample group, the 1 in 4 detection rate underscores the value of copy number analysis, especially in cases of syndromic autism.

The AGP study used Affymetrix 10K SNP arrays to analyse copy number changes in over a thousand multiplex families with idiopathic ASD (Szatmari et al. 2007). Using the most stringent cut-off values, 254 CNVs with an average size of 3.4 Mb were detected in 196 probands from 173 families. Two-thirds of copy number changes found were increases. Of these CNVs, 126 were recurrent or overlapping while another 18 overlapped with previously mapped chromosome rearrangements annotated in the Autism Chromosome Rearrangement Database (http://projects.tcag.ca/autism/). Apparent de novo rearrangements were seen in ten families, in three of which both affected sibs harboured the CNV, suggesting parental gonadal mosaicism. One of these CNVs on chromosome 2p16, found in two affected sisters, encompasses the neurexin 1 (NRXN1) gene. Based on its interaction with SHANK3 and the neuroligins (Feng et al. 2006), plus its role in synaptogenesis, this gene is a good functional candidate for autism. Another of these CNVs was a 1.1 Mb gain on the long arm of chromosome 1. This variant was detected in three families and overlaps a region implicated in intellectual disability (Sharp et al. 2006).

Another study has compared the association of CNVs with ASD in simplex and multiplex families (Sebat et al. 2007). High resolution ROMA was performed on 118 simplex, 47 multiplex and 99 control families with an array consisting of 85 000 probes. Seventeen de novo CNVs, found in 16 individuals (14 patients and two controls), were validated by other techniques. Only four of 17 CNVs had been reported previously and these were all > 4 Mb. The overall rates of spontaneous mutation were 10% (12/118) in sporadic cases of autism, 3% (2/77) in multiplex families and only 1% (2/196) in controls/unaffected siblings. Both de novo CNVs found in controls were duplications, whereas most CNVs in autism cases were deletions. The male to female ratio in patients with de novo CNVs was 1.8:1 compared to 5:1 for the study group as a whole. These data led the authors to propose that these spontaneous mutations detected in sporadic cases have a relatively high penetrance and so contribute more equally to disease between males and females. In contrast, unless germline mosaicism is present in one of the parents, multiplex families are unlikely to be explained by de novo CNV events. These families are more likely to harbour numerous heritable risk factors, each with a smaller effect on susceptibility.
In the first component of a CNV and genetic association scan using Affymetrix 5.0 arrays, Weiss et al. (2008) analysed copy number in probands from 751 multiplex families. By searching for CNV loci shared by three or more patients and variant in < 1% of parents, they identified 32 high confidence CNV regions, of which eight contained at least one de novo event. The one region that particularly stood out was a single recurrent deletion on chromosome 16, detected in five cases from four independent families and is discussed in more detail in Section 2.6.6.

Marshall and colleagues have used the Affymetrix 500K platform together with karyotyping to study 427 unrelated ASD cases (Marshall et al. 2008). Using their most stringent CNV calling algorithm, they identified a set of 1315 CNVs, with an average of three per genome and mean size of 603 kb, a similar number being observed in the set of 500 controls. Of these, 277 were found to be autism-specific. De novo CNVs were detected in 7.1% and 2.0% of simplex and multiplex families, respectively, consistent with the findings of Sebat et al. that association of de novo CNVs is increased for sporadic cases. Some of the loci described have previously been detected in cohorts of patients with intellectual disability. In addition, the karyotype analysis of idiopathic cases detected 3.5% with balanced translocations (not detected in the primary CNV analysis) and 2.2% unbalanced translocations (all detectable as CNVs).

An aCGH study of 397 ASD probands and 372 controls using ∼19 000 BAC DNA probes identified autism-specific CNVs in approximately 12% of cases (Christian et al. 2008). Nine CNVs were de novo, whilst 42 were inherited. This set of autism-specific CNVs overlaps with about 270 genes, many of which may now be considered candidate genes. CNVs ranged in size from 189 kb to 6.1 Mb. This set of CNVs included three cases of the well-characterised maternally-derived 15q11–13 duplication (Section 2.6.5) and four cases of the 16p11.2 deletion, a finding which was investigated further (Section 2.6.6) (Kumar et al. 2007). In the multiplex families with an inherited CNV, the concordance rate was 21/33 for the presence of the autism-specific CNV in affected sibs. These CNVs were enriched in female cases; changes were detected in 25 females and 21 males in a study group comprising 165 females and 232 males. In this study, only around 30% of CNVs detected in control samples were found in the DGV. This low rate highlights the importance of using an identical method of CNV detection together with a suitable number of control subjects for comparison.

Finally, a recent genome-wide CNV study using the Illumina 550K SNP array analysed 859 ASD cases and 1409 non-autistic controls for discovery (Glessner et al. 2009). A further 1336 AGRE cases and 1110 controls were then used for replication. On average, 15.5 CNVs were detected in each individual, for both case and control cohorts. However, it was notable that four genes that were significantly enriched
for CNVs in ASD cases (UBE3A, PARK2, RFWD2 and FBX040) are all involved in the ubiquitin pathway. Although this pathway has not previously been associated with autism susceptibility, the UBE3A gene lies within the previously identified 15q11–13 region (Section 2.6.5). Novel ASD candidate genes involved in neuronal cell-adhesion, such as NLGN1 and ASTN2, were also identified.

### 2.6.5 The 15q11–13 duplication

Proximal 15q11–13 duplications have long been associated with autism (Baker et al. 1994; Christian et al. 2008; Gillberg et al. 1991). In probands, they can be inherited or sporadic, but in either case the duplication is usually derived from the maternal chromosome. In contrast, inheritance from the paternal chromosome leads to a normal phenotype (Cook et al. 1997b). The duplication is variable in size and so is sometimes missed by karyotype analysis. For example, the AGP study detected chromosome 15q gains in seven samples from three families, at least two of which were missed in earlier karyotype analysis (Szatmari et al. 2007). In the other whole genome screens described (Section 2.6.4), de novo duplications of this locus were detected in 1/29 cases of syndromic ASD (Jacquemont et al. 2006), 1/264 ASD families assayed with ROMA (Sebat et al. 2007) and in 2/427 ASD cases assayed with Affymetrix SNP arrays (Marshall et al. 2008). Duplications at 15q11–13 ranging from 1.4 Mb to 7.6 Mb were also detected in 5/751 multiplex AGRE families (Weiss et al. 2008). The smallest of these contained only two genes, so may help prioritise candidate gene selection in this region.

### 2.6.6 ASD-specific CNVs at the 16p11.2 locus

One of the spontaneous CNVs detected by Sebat et al. was an ∼500 kb loss at 16p11.2 found in a female Asperger syndrome patient (Sebat et al. 2007). Although not detected by the 10K AGP scan (Szatmari et al. 2007), the importance of this locus has rapidly been verified in three subsequent studies (Section 2.6.4). The 16p11.2 deletion was found in two of the first 180 samples to be run in the 19K BAC aCGH study (Christian et al. 2008). The significance of this deletion was further assessed by quantitative PCR screening of a further 532 probands and 465 controls. The deletion was detected in two additional individuals with autism, but was not present in controls (Kumar et al. 2007). These deletions were verified with FISH and microsatellite analysis and a custom designed oligonucleotide array was used to map the breakpoints to the edges of 147 kb segmental duplications with 99.5% sequence identity. This deletion contains 25 genes and is similar to a deletion reported in identical twins presenting with mild intellectual disability, heart defects and seizures (Ghebranious et al. 2007). It also overlaps with a previously described microdeletion syndrome involved with developmental disabilities (Ballif et al. 2007). Detailed phenotype analysis of autistic individuals with
this 16p11.2 deletion could not detect any striking features that suggest this group of individuals are a distinct autism subtype. The reciprocal duplication product was identified in one subject with autism, but unlike the deletions was found to be inherited. The duplication was also detected in two controls, so its significance to autism susceptibility is uncertain. The deletion segregated with autism in one family; the proband’s affected brother carried the deletion and unaffected sister did not. However, affected sibs in the three other families did not harbour the deletion, demonstrating how there can be different autism susceptibility factors involved even within the same family.

Weiss et al. found de novo 16p11.2 deletions (see Figure 2.5) in five cases from 751 multiplex AGRE families (Weiss et al. 2008). Deletions were confirmed by MLPA in all cases. This deletion was only detected in 3/2814 controls. The association of this deletion with autism was subsequently confirmed in two other participant cohorts; being identified in 5/512 cases referred for developmental delay, intellectual disability or ASD, and in 3/299 cases of autism from an isolated Icelandic population. In two families from the replication cohorts for which the deletion was inherited, parents carrying the 16p11.2 abnormality exhibited mild intellectual disability or attention deficit hyperactivity disorder. The rate of the deletion was also elevated among Icelandic patients with a psychiatric or language disorder, although to a lesser extent than for autism. These findings are typical of microdeletion syndromes which often show a wide range of phenotypic variability. The reciprocal duplication (see Figure 2.5) was also elevated in two of the three ASD cohorts, but these were predominantly inherited. In this study, 16p11.2 events were mostly associated with early-onset cases.

In the study by Marshall et al., the 16p11.2 CNVs were detected in four ASD families (two gains and two losses) out of 427 (Marshall et al. 2008). Both deletions were de novo, whereas one of the duplications was maternally inherited. One of the deletions was found in a multiplex family where an affected brother did not harbour the CNV, again demonstrating the presence of multiple autism susceptibility factors even within the same family.

Finally, the study by Glessner et al. (2009) also detected 16p11.2 CNVs in probands which did not co-segregate with ASD in the rest of the family. In contrast to earlier studies, the similar frequencies seen in cases and controls did not provide additional support for this locus being involved in ASD susceptibility.

In contrast to the autism-associated 15q11–13 duplication, which is predominantly maternal in origin, cases of the 16p11.2 deletion both paternal and maternal in origin have been documented (Christian et al. 2008; Weiss et al. 2008), making any parent-of-origin effects unlikely.

Some of these autism sample cohorts overlap (for example the AGRE cohort was used in four of the studies described above: Christian et al. 2008; Glessner
Figure 2.5 Regions of microdeletion and microduplication on chromosome 16p11.2 (Weiss et al. 2008). Normalised intensity data from Affymetrix SNP arrays averaged every 11 to 12 probes across a 2 Mb region on chromosome 16. Means (closed circles) and standard deviations (vertical bars) for subjects with normal copy numbers are depicted in blue; subjects with duplications are denoted with red open circles, and those with deletions are denoted with green triangles. Annotated genes in the region of interest are shown (not to scale), with grey denoting brain expression and black denoting unknown or little brain expression. Arrows represent the segmental duplications mediating the rearrangements, with three genes located within the segmental duplication. Reproduced with kind permission. Copyright © 2008 Massachusetts Medical Society. All rights reserved. See plate section for colour version.
et al. 2009; Sebat et al. 2007; Weiss et al. 2008), thus giving the false impression of independent replication. This problem is not unique to autism genetics (Chinnery, 2007) and can be resolved by further independent replication. Nevertheless, these studies indicate that this locus on chromosome 16 is implicated in 0.3–1% of cases of ASD. As there are ∼25 genes in this region, it remains to be determined which gene, or combinations of genes, are implicated. Detection of smaller CNVs, or balanced translocations overlapping this region, and searching for rare ASD-specific sequence variants in this set of genes may shed light on the matter.

2.6.7 CNVs in schizophrenia and overlap with autism

CNVs have also been implicated in the aetiology of other psychiatric disorders such as schizophrenia. Using ROMA 85K and Affymetrix 500K SNP arrays, Walsh et al. screened two independent cohorts for structural variants not present in the DGV and over 100 kb in size (Walsh et al. 2008). In both cohorts they detected a significant increase in the number of these CNVs that alter genes, when comparing individuals with schizophrenia to control subjects. In the primary cohort, almost all rare variants detected were different. However, in the replication cohort, they detected two cases of 16p11.2 duplication, at the same locus that has recently been associated with autism (Section 2.6.6). In addition, a 115 kb deletion was detected on chromosome 2 which disrupts NRXN1, further demonstrating the genetic overlap between autism and schizophrenia.

A more recent meta-analysis has since confirmed the 16p11.2 duplication as a schizophrenia susceptibility factor, with an odds ratio of 8.4 (McCarthy et al. 2009). These new data also show that 16p11.2 dosage is inversely correlated with head circumference, suggesting that early brain growth rate may be a possible mechanism to explain the role of this CNV in neurodevelopmental disorders.

A larger study looking specifically for de novo variants associated with schizophrenia identified three loci: 1p21.1, 15q11.2 and 15q13.3 (Stefansson et al. 2008). The last of these CNVs is situated at the distal end of the Prader-Willi/Angelman locus, between breakpoints 4 (BP4) and 5 (BP5) and also has been detected in ASD cohorts (Miller et al. 2008) and was demonstrated to segregate in a multiplex autism family (Pagnamenta et al. 2008). A further study describing smaller (680 kb) recurrent deletions within the BP4-BP5 region, suggests that haploinsufficiency of CHRNA7 is most likely to underlie the neurodevelopmental phenotypes seen in the 15q13.3 microdeletion syndrome (Shinawi et al. 2009).

2.7 Final remarks

As molecular genetic technologies and knowledge of the genetics of ASD advance, so will the strategies used to further investigate the aetiology of these
disorders. Genotyping technology has rapidly progressed, providing increased throughput and decreased cost per genotype and quantity of DNA per sample needed for experiments. This has made genome-wide association studies for ASD and other complex diseases a reality, enabling the identification of common polymorphisms with small to moderate effects on disease susceptibility. However, the need for increased cohort size for such studies is still a pressing issue.

New sequencing technologies, such as the 454 and Genome Analyser systems of Roche and Illumina respectively, allow sequencing at a scale not previously possible. Therefore, research is now progressing towards the resequencing of megabase quantities of DNA, including whole exomes (the total coding sequence in the genome) in many individuals. As costs inevitably continue to decrease, this will eventually lead to the sequencing of the entire genomes of individuals with ASD, allowing the identification of all variation within their DNA. Such studies will aid the identification of rare mutations of strong effect, as well as providing data for association and linkage analyses. Such studies are in the foreseeable future, and will usher in an exciting new age of ASD genetics research.

The direction of research into ASD is also likely to increasingly change. Already, a change in focus to CNV variation has been possible due to advances in microarray technology and the methods of SNP genotyping currently being employed. Although unexpectedly high levels of CNVs in controls make interpretation of results difficult, the seven genome-wide studies described paint a picture that highlights the importance of CNVs in relation to ASD. Clinical diagnosis may soon become possible for the most abundant and penetrant of these CNVs. CNVs will also aid identification of genes involved in the molecular mechanisms underlying ASD. In addition, high resolution CNV screening of ASD cohorts prior to further genetic analyses will give future linkage and association studies more power by leading to cohorts which are less heterogeneous.

Although many genes have been implicated as possible candidates for ASD susceptibility, verification has been achieved for only a small number of these. As described previously, a combination of genomic deletions plus other deleterious sequence variants has led to SHANK3 being considered a bone fide ASD susceptibility factor (Durand et al. 2007; Moessner et al. 2007). NRXN1 has also been validated as an ASD susceptibility locus. As well as being present in single-gene ASD-associated CNVs (Szatmari et al. 2007), it has been interrupted in balanced translocations, and rare sequence variants have also been identified (Kim et al. 2008b). More effort is also likely to be spent on understanding the epigenetics of those genes proving to be strong candidates for ASD, as it is becoming increasingly clear that the regulation of genes is a highly complex process.

Another pressing need is for an increase in the number of available samples for these genetic experiments. In order to have sufficient power to detect genes
of weak effect (or very rare variants with moderate to strong effects), it has been estimated that 10 to 20 times more samples are needed than are presently available for use in ASD studies (around 20–40 000 samples in total) (O’Roak and State, 2008). While collection of samples is ongoing, the time and effort needed to carry out the diagnostics is not trivial.

Within the framework of a genetically complex heterogeneous disorder such as ASD, common genetic predisposing factors are likely to be enriched in multiplex families, whereas sporadic cases are more likely to be caused by rare de novo chromosomal rearrangements or environmental factors (Risch, 2001). These two classes are assumed to be genetically distinct with different underlying aetiologies (two different genetic mechanisms contributing to risk: spontaneous mutation and inheritance, with the latter being more frequent in families that have multiple affected children) (Sebat et al. 2007). Therefore, such differences should be accounted for in future studies. In addition, syndromic autism (where other syndromes such as Fragile X, tuberous sclerosis, amongst others, are the cause of autism) and non-syndromic autism should also be addressed differently, since they have different aetiologies.

The need to use different strategies reflects the complex aetiology of ASD with multiple interacting genes and pathways possibly involved. Several approaches such as association studies, whole genome screens, candidate gene studies taking different endophenotypes into account, and large scale sequencing efforts will be essential to discover the causal variants involved in ASD. In the near future, it is hoped that new experiments, especially those as part of large collaborative efforts such as the AGP, will achieve these goals.

2.8 References


Unravelling the genetics of autism spectrum disorders


A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Human Molecular Genetics*, 7: 571–578.


Unravelling the genetics of autism spectrum disorders


Researching the Autism Spectrum


Brain imaging and the neuroanatomical correlates of autism

MICHAEL SPENCER, ANDREW STANFIELD AND EVE JOHNSTONE

Although brain structure in Autism Spectrum Disorders (ASD) has been extensively investigated using magnetic resonance imaging techniques, considerable heterogeneity across studies exists for findings at the level of individual brain structures and regions. An important theme to emerge, however, is of structural alterations within the neural circuit that has become known as the ‘social brain’ – including the amygdala, superior temporal sulcus, fusiform face area and orbito-frontal cortex. Evidence points also to altered structure in the caudate nucleus in association with restricted and repetitive behaviours. Diffusion tensor imaging studies suggest aberrant connectivity between social brain structures and also between these areas and other cortical regions. Important future roles for structural neuroimaging will include longitudinal studies to investigate developmental trajectories in ASD, and efforts to join together neuroimaging and genomic techniques and to relate these findings to neuropathological studies.

3.1 Background

The notion that mental illness is a somatic disorder of the brain was put forward in 1845 by Wilhelm Griesinger (Griesinger, 1845), first Professor of psychiatry and neurology in Berlin, and has been actively investigated ever since. The initial work was neuropathological as there existed no means of visualising the brain in life but clear cut results were obtained in some disorders (Alzheimer, 1897; Wernicke, 1881) and where no such findings could be demonstrated as in schizophrenia, work still continued (Dunlap, 1924; Klippel and Lhermitte, 1909).
The introduction of pneumoencephalography in 1919 – whereby the cerebrospinal fluid around the brain was replaced by a gas thus allowing images of the brain to be visualised on x-ray – allowed the brain to be examined in life and it was introduced into psychiatric research practice in the 1920s. Studies continued throughout the 1930s and to a lesser extent thereafter. There were technical difficulties with pneumoencephalography but the overriding problem was its association with unpleasant side-effects such as headache and vomiting and considerable risk, so that it was considered unethical to use. In 1973, Hounsfield devised structural imaging by the non-invasive method of computed tomography (CT) and it became possible to carry out controlled studies using this new technology (e.g. Johnstone et al. 1976). Although now CT scans are done very quickly, this was not the case shortly after the technique was introduced when a CT examination of the head could take over an hour. This involved significant amounts of radiation thereby limiting the application of CT scanning in research. In recent years, for psychiatric research purposes CT has essentially been superseded by structural magnetic resonance imaging (MRI) initially referred to as NMR or nuclear magnetic resonance. This term was used in 1946 by Bloch and Purcell to describe the physical phenomenon whereby under the influence of a strong magnetic field, protons within the nuclei of hydrogen atoms become aligned with the field. If a subsequent brief pulse of radio waves with a specific frequency is applied, altering the alignment of these protons, the termination of this radio pulse is accompanied by a realignment of these protons back to the magnetic field. This causes them to release a pulse of energy that can be detected indicating the presence of the particular tissue type that responds optimally to the applied radio frequency.

The application of this technique to man, with the ability to reconstruct the data to create an image was later developed with pioneering work being conducted by Mansfield and Maudsley (Mansfield and Maudsley, 1977), Lauterbur (Lauterbur, 1979) and Mallard and colleagues (Mallard et al. 1979). MRI is sensitive to subject movement which can cause difficulties but it is now the structural imaging modality of choice because of the absence of ionising radiation and its high spatial resolution, good soft tissue contrast and, in brain studies, separation of grey and white matter. The absence of ionising radiation is advantageous particularly in young subjects and in those where repeated examination is going to be required. The fact that it does not depend on x-rays means that there is no bone artefact which, with CT, obscures the posterior fossa.

The reporting of cerebral MRI data in clinical practice is most commonly performed by means of the direct visual inspection of film print-outs, typically providing a relatively small but representative range of axial and sagittal images of the brain. In recent years, the inspection by neuroradiologists of volume data presented on a computer screen has become increasingly widespread.
3.2 Important considerations relating to autism spectrum literature

3.2.1 Heterogeneity of the autism spectrum

Since its first description by Kanner (1943), the concept of autism has expanded such that it is now generally accepted that it represents not a discrete condition, but rather part of a spectrum of conditions. These conditions can vary dramatically in their clinical features and even within a diagnostic category there is a wide range of possible presentations. This heterogeneity between and within the various components of the autism spectrum has implications for the neurobiological study of autism spectrum disorders (ASD), as it is possible that different clinical presentations may reflect differences in underlying brain structure and function.

The effects of this heterogeneity can be minimised between research studies by the use of standardised diagnostic instruments. There are a number of such instruments, with the most widely used at present being a combination of the Autism Diagnostic Interview – Revised (ADI-R) (Lord et al. 1994) and the Autism Diagnostic Observational Schedule – Generic (ADOS-G) (Lord et al. 2000). However, not all studies use the same instrument or combination of instruments and even if the same diagnostic methods are used, the inclusion criteria for participants may still vary, with some studies recruiting only individuals with autism and others including those with disorders from across the spectrum. These differences in diagnostic methodology and inclusion criteria may account for some of the heterogeneity observed in the autism neuroimaging literature.

It should be noted that problems of heterogeneity in the neuroimaging literature are not confined to ASD. There is no biological marker for most disorders of mental health and diagnoses are made on the basis of the clinical picture and the course of the condition over time. Where diagnoses are made on this basis there are bound to be uncertainties, disagreements and illnesses which seem to lie across diagnostic borders. Reliability of diagnosis has been greatly enhanced by the introduction of operational definitions (e.g. those of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revised/DSM-IV-TR) (American Psychiatric Association, 2000). In this context the operational criteria for schizophrenia and bipolar illness of DSM-IV-TR and indeed other systems of definition exclude cases due to a ‘general medical condition’ whereas those for autism and ASD do not. A variety of medical conditions such as epilepsy (see Section 3.2.2) can in themselves be associated with changes in brain structure detectable by neuroimaging and therefore these aspects of heterogeneity in imaging studies may well represent a greater problem in the study of ASD and autism than they would for example in schizophrenia or bipolar disorder research.
3.2.2 Intellectual ability

A high co-occurrence of intellectual disability and ASD has long been noted. Intellectual disability is defined by significant limitations in intellectual functioning, an intelligence quotient (IQ) of less than 70, and impaired adaptive behaviour, originating before eighteen years of age (American Association on Intellectual and Developmental Disabilities, 2010). Prevalence rates for intellectual disability among individuals with autism are usually quoted as around 70–80% (Fombonne, 2005), although studies which consider the whole range of ASD, as opposed to more tightly defined autism, tend to report much lower rates (Chakrabarti and Fombonne, 2005). The high prevalence of intellectual disability in autism poses a number of difficulties for neuroimaging studies of autism. This is particularly evident for studies examining individuals with low IQ where the choice of control group may be difficult. To enlist a control group without intellectual disability risks finding brain structural differences which are related to the IQ disparity (e.g. Spencer et al. 2005), in addition to those which are related to the expression of autistic features; conversely to control for IQ in this situation may lead to false negative findings due to the association between autism and intellectual impairment. If, however, a control group containing intellectually disabled individuals is to be chosen then the question arises as to whom exactly should be included – i.e. how does one select a control condition from among the multitude of conditions (known and unknown) which are associated with intellectual disability?

Another related consideration is that individuals with epilepsy, present in about 20–25% of individuals with moderate to severe intellectual disability (Lhatoo and Sander, 2001), and cerebral palsy, present in around 15–40% of individuals with severe intellectual disability (Fryers and Russell, 1997), are typically excluded from structural imaging studies. The exclusion of these individuals is principally due to the strong association between these conditions and structural abnormalities on neuroimaging (Bruggemann et al. 2009; Dabbs et al. 2009; Korzeniewski et al. 2008; Ong et al. 2009), and hence their potential role as confounding factors. In other words, if epilepsy were more prevalent in the subject group than in the control group of a study (such as a study of ASD), then the risk may arise that neuroimaging findings associated with epilepsy might be misattributed to ASD.

In fact, relatively few neuroimaging studies of autism have included subjects with intellectual disability. While this avoids the complications discussed above and has obvious practical advantages in terms of acceptability of the scanning procedure and the ability to administer cognitively relatively demanding functional MRI (fMRI) tasks, it does mean that the neuroimaging literature in autism cannot be considered as representative of the generality of the autistic population. This
is particularly significant in the interpretation of any findings, as it cannot be assumed that intellectually impaired individuals will manifest the same brain-to-behaviour relationships as are seen in those with relatively high IQ.

3.2.3 Gender

Although there is an approximately 4:1 ratio of males to females with autism, this is not reflected in the structural neuroimaging literature, in which primarily males are considered. The gender disparity in the population prevalences of Asperger syndrome and non-specific pervasive developmental disorders, though less well characterised than for autism, is likely to be even more marked. While a number of recent studies have attempted to address this issue (see Section 3.7), the degree to which the overwhelming majority of the literature may be generalised beyond the male population is uncertain.

3.2.4 The timing of brain development in ASD

In recent years increasing interest has focused upon differences in the developmental time course of brain structures in ASD as compared to unaffected individuals. When cross-sectional studies from across the age range have been combined using meta-analytical methods, significant moderating effects of age have emerged for a range of brain regions (Redcay and Courchesne, 2005; Stanfield et al. 2008). Consequently, differences in brain anatomy between individuals with ASD and unaffected individuals may be evident at certain ages, but not at others. These developmental differences may provide clues as to the pathogenetic processes which lead to ASD and could aid in the development of future interventions. One important caveat is that the results to date are based upon relationships with age in cross-sectional studies and so must be assumed to be preliminary in nature. Longitudinal studies which follow up the same group of autistic individuals from infancy are required to confirm or refute these findings.

If, however, there are differences in the timing of brain development in ASD there are obvious implications for the interpretation of study results. Negative findings for a region do not necessarily exclude it from being important in ASD, as it is possible that structural differences would have been seen had the participants been scanned at a different age. The age of clinical diagnosis of autism is typically 3–4 years – however, the meta-analysis conducted by Redcay and Courchesne (2005) suggested a period of marked overgrowth and subsequent relative cessation of growth of the brain as occurring within the first 2–4 years of life. The authors therefore suggested that examining the neuroanatomy of participants older than this will inevitably result in the measuring of the outcome of a pathological process, rather than the actual pathology itself (Redcay and Courchesne, 2005). However, this is clearly not a reason to exclude older children and adults from
neuroimaging studies – as knowledge of the process outcome is also important when determining structural differences. Rather, it points to the importance of considering the question to be addressed when planning a study, bearing in mind the possible confounding factors, and carefully choosing the appropriate sample for study.

3.3 Qualitative MRI findings

Naked eye inspection of MRI scans may reveal both anomalies, i.e., variations in structure of uncertain significance and abnormalities, i.e. variations in structure which would be regarded as outwith normal limits and could well be indicative of specific pathology. A broad range of qualitative anomalies of brain structure have been described in association with psychiatric disorders, such as white matter hyperintensities, dilatation of the lateral ventricles, thinning of the corpus callosum, cavum septi pellucidi (a separation of the septal laminae of the septum pellucidum) and dilated Virchow-Robin spaces. Figure 3.1 illustrates two such anomalies – thinning of the corpus callosum (Figure 3.1A–C) and lateral ventricular enlargement (Figure 3.1D–F). In routine clinical practice many of these anomalies are regarded as incidental findings on MRI scans, and the significance of their presence in the clinically well human – as well as the nature of their relationship with disease states – is poorly understood.

Qualitative abnormalities of brain structure, apparent on visual inspection by a neuroradiologist of a structural MRI scan, have been described in a range of neurodevelopmental conditions, most notably idiopathic intellectual disability (Decobert et al. 2005; Schaefer and Bodensteiner, 1999; Spencer et al. 2005) and schizophrenia (Degreief et al. 1992; Galderisi et al. 2000; Lubman et al. 2002; Nopoulos et al. 1997). A number of studies report such clear cut abnormalities of brain structure as occurring in association with autism. These abnormalities include defects of neuronal migration such as polymicrogyria, schizencephaly, macrogryria and focal pachygyria (Berthier et al. 1990; Piven et al. 1990; Schifter et al. 1994) and abnormalities of the septum pellucidum (Machado et al. 2003). Thinning and agenesis of the corpus callosum have been reported using qualitative assessment methods (Machado et al. 2003), while quantitative measurements of reduced corpus callosal volume have been reported within some studies (Egaas et al. 1995; Hardan et al. 2000; Manes et al. 1999; Piven et al. 1997) but not others (Elia et al. 2000; Gaffney et al. 1987b) (see Section 3.5.3). Enlarged Virchow-Robin spaces (Taber et al. 2004; Zeegers et al. 2006), arachnoid cysts (Zeegers et al. 2006) and Chiari I malformation (Zeegers et al. 2006) have also been reported in autism. For reasons mentioned earlier, it is not clear whether these abnormalities are related to autism per se or associated with co-morbidities such as epilepsy. It has been
Figure 3.1 A–C, examples of absent (A), moderate (B) and marked (C) thinning of the corpus callosum (indicated as CC) on midsagittal section; D–F, examples of absent (D), moderate (E) and marked (F) enlargement of the frontal horns of the lateral ventricles (indicated as LV) on coronal section. Coronal images are displayed in neurological convention (i.e. left is left). (Adapted from Spencer, M.D., Gibson, R.J., Moorhead, T.W.J. et al. (2005). Qualitative assessment of brain anomalies in adolescents with intellectual disability. American Journal of Neuroradiology, 26: 2691–2697, with permission of the copyright holder, the American Society of Neuroradiology.)

reported, however, that the overall yield of qualitative anomalies in teenagers with special educational needs is related to the degree of intellectual impairment as measured using IQ (Spencer et al. 2005) – hence it seems likely that within an ASD sample such abnormalities would predominantly occur in those individuals with the greatest degree of intellectual disability.

In terms of volumes of ventricular spaces in autism, lateral ventricular enlargement has been reported in some studies (Balottin et al. 1989; Damasio et al. 1980;
Brain imaging and the neuroanatomical correlates of autism

Piven et al. 1995) but not others (Hardan et al. 2001b) and enlargement of the fourth ventricle has been reported in some studies (Gaffney et al. 1987a) but not others (Garber et al. 1989; Holttum et al. 1992). In addition, one study has reported enlargement of the third ventricle in autism (Hardan et al. 2001b).

Overall, the yield of qualitative abnormalities of brain structure on MRI has generally been found to be low (Battaglia and Carey, 2006; van Karnebeek et al. 2005). Cortical malformations such as polymicrogyria and schizencephaly are associated with epilepsy (Lagae 2000), and their origin in aberrant neuronal migration may provide evidence for the concept of a neurodevelopmental disturbance associated with autism. Other abnormalities such as enlarged Virchow-Robin spaces may occur as incidental findings of no apparent clinical importance. This non-specificity and the low overall yield of qualitative anomalies of brain structure probably means that although qualitative visual assessment is the most readily accessible and perhaps longest established MRI analysis methodology, its research value in the investigation of brain structure in ASD still remains to be established.

3.4 Quantitative structural MRI image analysis techniques

3.4.1 Region of interest

Region of interest (ROI) approaches are well established in the neuroimaging literature and are the most commonly used techniques for the volumetric analysis of the brain in ASD. They involve the delineation of specific brain structures on MRI scans, usually through the use of a manual operator – a labour intensive process which is naturally susceptible to human error. Initially this work relied entirely on manual tracing but software assisted methods were introduced in the 1990s. However, the process remains time consuming and developments in automated methodology to trace brain structures and regions are likely to become increasingly important in the future.

There are a number of important factors which must be considered when interpreting the results of an ROI study. The method used to delineate the structure must be shown to have acceptable intra-rater and inter-rater reliability, i.e. it must be possible for the same rater and at least one other rater to repeat the method and arrive at approximately the same result. The method must also be shown to be valid (i.e. the limits used to delineate the structure must be defined using landmarks which accurately represent the boundaries of the structure concerned). It is important to note that some structures, such as the amygdala, are very difficult to define anatomically using standard MRI techniques – although this is likely to improve as increasingly sophisticated technology becomes available. Some argue
that this has led, at least to some degree, to the use of arbitrarily chosen landmarks and to a lack of universally agreed boundaries for certain structures, and thus to a limitation in comparability between studies (Brierley et al. 2002). What is clearly required in ROI-based research is the adherence to stringent protocols and the explicit methodological reporting of any boundaries and landmarks employed. In addition, due to limitations in technology, early ROI studies employed midline areas of structures as proxies for volume measurements and it is not clear that such assumptions are valid (Courchesne et al. 1988; Gaffney et al. 1987a; Hashimoto et al. 1993).

Even considering the above caveats, manual ROI approaches still have a number of positive features and remain one of the most widely accepted neuroanatomical analysis techniques. The corpus callosum is a structure for which reliable landmark-based tracing methods have been established (Figure 3.2), and this has led to important findings concerning alterations in corpus callosum volume in ASD (see Section 3.5.3). A fundamental advantage of the ROI approach is that it is strongly linked to neuroanatomy as opposed to derived measures – such as those from computation-based morphometric techniques – and it can therefore enable reasonably confident interpretation of findings. In contrast to many automated methods, relatively small amounts of image preprocessing are required before region delineation occurs, meaning that there is little risk of error being introduced at this stage. This also means that ROI techniques are suitable for use for brains with gross structural abnormalities which often require to be excluded from automated analysis. Finally, due to their time consuming nature, ROI
Figure 3.3 Reduced thalamic grey matter density as measured using voxel-based morphometry in intellectually disabled adolescents with autistic features as compared to controls scoring below the threshold for ASD. From left to right, the three images illustrate the same findings on sagittal, coronal and axial sections, respectively. The coronal image is displayed in neurological convention (i.e. left is left). (Adapted from Spencer, M.D., Moorhead, T.W.J., Lymer, G.K.S., et al. (2006). Structural correlates of intellectual impairment and autistic features in adolescents. Neuroimage, 33: 1136–1144, with permission of the copyright holder, Elsevier Limited.) See plate section for colour version.

studies are usually, as the term suggests, directed towards regions for which specific hypotheses exist, rather than consisting of a more general search of the entire brain.

3.4.2 Voxel-based morphometry

Voxel-based morphometry (VBM) is a computerised technique for the quantitative analysis of structural magnetic resonance imaging (MRI). VBM enables multiple brain images to be combined and compared in terms of focal differences in brain tissue (typically grey or white matter) density or volume. VBM takes its name from the voxel – standing variously for ‘volumetric pixel’ or ‘volume element’ – which is a unit of volume located within a stereotactic coordinate-based grid.

The reader is referred to an important description of the methods of VBM, as authored by Ashburner and Friston (2000). Although several variations of VBM methodology have been described, the basic processes that are central to the method are the alignment and normalisation of brain scans to a standard stereotactic space, their automated reclassification into component grey and white matter tissue types, and the statistical investigation of the association between grey or white matter structure and one or more variables of interest. These variables of interest may include categorical variables such as ASD versus control group membership (an example is provided in Figure 3.3 – which illustrates the finding of reduced thalamic grey matter density in a group of adolescents with ASD traits as compared to controls) or dimensional measures such as symptom ratings derived
from questionnaires or other standardised instruments (an example is provided in Figure 3.4, which illustrates the finding of a correlation between the score on the Autism Behavioural Checklist (Krug et al. 1993) and grey matter density in the medial temporal lobe of children with ASD).

An important benefit of VBM over other image analysis methods is that, because it is automated and the scans do not require manual editing, it avoids potential sources of bias and error associated with hand-tracing techniques. Furthermore, it enables a ‘whole brain’ analysis that does not require the prior selection of ‘regions of interest’ – and is therefore not limited to detecting results within pre-selected areas. On the other hand it could be argued that this encourages non-hypothesis driven research. The fact that the alignment and normalisation of brain scans to a standard stereotactic space is a central element of VBM means that major abnormalities of brain size and structure are disregarded and brains that are very irregular in their gross structure cannot be assessed by this method. Opinions on the relative merits of qualitative (ROI) and quantitative (VBM) analysis vary and both have advantages and disadvantages. A counsel of perfection would be to employ both but, primarily for reasons of expense and time, this is relatively rarely done.
3.4.3 Other shape-based approaches

Aside from the volume-based or tissue density-based techniques of region-of-interest and VBM, discussed above, there are a number of other possible approaches to deriving quantitative neuroanatomical information from MRI scans. These include manual and automated methods which aim to determine the shape of subcortical structures, the degree of cortical folding and the relative position of various major gyri and sulci (see ‘Cerebral cortical folding’ within Section 3.5.2). Various factors are thought to affect the pattern of cortical convolutions including brain growth, the balance of local and long range connectivity and the mechanical properties of the cerebral cortical layers (Toro and Burnod, 2005). In turn, these factors are likely to be determined by genes, the environment and their interaction. The examination of cortical folding may therefore provide information regarding the nature and timing of pathogenetic processes. In addition, sulco-gyral shape and even position are thought to change with age, therefore differences between groups may also relate to processes which are ongoing throughout life (Blanton et al. 2001; Kochunov et al. 2005; Magnotta et al. 1999).

3.4.4 Diffusion tensor imaging

A relatively recent development in magnetic resonance technology which is becoming increasingly important in the field of autism research is diffusion tensor imaging (DTI) – an MRI modality that allows the direction of flow of water molecules within brain tissue to be estimated. In white matter, the direction of tracts is strongly related to the principal diffusion direction of water protons. As described by Basser et al. (1994), the anisotropic diffusion of water – which reflects the diffusion of water molecules along axons within white matter tracts – can be measured, providing information as to the directionality and integrity of white matter structures within the brain. When axons in white matter are tightly packed, run in the same direction and/or are well myelinated the level of anisotropy (expressed as fractional anisotropy (FA)) will be high. The use of DTI therefore allows researchers to make inferences about white matter microstructure in vivo. A further development in DTI methodology, DTI tractography, enables the three-dimensional characterisation of white matter pathways within the brain (see Conturo et al. 1999). DTI tractography allows the reconstruction of fibre bundles and enhances our ability to study the structural connectivity of distinct brain regions. Given the view that autism may be a disorder of brain connectivity (Frith, 2004) it is evident that the ability of DTI to study anatomical connectivity in vivo is of particular relevance and potentially holds great promise for the future study of the condition.
3.5 Quantitative structural MRI imaging findings, grouped by brain region

3.5.1 Whole brain

Although not identified by all studies, increased mean brain volume of individuals with ASD as compared to controls is one of the most consistent neuroimaging findings in autism research (Aylward et al. 2002; Courchesne, 2002; Hardan et al. 2001b; Piven et al. 1995). Studies of infant head circumference, which is strongly correlated with brain size in very young children, have identified greater growth in the first year of life in infants who later develop ASD (Courchesne et al. 2003; Dawson et al. 2007; Mraz et al. 2007). It is less clear, however, whether this persists throughout life, or whether the rate of brain growth in autistic children then falls behind that seen in typically developing children, leading to a gradual normalisation in size. It has been reported that brain weight is heavier in children with autism than controls but lighter in adults with autism than controls (Bauman and Kemper, 1997). MRI studies of young children do appear to show greater enlargements than are seen in older individuals (Courchesne et al. 2001; Sparks et al. 2002), however, increased brain volume has also been reported in some adults with ASD (Piven et al. 1995). A meta-analysis which combined postmortem head circumference and MRI data concluded that there is a period of early overgrowth followed by a reduction in growth rates and a subsequent normalisation in volume (Redcay and Courchesne, 2005). However, it is important to note that most of the existing studies examining this issue have used cross-sectional designs and the results may not be directly applicable to the study of longitudinal changes in brain structure. A preliminary longitudinal study investigated children aged 8–12 years measuring brain volume and cortical thickness at baseline and at follow-up after a 30-month interval and found evidence of greater reductions over time in grey matter volume and cortical thickness in individuals with ASD than in controls – with the changes in cortical thickness being related to higher ratings on ADI-R subdomains (Hardan et al. 2009a). In this study no differences in brain volume between individuals with ASD and controls were found to occur at either time-point – possibly reflecting the fact that these children were all older than the 2–4-year-olds within whom brain enlargement has previously been reported as occurring (Courchesne et al. 2001). The conduct of longitudinal imaging studies to definitively determine the timing of brain enlargement in ASD is clearly a priority.

The causes underlying enlarged brain volumes in autism remain unknown at present. Little work to determine these has as yet been conducted and there are no well replicated findings. It may be that differential trajectories of total brain volume exist for different subgroups of individuals with ASD. One study
investigated brain volumes in subgroups of people with ASD and reported increased grey matter volume in adolescents with autism but not Asperger syndrome as compared to controls (Lotspeich et al. 2004). It has been reported in one study that there is a relationship between increased brain volume and a low activity genetic variant of monoamine oxidase A (Davis et al. 2008) which is an enzyme responsible for the breakdown of catecholamines in the brain. This would indicate the involvement of factors which are genetically controlled. The involvement of issues relating to monoamine oxidase A has been reported in a variety of mental health disorders over the years. A tantalising link between ASD genetics and brain volume involves the PTEN (Phosphatase and tensin homologue on chromosome ten) gene – mutations in which have been reported in individuals with ASD and macrocephaly (Butler et al. 2005). Pten mutant mice demonstrate neuronal hypertrophy, macrocephaly and abnormalities of social interaction with some parallels to certain aspects of the ASD phenotype (Kwon et al. 2006). An important caveat is that, even if replicated, such genetic findings do not indicate cause as such but rather a vulnerability which acting together with other factors – genetic and otherwise – may push an individual towards developing a condition.

Not only is the cause of brain enlargement and the evident abnormality of brain growth in ASD unclear but it is not known whether the same processes drive brain growth in ASD as in typically developing children. This raises the question as to whether the increase in brain size reported to occur in ASD represents an increase in normal growth processes or whether it is the product of some alternative process of abnormal neurodevelopment.

3.5.2 Cerebral hemispheres

Grey / white matter and lobar volumes

Overall the cerebrum is reported to be enlarged in ASD (Stanfield et al. 2008). What is less clear is the timing of the enlargement, whether it occurs to the same degree across all lobes and whether it is localised to one particular tissue compartment (grey matter or white matter).

Although there are few studies which have examined the relationship between age and cerebral volume, given that the cerebrum makes up approximately 90% of the total brain volume it is difficult to envisage a situation in which age would affect whole brain size and not total cerebral volume. There is, however, evidence that not all lobes of the cerebrum are affected equally. The vast majority of studies have found enlargements of either the grey or white matter compartments in the frontal, temporal and parietal lobes in individuals with ASD, although the evidence for the latter is less strong (Carper and Courchesne, 2000; Carper et al. 2002; Hazlett et al. 2005; 2006; Palmen et al. 2004; 2005). In contrast, there appears
to be relative sparing of the occipital lobe with none of the aforementioned studies finding significant increases in either total occipital grey or white matter volume, although some did report trends towards significance (Hazlett et al. 2005; Palmen et al. 2004; 2005).

Although there is some inconsistency within the literature, increases in both the grey and the white matter compartments of the cerebrum have been reported to occur in ASD. Studies which have examined cortical (grey matter) thickness have found increases to occur in individuals with autism, which may account for the increased grey matter volume (Chung et al. 2005; Hardan et al. 2006c). An increase in the thickness of grey matter is consistent with post-mortem studies of autism and may be related to an increase in cell number or size (Bailey et al. 1998). As regards white matter, one study has suggested that regional differences may occur within an enlarged white matter compartment (Herbert et al. 2004). In this study the authors found an increase in volume in superficial (mainly lobar) white matter which was not seen in deeper white matter, including the corpus callosum and internal capsule. Myelination occurs in superficial white matter later and for longer than it does in deeper white matter, where it is usually complete by birth. The authors speculate that interference with myelination occurring post-natally, with a sparing of the process in utero, may have led to their results (Herbert et al. 2004), raising interesting questions about the timing of the insult.

It should be noted that in individuals who are not affected by autism, cerebral growth is dependent upon both region and tissue compartment, rather than proceeding in a uniform fashion throughout the brain (Giedd et al. 1999). This raises the possibility that in individuals with ASD the pattern of relative lobar and grey/white matter enlargement may depend on the age of the participants, with different lobes and compartments of the brain appearing enlarged at different times throughout development.

Frontal lobe sub-regions

The frontal lobe is considered to be the seat of executive function, which has frequently been found to be impaired in ASD (Hill, 2004). In addition, it is home to Broca’s area, the main brain region involved in expressive language, and is involved in social cognition through connections with limbic regions. There is therefore good reason to suspect that individuals with ASD will show frontal lobe neuroanatomical differences in comparison with typically developing individuals. Indeed, VBM studies provide evidence of structural abnormality of frontal lobe structures in ASD – although conflicting findings are reported. These include reports of reductions (Abell et al. 1999) as well as increases (Rojas et al. 2006; Waiter et al. 2004) in grey matter and reduced white matter (Schmitz et al. 2008; Waiter et al. 2005) in frontal lobe regions.
A reversal of asymmetry of Broca’s area has been found in two studies, such that the right side is greater in size than the left (De Fossé et al. 2004; Herbert et al. 2002), suggesting that an insult to the process of cerebral lateralisation may be important in autism. This finding gains indirect support from studies which have shown an increase in non-right handedness among individuals with ASD (Dane and Balci, 2007; Escalante-Mead et al. 2003). There is also some evidence that an increase in the size of the orbitofrontal cortex may be related to a greater degree of restricted and repetitive behaviours in individuals with ASD (Hardan et al. 2006b). This would be consistent with the rich connectivity between this region and the caudate nucleus, which is also found to be enlarged in ASD and associated with repetitive behaviours (Hollander et al. 2005; Rojas et al. 2006).

Cingulate cortex

The cingulate cortex is located on the medial surface of the human brain and runs parasagittally curving around the corpus callosum. In 1937, James Papez proposed that the cingulate cortex was critical to the subjective experience of emotions (Papez, 1937). The anterior cingulate cortex (ACC) has been extensively studied through electrophysiological, neuropathological and neuroimaging studies, and is believed to regulate a range of functions related to emotion, including autonomic functions such as blood pressure and heart rate, and cognitive functions such as reward and decision making (Bush et al. 2002). Recent reports suggest abnormal activation in the ACC in individuals with ASD in reward related fMRI paradigms (Schmitz et al. 2008) and emotion processing fMRI paradigms. In addition Chiu et al. (2008a) proposed that changes in anterior cingulate gyrus function were particularly associated with a dysfunction in self-referential processing.

Structural differences in the anterior cingulate cortex have been described in ASD. Haznedar and colleagues (Haznedar et al. 1997) divided the anterior cingulate cortex into three parts and found the dorsorostral region to be decreased in size whereas the dorsoventral region was increased in size in adults with ASD. Reductions in glucose metabolism in the dorsorostral region were also seen indicating a reduction in the activity of this region. Chiu and colleagues (Chiu et al. 2008b) found no difference in anterior cingulate volume in children with ASD but did not subdivide the structure so these findings may disguise the sub-regional differences described by Haznedar and colleagues (Haznedar et al. 1997). Several VBM studies have reported structural abnormalities of the cingulate gyrus (particularly the ACC) in ASD – including reports of reduced grey matter density (Kwon et al. 2004), increased grey matter volume (Waiter et al. 2004) and reduced white matter volume (Ke et al. 2008).
Lateral temporal lobe sub-regions

The fusiform face area (FFA) is located on the ventral surface of the temporal lobe and is involved in the processing of facial stimuli (Kanwisher et al. 1997). Impairments in facial affect recognition are well established in ASD and the FFA has been found to show altered activations when individuals with ASD view facial stimuli (Dalton et al. 2005; Deeley et al. 2007). Although there is some debate as to the nature of these functional differences in the FFA, VBM studies provide evidence of neuroanatomical abnormalities in the fusiform gyrus in ASD (Kwon et al. 2004; Waiter et al. 2004).

The superior temporal sulcus (STS) divides the superior and the middle temporal gyri (STG, MTG respectively). This region of the brain has long been known to be associated with auditory perception but more recently has been suggested to be important in the perception and initial analysis of more complex social stimuli, particularly those with a temporal component (Zilbovicius et al. 2006). Consistent with this idea, functional imaging studies have reported activation differences in the superior temporal sulcus region during emotion processing tasks in individuals with ASD (Freitag et al. 2008; Gervais et al. 2004; Hadjikhani et al. 2007; Herrington et al. 2007; Pelphrey et al. 2005).

From a structural perspective, a decrease in cortical thickness has been reported to occur around the superior temporal sulcus in individuals with autism, the degree of which was associated with the severity of the expressed autistic features (Hadjikhani et al. 2006). Anterior shifting of the relative position of the superior temporal sulcus within the brain has also been reported (Levitt et al. 2003). A number of VBM studies have reported structural abnormalities of superior temporal sulcal structures – including the STG and MTG – in ASD. These include findings of reduced (Boddaert et al. 2004) as well as increased STS grey matter (Waiter et al. 2004), reduced (McAlonan et al. 2005) as well as increased STG grey matter (Waiter et al. 2004), reduced (Brieber et al. 2007) as well as increased MTG grey matter (Abell et al. 1999), increased STG white matter (Spencer et al. 2006) and reduced MTG white matter (Waiter et al. 2005). Wernicke’s area is a poorly defined region located at the posterior end of the superior temporal gyrus which is involved in receptive language functions. Some studies have identified a change to the asymmetry of the structures which make up Wernicke’s area; however, conflicting findings as to the direction of this change are reported (Herbert et al. 2002; Rojas et al. 2002; 2005).

Parietal sub-regions

One study has reported grey matter deficits occurring in a network of cortical sites, including the medial parietal lobe bilaterally (McAlonan et al. 2005).
Increased grey matter within the left inferior parietal of individuals with ASD as compared to controls has been described (Brieber et al. 2007), in common with similar findings in individuals with attention deficit hyperactivity disorder (ADHD) as compared to controls as reported within the same study.

Occipital sub-regions

Two VBM studies of brain structure in ASD report conflicting findings of decreased (Abell et al. 1999) as opposed to increased (Waiter et al. 2004) grey matter density in the region of the left inferior occipital lobe and occipito-temporal junction. It may be that age-related effects account for this apparent difference, as participants in the study showing reduced grey matter density were a mean of approximately 12 years older than those in whom increased grey matter density was found.

Cerebral cortical folding

Anterior and superior shifting of a number of major frontal and temporal lobe sulci has been reported which authors have interpreted as representing an immature pattern of cortical development (Levitt et al. 2003). Another study found an increase in the depth of the frontal operculum in higher IQ individuals with autism, parietal operculum in those with lower IQ and intraparietal sulcus in those with Asperger syndrome (Nordahl et al. 2007). In addition, the depth of the intraparietal sulcus was positively correlated with the degree of repetitive behaviours in those with Asperger syndrome. A further study reported an increase in the left prefrontal gyrification index (i.e. greater cortical folding) in children and adolescents with autism relative to normal controls (Hardan et al. 2004). The same relationship was not seen in adults. Differences were also seen in the relationship between gyrification index and age with a negative association occurring in the controls but not in participants with autism, a finding consistent with the idea that the autistic brain continues to develop differently post-natally.

3.5.3 Subcortical regions

Amygdala and other medial temporal lobe findings

The amygdala is a collection of nuclei which lies in the medial temporal lobe, sitting just anterior to the hippocampus. It is known to play an important role in social cognition including the mediation of fear and arousal and the attribution of emotional valence to stimuli. There is evidence from functional neuroimaging studies that amygdala function is disturbed in individuals with autism, particularly with respect to emotion processing (Ashwin et al. 2007; Dalton et al. 2005; Pinkham et al. 2008; Williams et al. 2006).
Table 3.1 Region of interest studies comparing amygdala volume between individuals with ASD and controls

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Diagnoses</th>
<th>ASD participants</th>
<th>Controls</th>
<th>Findings in ASD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (M:F)</td>
<td>Age</td>
<td>IQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sparks et al. (2002)</strong></td>
<td>Autism</td>
<td>29 (26:3)</td>
<td>3.9</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PDD-NOS</td>
<td>16 (12:4)</td>
<td>4.1</td>
<td>–</td>
</tr>
<tr>
<td><strong>Schumann et al. (2004)</strong></td>
<td>LFA</td>
<td>18 (18:0)</td>
<td>13.1</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>HFA</td>
<td>21 (21:0)</td>
<td>12.7</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>Asp</td>
<td>24 (24:0)</td>
<td>13.0</td>
<td>106</td>
</tr>
<tr>
<td><strong>Nacewicz et al. (2006)</strong></td>
<td>Autism / Asp / PDD-NOS</td>
<td>16 (16:0), comprising 11 autism and 5 Asp/</td>
<td>14.3</td>
<td>97</td>
</tr>
<tr>
<td>Study ii*</td>
<td></td>
<td>PDD-NOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nacewicz (2006) Study i</strong>*</td>
<td>Autism</td>
<td>12 (12:0)</td>
<td>16.8</td>
<td>–</td>
</tr>
<tr>
<td><strong>Aylward et al. (1999)</strong></td>
<td>Autism</td>
<td>14 (14:0)</td>
<td>20.5</td>
<td>106</td>
</tr>
<tr>
<td><strong>Boucher et al. (2005)</strong></td>
<td>Autism</td>
<td>10 (10:0)</td>
<td>23.9</td>
<td>–</td>
</tr>
<tr>
<td><strong>Haznedar et al. (2000)</strong></td>
<td>Autism</td>
<td>17 (15:2)</td>
<td>27.7</td>
<td>55–125</td>
</tr>
<tr>
<td><strong>Pierce et al. (2001)</strong></td>
<td>Autism</td>
<td>7 (7:0)</td>
<td>29.5</td>
<td>84</td>
</tr>
<tr>
<td><strong>Rojas et al. (2004)</strong></td>
<td>Autism</td>
<td>15 (13:2)</td>
<td>30.3</td>
<td>98</td>
</tr>
</tbody>
</table>

Age and IQ given as means.
PDD-NOS – pervasive developmental disorder not otherwise specified; LFA – low functioning autism; HFA – high functioning autism; Asp – Asperger syndrome.
* Presented in the same paper.
–, data not provided.
As with structural neuroimaging findings for whole brain volume there is evidence to suggest that amygdala development may proceed differently in people with autism than it does in those with typical development. ROI findings concerning amygdala volume are summarised in Table 3.1.

The findings of most studies suggest that larger amygdalae are confined to younger people with autism, with older individuals showing no difference or even a reduction in volume as compared to controls (Schumann et al. 2004; Stanfield et al. 2008). Increased grey matter density in medial temporal lobe structures including the amygdala and the hippocampus may be associated with more severe parentally rated autistic symptomatology in children with ASD (Salmond et al. 2005). Early amygdala damage has been found to be associated with difficulties in aspects of social cognition whereas later damage has not (Shaw et al. 2004), suggesting that this early amygdala overgrowth may be important in the development of ASD. Furthermore, amygdala enlargement in young children has been reported to be correlated with impairments in social interaction (Schumann et al. 2009) and joint attention (Mosconi et al. 2009). It has been proposed that an enlarged amygdala in early life in people with ASD leads to chronic feelings of fear and a heightened stress response, which in turn cause damage to the amygdala and a subsequent reduction in size (Schumann and Amaral, 2006). The association between amygdala enlargement and anxiety in children with ASD (Juranek et al. 2006) adds weight to this hypothesis. In addition to demonstrating reduced amygdala volume in older but not younger children as compared to controls, Nacewicz and colleagues (2006) demonstrated correlations between reductions in amygdala volume and increased gaze avoidance and greater social impairment as measured by ADI-R subdomains. Related evidence for a central role of the amygdala in ASD comes from a gaze-tracking fMRI study which found that activation of the amygdala during face-processing tasks in ASD was strongly correlated with the time that the participant spent fixating the eye-regions of the stimuli (Dalton et al. 2005). This finding requires replication but nonetheless suggests that eye-fixation in ASD is highly emotionally salient and possibly aversive and that this may contribute to the impairment in eye contact frequently observed in ASD. Another potential link between amygdala structure and behavioural impairments in autism is suggested by a recent case report which documented a lack of inter-personal distance awareness in an individual with bilateral amygdala damage (Kennedy et al. 2009), which is particularly interesting given the fact that individuals with ASD often appear to display impaired judgement and/or modulation of inter-personal space.

Primarily involved in memory, the hippocampus has been variously shown to be enlarged, reduced or not different in size in ASD. However, in contrast to the amygdala, no significant effect of age has been found on the results and when the existing ROI studies were combined using meta-analytical techniques, no
## Table 3.2 Region of interest studies comparing corpus callosum size between individuals with ASD and controls

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Diagnoses</th>
<th>ASD participants</th>
<th>Controls</th>
<th>Findings in ASD group</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>N (M:F)</td>
<td>Age</td>
<td>IQ</td>
</tr>
<tr>
<td>Boger-Megiddo et al. (2006)</td>
<td>Autism/PDD-NOS</td>
<td>29 (26:3)</td>
<td>3.9</td>
<td>–</td>
</tr>
<tr>
<td>Vidal et al. (2006)</td>
<td>Autism</td>
<td>24 (24:0)</td>
<td>10.0</td>
<td>96</td>
</tr>
<tr>
<td>Elia et al. (2000)</td>
<td>Autism</td>
<td>22 (22:0)</td>
<td>10.9</td>
<td>‘Mental age’ 1.7 years</td>
</tr>
<tr>
<td>Gaffney et al. (1987a)</td>
<td>Autism</td>
<td>13 (10:3)</td>
<td>11.3</td>
<td>84.9</td>
</tr>
<tr>
<td>Manes et al. (1999)</td>
<td>Autism</td>
<td>27 (22:5)</td>
<td>14.3</td>
<td>‘Mental age’ 4.6 years</td>
</tr>
<tr>
<td>Kilian et al. (2008)</td>
<td>NC autism/MC autism</td>
<td>28 (28:0)</td>
<td>14.6</td>
<td>97</td>
</tr>
<tr>
<td>Egaas et al. (1995)</td>
<td>Autism</td>
<td>51 (45:6)</td>
<td>15.5</td>
<td>–</td>
</tr>
<tr>
<td>Piven et al. (1997)</td>
<td>Autism</td>
<td>35 (26:9)</td>
<td>18.0</td>
<td>91</td>
</tr>
<tr>
<td>Hardan et al. (2000)</td>
<td>Autism</td>
<td>22 (22:0)</td>
<td>22.4</td>
<td>100</td>
</tr>
<tr>
<td>Hardan et al. (2009b)</td>
<td>Autism/PDD-NOS</td>
<td>22 (22:0)</td>
<td>10.7</td>
<td>95.1</td>
</tr>
</tbody>
</table>

Age and IQ given as means.
PDD-NOS – pervasive developmental disorder not otherwise specified; NC – normocephalic; MC – macrocephalic.
–, data not provided.
significant difference in hippocampal volume was identified between people with autism and controls (Stanfield et al. 2008). VBM studies have reported increased grey matter volume in the hippocampus in individuals with ASD (Rojas et al. 2006), and these differences may be related to increased autistic symptomatology (Salmond et al. 2005).

In contrast to the interest in the amygdala and hippocampus the parahippocampal gyrus has been considered in only one ROI study of 10 participants and has been found to be reduced in volume (Boucher et al. 2005). This finding gains support from VBM studies which have identified reduced grey matter volume in this structure (Ke et al. 2008). However, such results require replication before they can be considered to be reliable.

Corpus callosum findings

The corpus callosum (see Figures 3.1 and 3.2) is the largest white matter tract in the human brain and serves interhemispheric communication between homologous cortical areas. Its fibres are mainly myelinated and are topographically organised such that the different sub-regions contain axons from different areas of the cortex (Witelson, 1989). Reductions in the size of the corpus callosum may therefore represent a specific reduction in interhemispheric connectivity, a more generalised reduction in the size of the cerebral areas from which the fibres originate and/or reductions in the degree of myelination of the callosal axons.

ROI studies, summarised in Table 3.2, have consistently found the total corpus callosum to be reduced in cross-sectional area in autism (Stanfield et al. 2008), although whether these reductions are confined to specific callosal sub-regions is less clear (Egaas et al. 1995; Manes et al. 1999; Piven et al. 1997; Vidal et al. 2006). Using VBM Chung and colleagues (Chung et al. 2004) found reduced white matter concentration in both the anterior and posterior callosum, while Waiter and colleagues (Waiter et al. 2005) found white matter volume deficits in similar areas. Recent studies have demonstrated associations between corpus callosum volume reductions and social impairments, repetitive behaviours, sensory deficits and impaired performance on executive function tasks (Hardan et al. 2009b; Keary et al. 2009).

Thalamus findings

The thalamus is widely recognised as a key structure in many neural pathways and is of particular relevance to the study of autistic features, given its central role in information processing within the brain. There are a number of recent reports of reduced thalamic volume in individuals with ASD, including VBM findings of reduced grey matter (Spencer et al. 2006; Waiter et al. 2004) as
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Diagnoses</th>
<th>ASD participants</th>
<th>Controls</th>
<th>Findings in ASD group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aylward et al. (1999)</td>
<td>Autism</td>
<td>11 (11:0)</td>
<td>29 (19:6)</td>
<td>32</td>
</tr>
<tr>
<td>Hardan et al. (2003)</td>
<td>Autism</td>
<td>40 (38:2)</td>
<td>19.3 (39:1)</td>
<td>18.6 (39:2)</td>
</tr>
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<td>Hollander et al. (2005)</td>
<td>Autism/Asp/PDD-NOS</td>
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<td>28.4 (15:2)</td>
<td>29.4 (15:2)</td>
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<tr>
<td>McAlonan et al. (2002)</td>
<td>Asp</td>
<td>21 (19:2)</td>
<td>32 (22:2)</td>
<td>33 (22:2)</td>
</tr>
<tr>
<td>Sears et al. (1999) Study i*</td>
<td>Autism</td>
<td>35 (26:9)</td>
<td>18.0 (20:16)</td>
<td>20.2 (20:16)</td>
</tr>
<tr>
<td>Haznedar et al. (2006)</td>
<td>Autism/Asp</td>
<td>17 (15:2)</td>
<td>27.7 (15:2)</td>
<td>28.8 (15:2)</td>
</tr>
<tr>
<td>Langen et al. (2007) Study i**</td>
<td>Autism/Asp</td>
<td>21 (21:0)</td>
<td>11.1 (21:0)</td>
<td>10.4 (21:0)</td>
</tr>
<tr>
<td>Langen (2007) Study ii**</td>
<td>Autism/Asp</td>
<td>21 (19:2)</td>
<td>20.1 (20:1)</td>
<td>17.3 (20:1)</td>
</tr>
</tbody>
</table>

Age and IQ given as means.

PDD-NOS – pervasive developmental disorder not otherwise specified; Asp – Asperger syndrome.

*,**Presented in the same paper.

–, data not provided.
illustrated in Figure 3.3, and reduced thalamic volume using manual tracing techniques (Tsatsanis et al. 2003).

Several studies have identified a lack of the normal positive relationship between brain size and thalamus volume in ASD (Hardan et al. 2006a; Hardan et al. 2008; Tsatsanis et al. 2003), suggesting that the increase in cortical volume in ASD may not be paralleled by an increase in cortico-subcortical connectivity, as would be expected in typically developing individuals.

**Basal ganglia findings**

There is a general consensus that the caudate is increased in volume in people with ASD (Brambilla et al. 2003; Stanfield et al. 2008) and findings are summarised in Table 3.3.

As mentioned earlier, the caudate and the orbitofrontal cortex are richly connected and enlargements of both have been found to be positively associated with the degree of restricted and repetitive behaviours in ASD (Hardan et al. 2006b; Hollander et al. 2005; Rojas et al. 2006) suggesting that an abnormality in the structure of this circuit may underlie the development of such behaviours. This is reminiscent of the fronto-striatal dysfunction reported to occur in obsessive-compulsive disorder (van den Heuvel et al. 2005). It should be noted that Rojas and colleagues (Rojas et al. 2006) also reported that caudate size was positively related to the degree of social impairment and communication indicating that the effects of its dysfunction may not be confined solely to repetitive patterns of behaviour.

Results for other sub-regions of the basal ganglia are less consistent – with one study (Hollander et al. 2005) but not others (Hardan et al. 2003; Herbert et al. 2003) reporting an increase in putamen volume.

3.5.4  **Cerebellar findings**

The contribution of the cerebellum to non-motor processes has been increasingly recognised in recent years. The cerebellum is extensively connected to many non-motor areas of the brain and a detailed characterisation of cognitive features in patients with cerebellar lesions reported a range of deficits including impaired executive function, impaired visual–spatial memory and language impairments. These effects appeared to amount to ‘a general lowering of intellectual function’ (Schmahmann and Sherman, 1998).

Post-mortem studies of the cerebellum have consistently identified a loss of Purkinje cells in the cerebellar hemispheres in autism (Bauman and Kemper, 2005) and a reduction in the midsagittal area of the neocerebellar vermis was one of the first quantitative neuroanatomical abnormalities reported in ASD (Courchesne et al. 1988). This finding has been replicated (Hashimoto et al. 1995), however, it has been argued that vermal reductions may reflect differences in IQ between
cases and controls as opposed to being associated with autism per se. Investigations of cerebellar vermis volume in ASD have revealed often conflicting findings and opposing directions of volume changes in different lobule areas within the vermis. However, combining existing reported findings together suggests that younger individuals with ASD show reductions in the cerebellar vermis which are not seen in older individuals (Stanfield et al. 2008), a pattern opposite in direction to that suggested for the whole brain. Although this may seem paradoxical it is consistent with the finding that the frontal lobe and the neocerebellar vermis show a reciprocal relationship with respect to size (Carper and Courchesne, 2000). In contrast to the vermis, studies of the cerebellar hemispheres tend to show an increase in volume, despite the post-mortem evidence of reduced cell number; whether it shows the same pattern of growth that is suggested for the whole brain volume is unknown (Hardan et al. 2001a; Herbert et al. 2003; Sparks et al. 2002).

Unsurprisingly, the cerebellum is an area within which structural abnormalities have been reported in a number of VBM studies of ASD. Several studies report increased grey matter within the cerebellum (Abell et al. 1999) and some studies also report reductions in grey matter (McAlonan et al. 2002; Rojas et al. 2006) and reductions in cerebellar white matter volume (Boddaert et al. 2004; McAlonan et al. 2005). It has furthermore been reported that reduced cerebellar grey matter volume is associated with increased repetitive and stereotyped behaviours in autism (Rojas et al. 2006). There is evidence that grey matter volume in the cerebellum may be differentially affected in ASD according to the level of intellectual functioning. Salmond and colleagues (Salmond et al. 2007) found that while individuals with ASD of below average intellectual functioning demonstrated reduced cerebellar grey matter density, increased grey matter density was evident in those of higher intellectual functioning.

These cerebellar findings are consistent with reports within the functional MRI literature which document differences in cerebellar function in individuals with autism during motor (Allen and Courchesne, 2003; Allen et al. 2004) and emotion processing tasks (Critchley et al. 2000).

3.5.5  Brainstem findings

The brainstem is made up primarily of three regions: the medulla, pons and midbrain. Although these brain regions received significant early interest they have been little considered in recent neuroimaging studies of ASD. Reductions in the size of these regions have been found in some studies, although these mainly concerned cross-sectional areas and findings are heterogeneous (Stanfield et al. 2008) and therefore ought to be interpreted with caution. Findings of one recent study suggest that reductions in total brainstem grey matter are correlated with greater oral sensory symptom severity in children with ASD (Jou et al. 2009),
possibly reflecting the sensory involvement of brainstem structures such as the nuclei of the vagus nerve, the innervations of which are widespread and include the palate, pharynx and larynx.

### 3.6 Diffusion tensor imaging studies

Recent years have seen a considerable expansion in the investigation of white matter structure and connectivity in ASD using DTI. Findings to date suggest that this technique holds promise in identifying disrupted connectivity between brain areas subserving cognitive domains that are particularly central to the ASD phenotype, and in demonstrating correlations between DTI findings and clinical symptomatology.

The DTI investigation of structural connectivity between areas subserving social intelligence finds reports of reduced fractional anisotropy (FA) in the proximity of the superior temporal sulcus, temporal stem and amygdala (Barnea-Goraly et al. 2004; Lee et al. 2007), as well differences in limbic tract volume in ASD as compared to controls (Pugliese et al. 2009). Furthermore, Conturo and colleagues (Conturo et al. 2008) identified reduced diffusivity in the right hippocampal-fusiform pathway and demonstrated that this abnormality was related to important behavioural measures – namely impaired face recognition and block design object processing.

A number of studies have investigated the relationship between altered connectivity in ASD and the severity of clinical symptoms – such as repetitive behaviours and social impairment – as measured by the ADI-R. In this way it has been reported that higher ADI-R ratings of repetitive behaviours are associated with reduced FA in the right anterior cingulate cortex (Thakkar et al. 2008) as well as a range of more posterior brain regions including the splenium of the corpus callosum, the temporo-parietal lobe and the cerebellum (Cheung et al. 2009). ADI-R ratings of impaired social interaction have been related to reduced FA in the left superior cerebellar peduncle (Catani et al. 2008), which the authors hypothesised as possibly reflecting impaired feedback from the cerebellum and hence a reduction in the ability of such inputs from the cerebellum to modify social behaviour. This finding is concordant with other reports of reduced FA in the left superior cerebellar peduncle in ASD (Brito et al. 2009). Impaired social interaction and abnormalities in communication, as measured by the ADI-R, have also been related to reduced FA within fronto-striatal and posterior corpus callosal regions (Cheung et al. 2009).

Studies have reported reduced FA in the region of the corpus callosum (Alexander et al. 2007; Brito et al. 2009; Keller et al. 2007), with these findings being related to reduced cognitive performance on measures of performance IQ. Further studies have reported abnormal frontal fibre connectivity (Sundaram et al. 2008; Sahyoun et al. 2010), as well as suggesting abnormal trajectories of white matter
maturation in young children with ASD – particularly within left frontal regions – comprising accelerated age-related increases in FA (Ben-Bashat et al. 2007).

This structural evidence for dysconnectivity in ASD finds further support from functional imaging studies which have identified a mixture of under- and over-connectivity between brain regions in ASD – such as the finding of reduced functional connectivity between the fusiform gyrus and frontal regions during face-processing tasks (Koshino et al. 2008). Functional dysconnectivity involving the fusiform gyrus in terms of reduced connectivity with the left amygdala and increased connectivity with the right inferior frontal gyrus during face-processing tasks has also been reported to be correlated with greater degrees of social impairment (Kleinhans et al. 2008).

3.7 Neuroanatomical findings in females with ASD

There are only two studies to date which have specifically examined the neuroanatomy of women with ASD. Both have found broadly similar findings to those in males (Bloss and Courchesne, 2007; Craig et al. 2007); however, Bloss and Courchesne identified more extensive temporal and cerebellar abnormalities in the female group, suggesting that a greater degree of disruption to brain structure may be associated with the expression of ASD in women than in men. If replicated, these findings may represent a neuroanatomical reflection of the hypothesis that females with autism are affected by a greater degree of ‘genetic loading’ than males with autism (Tsai et al. 1981; Tsai and Beisler, 1983).

There is an established gender related dimorphism of brain structure and development in typically developing individuals (Allen et al. 2003; Giedd, 2004; Giedd et al. 1999; Goldstein et al. 2001; Gur et al. 1999; Haier et al. 2005; Im et al. 2006; Nopoulos et al. 2000), therefore it is important that future studies examine further the effects of gender on brain structure in groups with ASD. Given the proposal that autism may represent an extreme form of male intelligence (Asperger, 1944; Baron-Cohen et al. 2005) the identification of gender specific brain structural differences in individuals with ASD may well provide information regarding important aetiological and pathogenetic processes across the autism spectrum.

3.8 ‘Low-functioning’ autism, ‘high-functioning’ autism, Asperger syndrome and non-specific pervasive developmental disorders

Until this point no distinction has been made between the disorders which are considered to make up the autism spectrum. In the main this is reflective of the original research in which disorders from across the spectrum are often combined as a uniform group. Given that even distinguishing between individuals
with ASD and unaffected individuals can at times be difficult, and that there is likely to be significant heterogeneity even within each diagnostic category, the validity of defining different components of the autism spectrum is unclear. The boundary between autism and Asperger syndrome can be clinically difficult to establish and the place of non-specific pervasive developmental disorders (PDD-NOS) on the spectrum is even less clear. Finally, as alluded to earlier, the picture is further complicated by the issue of IQ, with some groups distinguishing ‘low’- and ‘high’-functioning autism on the basis of the generally held IQ cut-off for intellectual disability (i.e. IQ less than 70). Although several groups, as described below, have attempted to address these difficulties in classification using structural neuroimaging, more research is required before any firm conclusions can be drawn.

One group has published a series of studies examining a population of children and adolescent males with either ‘low-functioning’ autism (LFA), ‘high-functioning’ autism (HFA) or Asperger syndrome. The LFA and HFA groups were found to have significantly more cortical grey matter than controls, with individuals with Asperger syndrome showing non-significant enlargements relative to controls (Lotspeich et al. 2004). In addition, the relationship between performance IQ and cortical grey matter volume was found to differ significantly between the HFA and the Asperger syndrome groups (Lotspeich et al. 2004). A similar pattern was also found for hippocampal volumes across the whole age range of this group, whereas for the amygdala it was only seen in the younger participants (Schumann et al. 2004). The LFA, HFA and Asperger syndrome groups were also found to show differences in sulcal depth compared to controls; notably these differences were not seen in the same sulci. Finally, VBM was used in a subset of these participants to compare individuals with HFA and Asperger syndrome with the former showing greater grey matter density in the cingulate gyrus compared to the latter (Kwon et al. 2004).

Other groups have compared brain structure between the different components of the autism spectrum disorders and have also identified similarities and differences between such groups. Sparks and colleagues (Sparks et al. 2002) found that the amygdala was enlarged in young children with autism as compared to those with PDD-NOS, but did not identify any difference in cerebral, cerebellar or hippocampal volumes – results which partially replicate but generally contrast with those described above. Salmond and colleagues (2007) compared LFA and HFA using VBM and found that while both groups shared differences in parts of the cerebellum, fusiform gyrus and frontal cortex as compared to controls, when they were directly compared to each other they demonstrated differences in other parts of the cerebellum, dorsolateral prefrontal cortex and post-central gyrus.
3.9 Conclusions and future directions

Perhaps the most striking feature of the ASD neuroimaging literature is the heterogeneity of the findings to date (Stanfield et al. 2008). As discussed earlier, there are a number of factors inherent to ASD that are likely to lead to this variability including the descriptive nature of the diagnosis, the co-morbidity with intellectual disability and with other neurological disorders and possible gender related differences in brain structure. In addition, some studies have examined relatively small populations thus also tending to increase the heterogeneity of findings. Future studies should deal with these difficulties through the examination of large populations, probably recruited through multi-centre collaborations (Belmonte et al. 2008). The UK Medical Research Council Autism Imaging Multi-Centre Study (MRC-AIMS) – involving the Institute of Psychiatry, London and the Universities of Cambridge and Oxford – is the first UK multi-centre imaging collaboration in autism research and is currently underway. Such multi-centre collaborations will be increasingly important in the future, particularly with the advent of imaging genetics and consequently the greater importance of large sample sizes. The use of tightly defined clinical cohorts will also help to reduce heterogeneity, facilitate comparisons between studies and allow for the accurate examination of the structural underpinnings of specific autistic traits. This approach may be particularly fruitful given recent suggestions that the features which make up the autistic triad may not be as tightly associated as was originally thought (Happé et al. 2006). Studies which directly compare the different conditions which make up the autism spectrum are also required as are studies to determine the boundaries of the spectrum in relation to other related conditions. In addition, further studies of females with ASD and of individuals with ASD and low IQ are required so that the literature becomes more representative of the generality of the autistic population. The selection of an appropriate control group for the study of individuals with ASD and low IQ is imperative. Perhaps the closest to a ‘perfect’ situation will be the concurrent use of two control groups – one matched to the main subject group for IQ and one containing typically developing individuals.

Most groups exclude individuals with a history of epilepsy or cerebral palsy and, in view of the difficulties in the interpretation of imaging findings (highlighted above) raised by these potential confounding factors, this exclusion seems justified. The decision as to whether to exclude participants with other co-morbid conditions such as attention deficit hyperactivity disorder (ADHD) – which one study employing structured assessments within a population-derived sample found to occur in 28% of participants with ASD (Simonoff et al. 2008) – is more difficult. On the one hand structural brain abnormalities are well documented in ADHD (Castellanos et al. 2002; Sowell et al. 2003) – hence the potential role of ADHD
as a confounding factor in neuroimaging studies. However, the suggestion that shared biological pathways may exist between autistic and ADHD traits (Ronald et al. 2010) would support a view that participants with co-morbid ADHD and ASD should be studied in order to elucidate potentially important pathways in the aetiology of ASD. The issue of the composition of participant groups with respect to co-morbidity is a challenging one and ought to be the subject of continuing debate.

Bearing in mind these difficulties, there are a number of themes that can be drawn from the existing structural neuroimaging literature on ASD. Increasingly the evidence points to the presence of structural abnormalities in areas of the social brain including the amygdala, superior temporal sulcus, fusiform face area and the orbitofrontal cortex. Structural change to the caudate nucleus has also been consistently identified and may be related to the development of the characteristic patterns of restricted and repetitive behaviours seen in ASD, possibly through its relationship with the orbitofrontal cortex. In addition to the differences identified within specific brain regions, the findings from recent DTI studies suggest that the effects of aberrant connectivity between distributed areas of the brain are also likely to be important. Finally, although the evidence at present comes overwhelmingly from cross-sectional studies, there is an increasing consensus that individuals with ASD show differences in longitudinal brain development compared to those which occur in typically developing individuals.

In addition to addressing the difficulties mentioned above, future studies of ASD should aim to confirm and build upon existing findings. It is clear that longitudinal studies, some of which are already underway (Hazlett et al. 2005), are needed to either confirm or refute the suggestion that individuals with ASD show a different developmental trajectory to typically developing individuals. A longitudinal neuroimaging study of very young infants at high risk of developing ASD could be of particular benefit. Such studies are likely to be ethically and practically difficult; however, given their success in the examination of other conditions (Johnstone et al. 2005; Pantelis et al. 2003), they could prove to play a key role in unravelling the pathophysiological processes which lead to the development of ASD.

Furthermore, attempts to link brain structure to proposed aetiological factors are required. As new putative risk factors for ASD are identified through genomic techniques such as whole genome analysis for the detection of single nucleotide polymorphisms and copy number variations, neuroanatomical data will continue to be central to assessing the aetiological significance of these genetic factors. The search for specific gene-to-structure associates holds great promise of yielding new insight into the aetiology of ASD, including risk factors associated with the condition and the neuroanatomical associates of possible endophenotypes and extended phenotypes of ASD.
Finally, although recent years have brought significant technological advances, there remain limitations to the inferences that can be drawn from neuroimaging data. While it is possible to say that a structure differs in size, shape or density, one can often only speculate as to the actual changes to brain microstructure which underlie these differences. The development of DTI is a welcome step towards the *in vivo* determination of underlying microstructural abnormalities; however, the technology must advance considerably before it will allow firm conclusions to be drawn based upon neuroimaging findings alone. There is no prospect at present that technical advances in imaging will provide definition at a cellular level in the living subject. It is perhaps instructive to bear in mind that even with the promise that modern imaging technology has brought to the study of ASD, we must still turn to post-mortem tissue examination to establish the cellular and molecular basis of structural changes identified using brain imaging techniques.

### 3.10 Final remarks

The use of magnetic resonance imaging has led to significant advances in the understanding of the brain anatomy which underlies ASD. The prospect of future discoveries, relating to methodological and technological advances, makes this an exciting area of study to be involved in from a scientific perspective. At the last, however, it is important to remember why this research is conducted – for the benefit of affected individuals and their families. A greater understanding of the brain structures which underlie neurodevelopmental conditions such as ASD is vital in order to enable the focused study of their neurobiological underpinnings, and is therefore likely to form an important part of the journey towards eventually making real and measurable differences to the lives of individuals affected by these disorders.

### 3.11 Acknowledgements

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### 3.12 References


Researching the Autism Spectrum


Brain imaging and the neuroanatomical correlates of autism


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Magnetoencephalography (MEG) as a tool to investigate the neurophysiology of autism

SVEN BRAINTIGAM, STEPHEN SWITHENBY AND ANTHONY BAILEY

This chapter introduces a modern functional neuroimaging method, magnetoencephalography (MEG), and addresses how this technique is being applied to study dynamic brain activity and neural processing in autism. An outline will be given of relevant technical and analytical approaches, before discussing functional systems and presenting important findings associated with autism, using MEG. The focus is directed at aspects of neural processing that are affected in individuals on the autism spectrum, including auditory processing, semantic processing, face processing and theory-of-mind (progressed through study of imitation-related processes linked to activity within the ‘mirror neuron’ system). While MEG is a relatively new tool, the studies available to date lend some support to the notion that autism involves altered cognitive strategies as opposed to cognitive impairments or deficits. In addition, the research on this subject is reviewed, which suggests that MEG may help define and further characterise subclinical epilepsy and epileptiform activity (seizures) in individuals with autism spectrum disorders.

4.1 Instrumentation and measurements

Magnetoencephalography (MEG) is one of a range of functional neuroimaging methods that may be applied to the study of autism. It is of interest because it allows changes in activity to be followed dynamically with millisecond resolution, and thus provides direct information on the evolution of processing along neural pathways.
By far the most common method of imaging brain activity is functional magnetic resonance imaging (fMRI). At the heart of this technique is the weak dependence of the magnetic resonance signal on the oxygenation level of the blood, which in turn depends on brain activity. fMRI is capable of providing millimetre-scale functional images of the level of activity in the brain but with time resolution limited to the rate at which the oxygenation level changes, i.e. of the order of seconds. The technique has been used extensively to study autism (see Seyfert and Castellanos, 2005 and Sanders et al. 2008 for general reviews). Functional neuroimaging of face processing in autism is addressed by Dekowska et al. (2008) and Jemel et al. (2006). Issues concerning autism specificity (of putative impairments) are discussed by these authors. Semantic processing has been addressed by Wang et al. (2006) with a particular emphasis on abnormal laterality of activation in autism. These references should be regarded as entry points to the literature, as a more complete discussion of fMRI and imaging techniques other than MEG in the context of autism research is beyond the scope of the present chapter.

MEG is based on the detection of magnetic fields that are generated by currents flowing in neurons. MEG is preferentially sensitive to magnetic fields generated in the cerebral cortex, but modern, whole-head systems employing multiple sensor configurations can detect activity in sub-cortical regions. Typically, neural field changes are extremely small – ranging from $\sim 10^{-12}$ T (T: tesla) during interictal epileptic spikes to $\sim 10^{-14}$ T or less for evoked fields. By comparison, the Earth’s magnetic field is about $10^{-4}$ T, urban noise is about $10^{-7}$ T and a typical fMRI scanner operates at 1.5 T. Thus the Earth’s field, albeit small by technical standards, is some 10 billion times stronger than a brain response. The only practical individual detectors capable of recording such small field changes are superconducting loops that are coupled into Superconducting Quantum Interference Devices that respond to the changes in magnetic flux through the loops (Hämäläinen et al. 1993; Vrba, 1999). A loop may be configured as a small simple planar coil, in which case the detector measures the magnetic field perpendicular to the plane, or as a more complex shape such as a figure of eight, in which case the detector measures the magnetic field gradient. It would be more accurate to state these sensitivities in terms of magnetic flux but the distinction is not important within the context of this discussion.

A typical MEG imaging system has several hundred sensors (or measurement channels) surrounding a head-shaped recess in a liquid helium filled dewar (Figure 4.1). Typically the head to detector distance is 2–3 cm. The whole instrument is housed in a magnetically screened room that is required to reduce the ambient magnetic field noise, which may be as high as $\sim 10^{-7}$ T. The best instruments achieve noise levels approaching $10^{-15}$ T per square root of the bandwidth over which the signals are recorded, easily sufficient to detect the signals from the brain.
There are some subtleties associated with the sources that are detected in MEG. Externally detectable field changes require large numbers (≥ a few thousand) of neighbouring cells to carry aligned currents of suitable strength and duration to allow for spatial and temporal integration. It is generally assumed that these conditions are met through post-synaptic currents rather than currents associated with action potentials. Modelling the sources underlying MEG signals (‘source localisation’; see also next section) necessitates not only assumptions to be made about geometry and electrical properties of the source space (brain/head) but also about the potential source configurations. Information extracted from other brain
imaging techniques can inform source models, where, perhaps most commonly, structural MR information is used to define and restrict source volumes. Often, a spherical conductor is assumed restricting the MEG analysis to tangential sources, the strongest of which are typically currents flowing along pyramidal cells within cortical sulci (Hämäläinen et al. 1993). Although technically demanding, MEG has some significant advantages. It is a passive measurement that is completely non-invasive and makes very few demands on the subject. The instrument is silent in its operation. The MEG detector simply records the brain activity continuously as the subject carries out whatever task the investigator requires. Longitudinal studies are ethically possible and acceptable to subjects. Finally and most importantly, the detectors are sensitive to field changes occurring over timescales of milliseconds to seconds, thus complementing fMRI which is sensitive to longer term changes.

4.2 Analytical approaches

The primary outputs provided by any magnetoencephalographic scanner are readings of the variation in time of the magnetic fields (or their spatial gradients) produced by electrical activity in the brain and detected over defined positions on the head. It is these ‘raw’ signals which are pre-processed, analysed in various ways, correlated with experimental conditions and, possibly, with findings obtained from other imaging modalities and, ultimately, are interpreted within the framework of a given scientific investigation. Ever since the inception of MEG, a plethora of analytical techniques to extract information from the signals has been developed. New methods often emerge at a staggering rate. The analytical approaches range from straightforward topographical maps of signals to complex source estimation procedures typically involving anatomical information as well as sophisticated time-frequency and other abstract state–space representations of the data. The abundance of approaches implies that there is currently an absence of rigorous standard protocols for MEG analysis; however, certain approaches have crystallised that are used fairly consistently across studies. In this short account, three of the most relevant approaches to investigation and analysis will be described. These are not alternatives but well-documented practice for those striving for insight into autism.

The most direct and easily understood approach involves developing protocols that yield event-related fields (ERFs), the direct analogue of the more familiar event-related potentials (ERPs). Event-related approaches are commonly used to analyse electrophysiological data obtained from readings outside the brain itself. Typically, within a chosen experimental setting, a stimulus is presented to a subject repeatedly. The appearance of a stimulus marks a point in time, usually denoted as
stimulus-onset, with respect to which an epoch of data is defined which includes both pre- and post-stimulus intervals. The signal observed in the post-stimulus interval is often assumed to be independent of stimulus repetition but to be contaminated by random noise. This assumption may have limited validity, particularly in studies of higher order function.

Within the assumption of independence against repetition, the neural response can be recovered from the measured signal by averaging the response data (or trials) with respect to stimulus-onset. For random noise, this reduces the noise variance proportionally to the number of stimuli. The resultant waveform is usually called an ERP/ERF or simply an evoked response. Although the process of averaging may be applied at the levels of individual channels of measurement and individual subjects, it may be extended over several subjects to yield grand mean waveforms (Gevins and Remond, 1987). Typically, peaks in the evoked waveforms are correlated with the experimental parameters to map the temporal sequence of neuronal processing stages. The stimulus and subject dependence of the responses allows some insight into their functional significance.

The second approach, often undertaken after an initial ERF analysis, involves source estimation, the identification of the brain areas generating a given signal recorded by EEG or MEG. Such a signal will often be an average evoked response but single trials can be analysed as well. Every source estimation procedure has to face the so-called inverse problem, the mathematical transformation that uses the data as input and outputs the sources of the data. Here there is a problem that is shared with many algorithmic procedures – the inverse problem in MEG is deeply mathematically ambiguous. No matter how many detectors one uses and how high quality the data, there can always be silent currents (sources) in the brain that are not recorded by any of the detectors. These may be neurophysiologically relevant. Moreover, some sources leave only a very weak record – identifying them is difficult. The MEG inverse problem has been researched extensively (see, for example, Lin et al. 2006) and is solved pragmatically by simplifying the description of the sources or by adding additional physiologically reasonable assumptions.

The most basic and, until recently, most commonly used source estimation technique is that of equivalent current dipoles (ECDs). Formally, the use of equivalent current dipoles is equivalent to assuming that the electric and magnetic fields that are measured originate from discrete source regions, the spatial extent of which is small compared with the distances to the detectors. In this approximation, the dipole can be viewed as the spatial average of all source (or impressed) currents within that area. The impressed currents are due to the electromotive forces associated with biological (mainly synaptic) activity in neural tissue (Jackson, 1962; Katila, 1983).
In the last few years, source estimation techniques have developed to embrace distributed images of current sources. These may be generated by several distinct but in many cases related algorithms (Lin et al. 2006). They yield images that are broadly consistent and robust and may, in favourable circumstances, offer meaningful insights into functional anatomy at the centimetre level. Interpretation of such images should include consideration of the nature of the underlying algorithm.

The third investigative approach that will be highlighted is time-frequency analysis. This includes a wide range of mathematical algorithms that analyse neurophysiological signals in terms of oscillations that vary in frequency and time. There is a long history of studying fundamental brain rhythms such as theta (4–7 Hz) or alpha (8–13 Hz) waves that, under certain conditions, can be detected by visual inspection of the data and may indicate general states of the brain, e.g. increased alpha is often seen when subjects close their eyes.

Modern approaches have formalised and extended the analysis of oscillatory activity. In many cases, transient oscillatory brain activity is now considered in conjunction with well-defined stimuli, and is identified as either an evoked oscillatory response appearing at the same latency and phase in each single trial which is detectable in the averaged field, or an induced oscillatory response appearing with a jitter in latency from one trial to another, and therefore not observable in the averaged data (Tallon-Baudry and Bertrand, 1999). Both types of response provide information about brain dynamics beyond the understanding that can be extracted from the traditional evoked response which is broadband in nature, i.e. includes all frequencies. In particular, oscillations at higher frequency (> 20 Hz) in the so-called gamma-band have received much attention in recent years. Experimental data reveal that synchronisation of gamma-band activity is involved in processes such as working memory, perceptual awareness, semantic processing and sensory–motor integration and that synchronisation may be altered in pathological brain states (Uhlhaas and Singer, 2006). Theoretical considerations suggest that synchrony of oscillations is a fundamental property of neural systems. It appears to facilitate the coordinated interactions of large neuronal populations distributed within and across distinct regions of the brain; an interaction deemed necessary for most cognitive processes. The precise mechanisms underlying synchronisation through gamma oscillations are still unknown; however, interneuron networks are believed to play an important role (Bartos et al. 2007; Engel et al. 2001).

4.3 MEG studies of autism spectrum disorders (ASD)

Starting in the late 1990s, magnetoencephalography has been used increasingly as an investigative tool to study the neurophysiological basis of
autism, mirroring a more general trend of intensified usage of neuroimaging technologies in developmental disorders and paediatrics (Paetvu, 2002; Rumsey and Ernst, 2000). Many peer-reviewed papers utilising MEG have been published on cognitive anomalies considered to be characteristic of autism spectrum disorders adding to the established literature involving behavioural tests. To date, essentially all relevant MEG studies have focused on affected, often high-functioning, individuals with ASD. However, the first MEG based investigations of parents of children with autism are beginning to emerge, reflecting an ever-growing interest in the broader phenotype of autism. The remainder of this chapter provides a brief overview of recent findings of studies of autism made using MEG.

4.3.1 Epileptiform activity

The contribution of subclinical epilepsy to autism spectrum and developmental and acquired language disorders is commonly considered as one of the most important issues in developmental neurosciences. This importance derives from the observation that mute or dysfluent children with Landau-Keffler syndrome (LKS; acquired aphasia), autism or developmental language disorders, who show common features in their ability to decode speech, are at higher risk for epilepsy than children with the fluent, albeit aberrant, language of verbal children with autism (Kanner, 2000; Neville, 1999; Rapin, 2006). Although MEG is gaining widespread momentum as a clinical tool for seizure disorders, there appear to be only two MEG studies into epileptiform activity in individuals with autism.

Initially, researchers at the University of Utah studied electrophysiological responses during stage III sleep in 50 children with regressive ASD with onset between 20 and 36 months of age (16 with autism, 34 with PDD-NOS; 15 out of 50 with a clinical seizure disorder) and 6 children with Landau-Kleffner syndrome (5 with complex seizures). The MEG data demonstrated epileptiform activity during slow wave sleep in 82% of the children with ASD independent of the presence or absence of clinically relevant seizures. Using equivalent current dipoles to model abnormal activity, the authors found similar periSylvian generators (foci of electrical discharge) in both groups of patients (Lewine et al. 1999). It is generally agreed that this study has provided evidence that MEG has greater yield than traditional EEG sleep recordings and that this appears to be related to electrical characteristics of epileptiform discharges arising in the Sylvian fissure. However, the study has been strongly criticised on grounds of referral bias, methodological shortcomings and conflating regressive autism and LKS (Kallen, 2001; Neville, 1999).

More recently, a group of researchers at the Universitat Autònoma de Barcelona studied spontaneous neural activity under wakefulness in 36 children with early onset autism spectrum disorders (22 with autism, 9 with Asperger syndrome, and
MEG as a tool to investigate the neurophysiology of autism

5 with PDD-NOS) using MEG. An ECD model was employed to calculate the location of the neural generators underlying epileptiform activity. In about 86% of all children with ASD, the MEG data revealed specific abnormalities in the form of low amplitude monophasic and biphasic spikes as well as acute waves, predominately distributed in the perisylvian areas. A right-lateralisation of epileptiform spikes was only observed in patients with Asperger syndrome (Munoz-Yunta et al. 2008). This study, to some extent, replicates the prior investigation by the Utah group, and provides further evidence that subclinical epilepsy can be detected in many children with ASD. Unfortunately, further conclusions could not be drawn as comparable typically developing children were not investigated.

4.3.2 Auditory processing

Arguably, the dominant approach to understanding the neurobiological basis of language impairment in autism has been the study of abnormalities in low-level, early auditory processing. Many researchers have concentrated on the event-related M100 field in response to simple pure tones. The M100 or its electric counterpart N100 can be viewed as the brain’s first strong response to tones generated in primary auditory cortices and is readily detected by MEG (Roberts and Poeppel, 1996). Note that these components typically peak at around 100 ms after stimulus onset, hence M100 (N100). In the case of electrical (EEG) readings, this peak is negative (N) with respect to reference sites commonly used. For MEG, components are simply prefixed with ‘M’ as magnetic fields are reference free.

Past and present research has included studies of: the frequency dependence of M100 latency; the developmental trajectory of the M100 latency; and the hemispherical asymmetry of the M100 generators. The latency data seem to imply that individuals with autism show a normal pattern of responses in that M100 onset decreases with both tone frequency and age. However, reduced variation with respect to frequency changes and overall longer M100 latency clearly distinguish patients from typically developing controls. Much of this work has been reviewed very recently by researchers at the Children’s Hospital of Philadelphia who are also major contributors to this area of autism research (Roberts et al. 2008). In their view, MEG’s strength lies in examining primary and secondary auditory processes and providing independent electrophysiological markers of autism spectrum disorders.

In line with experiments based on pure tones, a group of researchers at the Neuromagnetic Imaging Center of the University of Colorado have investigated the 40 Hz oscillatory response elicited by simple tones (Wilson et al. 2007). When very short tones (clicks of ≤ 2 ms duration) are presented 40 times a second, the human brain generates a strong steady-state gamma-band response of the same
frequency of 40 Hz as the stimuli. This steady state response activity is thought to be correlated with intra-regional and short-range inter-regional processing, or local connectivity in more general.

Magnetic field data were obtained in 10 boys and male adolescents with autism and 10 male, age-matched typically developing individuals. Both groups listened passively to monaurally presented acoustic trains consisting of short tone pulses and 40 Hz gamma-band power was estimated over the contralateral hemisphere. The main finding was a significantly reduced left hemisphere steady state response in the children with autism. There was no significant inter-hemisphere difference in the control group. The authors noted the unexpected hemispheric asymmetry in their data and interpreted their data as indicating that, in individuals with autism, certain brain areas might be impaired in generating the high frequency oscillations that are likely to be involved in the synchronisation of short-range neural interactions.

The group have followed up on the 40 Hz oscillatory response study by measuring the magnetic field responses of 16 parents of children with autism and comparing the data with responses obtained in 11 adults with autism and 16 typically developing adult controls. This time, the authors analysed the 40 Hz induced and stimulus (phase)-locked oscillations with a standard evoked response paradigm, where subjects passively listened to 1 kHz sinusoidal tones presented for 200 ms repeated every 4 s. Independent of hemisphere, significantly higher induced gamma-power was observed in parents and individuals with autism compared to controls, while evoked gamma power was significantly highest in controls. Hemispheric asymmetry was observed for neuronal generators of the 40 Hz induced oscillations, with equivalent current dipoles (at M100 latency) located more anterior in the right than the left hemisphere. This was true for all three groups, but the asymmetry was strongest (and significant) in control subjects, weaker in parents and almost absent in individuals with ASD (Rojas et al. 2008). As this is effectively the first (MEG) study of its kind, the authors are aware that no strong conclusion can be drawn at present. However, it is reasonable to assert that gamma-band oscillations might be potentially useful endophenotypes for autism, given recent insight into the molecular and synaptic mechanisms underlying the generation of such macroscopic signals.

Turning to more naturalistic sounds, researchers at the University of Tokyo have employed vowel stimuli to elicit a mismatch negativity (MMN) in 9 adults with autism and 19 matched typically developing volunteers. The MMN is an event-related potential or field peaked at 100–200 ms after the onset of a physically deviant auditory stimulus in identical and repeated sequence. The response is commonly considered an index of the neural mechanisms of automatic detection of acoustic change (Näätänen, 2001).
Interestingly, significant group differences were observed in the across-phoneme condition eliciting mismatch negativities in response to deviant (Japanese) vowels /o/ in a sequences of vowels /a/. Compared to controls, the left-hemispherical MMN was significantly delayed in participants with autism and this latency delay was positively correlated with symptom severity (using the childhood autistic rating scale – Tokyo version, CARS-TV). No between-group differences were observed for mismatch negativity responses to tone- or vowel-duration changes (Kasai et al. 2005). This work is broadly consistent with pure tone studies: it provides evidence for delayed processing of change in speech sound.

4.3.3 Semantic processing

It is generally accepted that subtle abnormalities in semantic processing are always present in autism spectrum disorders, although linguistic ability can vary significantly across the spectrum, from severe language impairment to normal or even partially superior language skills. A recurring clinical observation in autism is a deficit in interpreting language in context, and studies of reading suggest that high-functioning children and adults with autism do not use sentence context fully under normal reading conditions (Happé, 1997; Walenski et al. 2006).

Commonly, the electrophysiological correlates of semantic processing in autism have been investigated by studying the N400 event-related potentials, which are robust markers of contextual integration. Although the N400, observed about 400 ms after stimulus onset (negative deflection in EEG; MEG equivalent M400 but often referred to simply as N4 or N400), is strongest in response to semantic violations, it is not simply an index of anomaly, but rather reflects the extent to which an individual word is expected on the basis of word, sentence or larger scale context (Kutas and Federmeier, 2000). Apart from the N400, other context-sensitive evoked responses exist. For example, at longer latency, so-called late positive components (LPCs) are observed at about 700–800 ms after stimulus onset. Such components are thought to reflect the formation of novel semantic representations and associations (Salmon and Pratt, 2002).

The only published MEG study of N400 responses in autism was performed by the authors of this chapter (Braeutigam et al. 2008). This work attempted to map out in detail N400, and stimulus-locked gamma-band neural responses recorded in 11 able adults with autism spectrum disorders (nine individuals had a clinical diagnosis of autism and two a clinical diagnosis of Asperger syndrome) and 11 typically developing controls (matched for age, gender and handedness with comparable but not strictly matched IQ scores) reading meaningful sentences and sentences ending with a semantically incongruous word (e.g. ‘The blankets were in a plate’). The MEG data, which revealed spatially extended evoked N400 and LPC
responses, as well as synchronised gamma-oscillations, provided clear evidence for specific neuronal processes sensitive to sentence context that differed in individuals with autism compared to controls. In particular, the N400 responses following incongruous words were weaker over left temporal cortices, whereas LPC responses to incongruous words and long-latency gamma-oscillations following congruous words were stronger over central and prefrontal regions in individuals with autism compared to the control group. Strikingly, incongruous words elicited long-lasting gamma-oscillations above 40 Hz in the clinical group, but not in typically developing subjects (Figure 4.2). In conclusion, these findings might indicate that appreciation of sentence context in individuals with ASD involves both more and different neural stages. However, it is unclear whether such neuronal stages reflect genuinely anomalous pathways (i.e. pathways that are never utilised in typically developing individuals).

4.3.4 Face processing

Face processing is one of the most active areas of investigation of autism. Those with ASD show clear behavioural differences that are established from infancy, including speed of processing, as well as a range of impairments that are
face linked, e.g. in patterns of eye contact (Dawson et al. 2005). Schultz has made the provocative suggestion that the deficit in face processing may cascade out via perception to generate the social and communicative deficits seen later in those with autism (Schultz, 2005).

During subsequent development, autism is manifest in reduced memory for faces and a deficit in recognizing facially expressed emotion. However, autism is also associated with an enhanced ability to recognise upside down faces and to extract information from some face features compared to typically developing individuals. Such observations underlie the suggestion that people with autism do not process faces as a whole but attend to individual features (Elgar et al. 2002). This is an example of the more general observation that people with autism use different strategies to accomplish familiar and important tasks.

There are many published neuroimaging studies of face processing in both the normal and the autistic population (Dekowska et al. 2008; Jemel et al. 2006). Within the normal population, it has been found that viewing faces activates selectively the ventral occipito-temporal cortex particularly, though not exclusively, in the right hemisphere. The area involved is sometimes termed the fusiform face area or ‘FFA’. This observation is consistent with previous behavioural studies in which prosopagnosia is linked with fusiform abnormality and event related potential ERP observations of an N170 component (negative deflection in EEG; MEG equivalent M170) that is elicited by viewing faces and which is located in the fusiform gyrus (see, for example, Seeck and Grüsser, 1992). Considerable effort has been expended in identifying the nature of the face specificity with the suggestion that it is predominantly associated with the nature of the visual stimulus rather than the details of the task or the expertise involved (Carmel and Bentin, 2002). Face linked activity is not confined to the FFA but has also been reported in the superior temporal sulcus and other regions (Dekowska et al. 2008). The functional roles of these activations are not clear but they have been associated with judgements of emotion and identity as well as pre-processing and examination of gaze, facial detail, movement, etc.

Much of the neuroimaging literature on face processing in autistic subjects has concentrated on the FFA with a general consensus that there is atypical activation (Hadjikhani et al. 2007; Jemel et al. 2006; O’Connor et al. 2005; Schultz et al. 2000). Although the earlier literature emphasised FFA hypoactivation there is now some debate as to whether this is intrinsic or is connected with the details of the task (e.g. the degree of engagement, see Dalton et al. 2005; Schultz, 2005). Jemel et al. (2006) have reviewed these issues.

There have been just two published MEG studies of face processing in autistic subjects, both by the authors of this article and their collaborators (Bailey et al. 2005; Kylläinen et al. 2006a; 2006b). These build on their MEG studies of face
Figure 4.3 The images show the equivalent-current-dipole locations (orange dots) for responses to statically presented images of faces at about 150 ms after stimulus in two subjects with autism spectrum disorders. The dipoles have been superimposed on individual structural (MRI) scans. These figures (adapted from Bailey et al. 2005) illustrate that the generator of the N170 response might locate more towards the medial aspects of the (inferior) temporal lobe and more towards striate cortex than in typically developing subjects. There is little consistency in dipole orientation (orange line), which suggests a greater-than-normal heterogeneity in individuals with ASD. See plate section for colour version.

processing in normal subjects that replicated previous observations of a reduced N170 component in the FFA though with reduced latency (Swithenby et al. 1998) as well as reports by other authors detailing the dependence of the response on the details of the stimulus (Halgren et al. 2000). Perhaps the most relevant MEG study of face processing in normal subjects is by Kylläinen et al. (2006a) who studied the responses of 10 boys (ages 8–11) and 10 adult males to photographs of faces (eyes open, shut, and with averted gaze) and motorbikes. The results for adults in the study replicated previous findings, including the inferior occipito-temporal cortex N170 response. The activity in the children at the same latency was less prominent, not lateralised and was evoked similarly by faces and motorbikes. Averted gaze stimuli produced longer latency right-lateralised activity in children only. These findings indicate that, even in middle childhood, the neural mechanisms underlying face processing are less specialised than in adults.

Bailey et al. (2005) studied 12 able adults with autism spectrum disorders (ASD) and 22 adult controls as they performed image categorisation and image identification tasks (same matching criteria as in Braeutigam et al. 2008). Those with ASD generated responses to images of faces in right extrastriate cortices at ~145 ms after stimulus onset that were significantly weaker, less lateralised and less affected by stimulus repetition (Figure 4.3). Early latency (30–60 ms) responses to face images over right anterior temporal regions were different for the two groups in the image identification task. Overall the study suggests that those with ASD develop differently located and functionally different extra-striate processing
pathways. These pathways are functionally competent for some aspects of face processing. However, it is currently unresolved whether such processing routes may provide advantage in socially linked cognition.

The most recent MEG study of face processing in those with ASD was carried out by Kylliäinen et al. (2006b) on 10 children with ASD and 10 mental age and gender matched children who were typically developing boys aged 7–12 years. The task was the same as that used previously (Bailey et al. 2005). Overall, the study demonstrated that the response differences between the two groups of children were less marked than between the adult groups and between children and adults. Both groups showed similarity in immaturity of face processing though there were subtle differences with, apparently, greater recruitment of extrastriate cortex in processing non-face (motorbike) stimuli and a less face-specific response. Together these findings suggest that there is divergence between the developing face and object processing systems. An interesting though as yet inconclusive observation was differences in longer latency responses to averted and direct gaze images with those with ASD responding more strongly to direct gaze. The authors speculate that this may be linked to an amygdala modulated face-processing system as described previously (Schultz, 2005).

4.3.5 Mirror neuron system

The term ‘mirror neuron system’ referred initially to a class of neurons in the monkey’s pre-motor cortex that responds both when an action is performed by the animal and when the same kind of action is observed. Since discovery, findings obtained from a large number of investigations suggest that mirror neurons may form a generic cortical system involved in matching observation and execution of goal-related motor actions not only in non-human primate brains but also in humans. Moreover, theoretical considerations propose that the function of mirror neurons might be part of, or a necessary precursor to, a human ability to assign and understand goals, intentions and beliefs of other people under normal conditions. In other words, over and above being responsible for aspects of motor learning and imitation, the mirror neurons might underlie our normal ‘mind-reading’ ability or theory-of-mind (Gallese and Goldman, 1998; Rizzolatti et al. 2001). This putative link between mirror systems and mind-reading ability is of particular interest to autism researchers as affected individuals often show clinically recognised signs of impaired recognition and interpretation of other peoples’ intentions, or, more generally, state of mind.

Although studies have been published addressing the broader issue of social cognition in autism (e.g. Domes et al. 2008; Iacoboni, 2009), so far only researchers at the Brain Research Unit of Helsinki University of Technology have employed
MEG to study the neural basis of imitation related processes. Initially, the group studied the neuronal response in four adult individuals with Asperger syndrome, one individual with autism and eight typically developing controls all of whom viewed passively and actively mirrored hand actions presented visually. Focusing on the 20 Hz oscillatory neuronal response generated in primary motor cortex, the authors found similar patterns of activity in both ASD and control groups in the passive hand-action viewing condition (Avikainen et al. 1999). Pointing to the limitation imposed by a rather small sample size, the authors concluded that impaired mind-reading and imitation skills found in ASD could not be explained in terms of a dysfunction of the motor cortex part of the action observation and execution system.

More recently, the group recorded the neural responses in subjects imitating oro-facial gestures presented as static images of human faces showing various lip forms typically associated with facial expressions. Eight adult individuals with Asperger syndrome and ten typically developing age-matched adults were studied. Here, the data analysis focused on the 40 Hz oscillatory response modelled as equivalent-current-dipoles at various latencies following imitation inducing stimuli. In the control subjects, the authors found a characteristic sequence of cortical activation rapidly progressing from occipital cortices to the superior temporal sulcus, to the inferior parietal lobe, to the inferior frontal lobe and, finally, to the primary motor cortex of both hemispheres. In affected subjects, a broadly similar pattern was found. However, activity in inferior frontal areas was both delayed and weaker, and activity in primary motor cortex was weaker in affected individuals compared to typically developing subjects (Nishitani et al. 2004). Noting that the clinical group showed normal task performance, the authors concluded that the observed abnormal imitation related cortical activity might be indicative of a more general mirror neuron dysfunction which, in turn, could account in part for imitation and social impairments.

4.4 Discussion

Magnetoencephalography has become more important for autism researchers over the past decade. Overall, the MEG data are broadly consistent with but build on results obtained from EEG or other functional neuroimaging studies addressing comparable issues. Interestingly, the data available to date often point to subtle anomalies in the brain response in individuals with autism. One example of this is the observation that the early auditory responses such as the M100 are clearly present but are characterised by different-from-normal dynamical range or generator location. Another is that the extra-striate cortices appear to be involved in differentiation between face and other objects as in typically developing
subjects, but the activity is anomalous with respect to the strength and location of the source(s), and the task condition. Clearly, context sensitive responses are seen in autism, but the activation exhibits abnormal lateralisation or strength. In the case of the mirror system as well, abnormalities in activation appear to be characterised by delay and reduction in strength rather than absence.

The current research findings appear, to some extent, to support models describing autism in terms of anomalous cognitive strategies rather than cognitive impairments or deficits per se (Happé, 1999). The long term goal for autism researchers across the discipline is to synthesise an overarching biological and psychological theory of autism (Baron-Cohen and Belmonte, 2005). The contribution that MEG is beginning to make is to provide insight into ‘connectivity’ at a local and wider scale as evidenced by both event related field and gamma-band analyses. Thus, one tries to understand how synchronisation and connectivity in functional neural networks may represent local to global relationships at the level of behaviour (Just et al. 2004; Rippon et al. 2007; Rubenstein and Merzenich, 2003). The MEG work to date tends to support the psychological theory of weak central coherence (WCC), which suggests a relative shift from global to local processing in individuals with autism (Frith, 1989; see Pellicano, Chapter 7 of this volume).

The present contributions of MEG to this debate are limited. However, it is clear that, in order to develop neurophysiological theories of autism spectrum disorders, it will be necessary to resolve: (a) the role of neuroanatomical (neuronal tracts) and functional (activation pathways) contributions to long-range connectivity; and (b) the extent to which behaviourally local and global processes are represented by independent neural entities (Dakin and Frith, 2005) and large scale, coordinated neuronal networks, respectively.

In conclusion, given the current rapid development, it appears safe to claim that MEG will contribute to autism research for many years to come. This is not to deny that there are obvious limitations. So far, studies are rather fragmented in terms of experimental design and scientific objectives, sample sizes are typically low, subject matching criteria vary substantially from one investigation to the next, and comparisons are often limited to ASD and typically developing populations rather than pathologies exhibiting some overlap with the autistic spectrum.

The research into autism, based on MEG as well as other techniques, faces important challenges as to whether the observed electrophysiological anomalies are indeed specific to autism, or merely indicative of a wider class of abnormal conditions. More work is needed to establish precisely how the altered brain responses relate to higher order behavioural, communication and language deficits. Only time will tell how the current research can contribute to a better understanding of heterogeneity of the autistic spectrum, its diagnosis and long-term treatment.
4.5 References


MEG as a tool to investigate the neurophysiology of autism


Näätänen, R. (2001). The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). Psychophysiology, 38: 1–21.


Epilepsy, autism and cognitive impairment are over-represented in all studies that take one of these major categories as the starting point. The rates of epilepsy and autism are related to the severity of cognitive impairment. Those with primary or early regressive autism show a steadily rising rate of epilepsy with age reaching 30–50% in some adult studies but without evidence of causative relationship. Seizures of all types occur with complex partial attacks being prominent but we have no convincing explanation for this relationship. However, in several particularly early onset epilepsies, autism and cognitive impairment develop with the epilepsy suggesting causation (i.e. an epileptic encephalopathy). This process seems to preferentially involve the temporal neocortex and medical or surgical treatment of the epilepsy may cause remission of autistic symptoms in these cases.

5.1 Introduction

In 1943, Kanner described 11 children with his then new ‘autistic disturbances of affective contact’ (Kanner, 1943). One of these 11 suffered from epilepsy. In 1971, Kanner reported on a follow-up of the 11 patients; by now, two patients – 18% of his original series – were suffering from epilepsy (Kanner, 1971). Thus, in this seminal report, which defined autism, the patients already formed a clinically heterogeneous group – those with and those without seizures.

What has become clear over the years since Kanner’s writings is that patients with autism are, in fact, at greater risk of seizures than are children with other types of developmental problems, such as developmental dysphasia or Down
syndrome (Wong, 1993). The frequency of epilepsy in autism, regardless of IQ, is higher than in ‘non-autism’ severe mental retardation (Gillberg et al. 1986), even though a population of individuals with severe mental retardation is likely to include a group with autism often with an additional diagnosable genetic syndrome.

Medical specialities may approach the same conditions from quite different perspectives, for reasons of referral bias or through the way that their discipline has come to recognise the condition. Autism and epilepsy are both good examples of this phenomenon and therefore when patients have both conditions this may lead to the assumption that one condition is primary and the other is a ‘co-morbidity’. Since cognitive impairment is so common in those who have autism and epilepsy we have in effect three disorders which need disinterested handling and have been somewhat artificially separated for the convenience of medical study. The literature and our research designs may reflect this bias of different starting points.

We will therefore review the evidence from the starting points of primary developmental autism including those who show regression in the second year; specific early onset epilepsy syndromes and epilepsy more generally. We will then develop these strands into an overall hypothesis.

There is an important potential interaction between the three domains of autism, cognitive impairment and epilepsy and that is the phenomenon referred to as epileptic encephalopathy. This is the hypothesis that some aspect of the epilepsy, particularly subclinical epileptic activity in sleep, is the cause of the additional impairments including cognitive decline and autism (Engel, 2001). In some specific situations which will be quoted, the circumstantial evidence for such a process is strong but in others is weaker or lacking. Specifically there is no strong evidence to support the notion that in general, or rather ‘in the average case’ (if such a case exists), autism should be construed as an epileptic encephalopathy.

5.2 Prevalence aspects

If one looks at studies of individuals with autism, the percentage of those with epilepsy varies greatly. The prevalence of epilepsy in the general population is 0.5%; the published figures on epilepsy in autism range from 4% to 47% (Carod et al. 1995). There appear to be at least two reasons for this rather large variation. One is the fact that each group of patients with autism contains a different mixture of disease entities within the whole, some of which have seizures and some of which do not. Second, the frequency of epilepsy varies with the length of the follow-up period, rising as the follow-up period lengthens. Although epilepsy in children with autism often appears during the first three years of life (Ritvo, 1990), new
cases emerge through childhood, adolescence and into adult life (Danielsson et al. 2005). The rate of epilepsy in autism tends to be highest in general population samples of cases with autism followed from childhood into adult life, and lowest in child and adolescent psychiatric clinic patients with autism looked at cross-sectionally at any time under 18 years of age.

Also, individuals with ‘classic’ autism usually have varying degrees of intellectual disability, and the rate of epilepsy is higher in those with lower IQ. Thus, if one considers the rate of epilepsy only in those with classic autism, the percentage is about 35% (Billstedt et al. 2005). In those with other types of autism ‘spectrum’ disorders, including Asperger syndrome, the rate is considerably lower, probably in the order of 5–15%. Thus, if one were to suggest an epilepsy prevalence rate for all the autisms (including cases with mental retardation and cases with low normal, normal or above average IQ), it would probably be in the range of 10–20%.

An epidemiological study of infantile autism conducted in a county in Norway found that 9 (32%) had epilepsy out of 28 individuals with autism (Herder, 1993). In a Spanish series of 62 children with autism (Carod et al. 1995), 47% had some kind of epileptic syndrome, including two children with brain tumors – which is an unusual finding in any autism series. Danielsson et al. (2005) and Billstedt et al. (2005), in their Swedish general population cohort of 120 individuals with classic autism (N = 87) and atypical autism (N = 33), found that 40% had developed epilepsy in early adult life. Gillberg et al. (2010), reporting from the same cohort, found that mortality was very high in autism (8% had died between ages 10 and 40 years), and that much of the increased mortality rate was attributable to epilepsy (including several cases of sudden unexplained death in epilepsy).

5.3 Gender aspects

Thirty years ago, Wing (1981) suggested that girls diagnosed with autism have more severe indices of brain damage than boys, this being one of the reasons that they are not as under-represented at very low IQ levels. Danielsson found that girls with autism were relatively much more likely than boys to suffer from epilepsy (Danielsson et al. 2005). In a large American series of 302 children with autism, Tuchman et al. (1991) reported that epilepsy occurred in 14%. In this series, girls were affected more frequently than boys (24% vs 11%). (When cognitive and motor disabilities were excluded, the risk of epilepsy in children with autism was only 6%.) Elia et al. (1995) also found females to be more frequently affected by seizures than males in an Italian series of subjects with autism and mental retardation.

A review and meta-analysis of all published reports 1963–2006 of epilepsy in autism concluded that females are at relatively much higher risk of the combination of epilepsy and autism than are males, and that epilepsy is much more
common (21%) in intellectually disabled children with autism than in those with normal levels of intelligence (8%) (Amiet et al. 2008). Nevertheless, there was a much higher rate of epilepsy in the more high functioning group as well (8% versus 0.5% in the general population), indicating a strong link between autism ‘per se’ and epilepsy (our conclusion).

5.4 Diagnostic/differential diagnostic aspects including EEG

Standard EEGs are helpful when they reveal frankly epileptiform activity (Rapin, 1997). Based on a review of the medical literature up to that time, Tsai et al. (1985) reported that the majority of children with autism have shown some kind of EEG abnormality whether they had seizures or not. However, if the abnormal EEG readings are limited to epileptiform findings, this figure declines. Rossi et al. (1995) examined 106 patients with autism and found that 23.6% had paroxysmal EEG abnormalities compared to 18.9% with actual clinical seizures. Chez et al. (2006) reporting on the largest autism-EEG cohort to date (N = 889), found 61% had epileptiform activity during sleep, in spite of having no diagnosed clinical seizure disorder (see also MEG findings, Chapter 4 (Section 4.3.1) of this volume).

When one looks at the picture from the public health point of view of how much epilepsy and mental retardation exist in a general population, there is the additional question of how much autism contributes to this cohort. An answer has been given by a population-based study of 6- to 13-year-olds which identified 98 children with active epilepsy and mental retardation and reported that an autistic disorder was present in 27% and an autistic-like disorder in 11% of these children (Steffenburg et al. 1995).

5.5 Autistic regression and epilepsy

About a fifth to one-third of autistic toddlers appear to regress in language, sociability, play and often cognition (Rapin 1995; Fernell et al. 2010). Some of this is probably not due to ‘real’ regression, but produced by the fact that children who develop ‘normally’ for about eighteen months or so thereafter do not have the communication ‘building blocks’ to develop more complex forms of language and cognition, and hence stop using what little language they may have had. The study by Billstedt et al. (2005) suggests that only about one in ten of all children with autism actually show some real regression early in life (and that another minority deteriorate in adolescence). Nevertheless, in a subgroup of all children with autism, regression is a real and very important phenomenon. In such cases, fluctuation in language or behaviour often raises the suspicion of epilepsy. Epilepsy or a paroxysmal EEG occasionally may be associated with autistic regression. However, according to one author, epilepsy probably plays a relatively minor, although
non-negligible, pathogenetic role in autistic regression (Rapin, 1995). Others (Baird et al. 2006) have not found any evidence of a link. Nevertheless a prolonged sleep EEG that includes study of stage III and stage IV sleep is recommended for children without seizures who have regressed or who have fluctuating deficits and for mute and poorly intelligible children who may have verbal auditory agnosia (Tuchman and Rapin, 1997). In the medical literature, there is a rare subgroup of children with chronic motor tics who had both autistic regression and seizures as described by Nass et al. (1998). Seizures consisted of absence or myoclonic patterns, usually resistant to antiepileptic drugs. The patients had a specific pattern of occipital spiking on EEG.

After language is developed and after 2 years of age, a few children may undergo a rapid regression in language, sociability, play and apparent cognition. This has been called Childhood Disintegrative Disorder (Heller syndrome) and is thought by some to be a separate disorder from classic autism. We, however, have seen this phenotype starting as classical Landau-Kleffner syndrome.

5.6 Types of seizures

Many patterns of seizures are seen in patients with autism – infantile spasms, atonic seizures, myoclonic seizures, atypical absence, complex partial and generalised tonic–clonic seizures. Most known EEG patterns are also found in this patient group including electrical status epilepticus in slow wave sleep (ESES). Infantile spasms and complex partial seizures are relatively more common than other seizure types.

In the first few months of life, infantile spasms is the seizure pattern most likely, by far, to be associated with later development of autistic symptoms. However, there is a case in the literature of a child with EEG and clinical symptoms that met the criteria of benign familial neonatal convulsions who later developed autism (Alfonso et al. 1997).

5.6.1 Atonic seizures

Atonic seizures refer to generalised seizures in which the dominant motor manifestation is loss of postural tone, associated with loss of consciousness, usually for several minutes. They are simply grand mal seizures with limpness – rather than stiffness and repetitive jerking. Such cases have been reported in children with autism in the Tuchman et al. (1991) series.

5.6.2 Myoclonic epilepsies of early childhood (minor motor seizures)

Myoclonic seizures refer to single or multiple brief, shock-like jerking movements of the head, trunk or extremities. The infant form of these epilepsies
begins in infancy or pre-school years and is often seen in combination with tonic-clonic patterns. It may be associated with bursts of slow 1- to 2.5-per-second spike-and-wave complexes on EEG.

Myoclonic seizures are seen in patients with autism but it is unusual to find them as an isolated seizure type. Most often they are found in combination with other seizure patterns, particularly tonic-clonic, and are classified as the myoclonic epilepsies (Gillberg and Steffenburg 1987; Olsson et al. 1988). As the exception to the rule, there are several cases in the medical literature of solitary myoclonic seizures and autism (Boyer et al. 1981; Gillberg et al. 1984). The Gillberg et al. (1984) case is a description of a boy with classical autism, XYY syndrome, and myoclonic seizures who became seizure-free on valproic acid, and thereafter quickly improved regarding both his severe behavioural symptoms and his language disturbances.

5.6.3 Absence epilepsy (petit mal)

Absence seizures refer to staring spells, usually less than 20 seconds in duration, sometimes with slight flickering of the eyes. There are associated bilateral 2 to 4 Hz spike-and-slow wave complexes on EEG. EEGs are indicated for children in whom epilepsy is suspected, but it should be kept in mind that non-epileptic staring spells are much more common than absence seizures (Rapin, 1997).

There are a few studies which have found absence seizures in patients with autism (Ritvo et al. 1990; Tuchman et al. 1991). The absence seizures may be described as atypical. There is a case in the literature of an 8-year-old boy where absence seizures were reported to ‘masquerade’ as autism. He had almost continuous bilateral synchronous 3 Hz spike-and-slow wave on EEG and improved dramatically – both psychiatrically and neurologically – with ethosuximide monotherapy (Gillberg and Schaumann, 1983).

5.6.4 Complex partial seizures (psychomotor epilepsy)

If a child blanks out or stares, there are two possible seizure types to consider. One is absence seizures, as described above. The other is complex partial seizures which usually last between 30 seconds and two minutes and are accompanied by a variety of automatisms, such as lip smacking, hand wringing or plucking at clothes. Other signs of a partial complex seizure might be a temporary ‘dreamy state’ or impaired consciousness with an affective disturbance such as fear or anger. The EEG may show either unilateral or bilateral foci, usually frontal or temporal.

It is easy to see how such seizure activity might be hard to pick out in a child with autism. Corbett (1982) raised the question about how likely it was that such seizure
activity might be under-reported in non-verbal children with autism. A population-based study of epilepsy in pre-pubertal children with autism or autistic-like conditions found that complex partial seizures were present in 71% of those that had an onset of seizures in early childhood (Olsson et al. 1988). In another study of young people with autism, aged 16 to 23 years, Gillberg and Steffenburg (1987) found the majority of those with epilepsy and a prepubertal onset had complex partial seizures. Danielsson et al. (2005) in their very long-term prospective follow-up study of children with autism found complex partial seizures (with or without generalisation) to be the most common type of epilepsy throughout the follow-up period.

5.6.5  Generalised tonic-clonic seizures (grand mal)

In seizure parlance, the word ‘tonic’ refers to a stiffening of the body with rigid extension of the trunk and extremities. The word ‘clonic’ refers to generalised seizures with repetitive bilateral clonic jerking of the extremities. In tonic–clonic (grand mal) seizures, there is typically alternate stiffening and jerking associated with loss of consciousness.

Generalised tonic–clonic seizures are the most frequent form of epilepsy in the general population. They are relatively common in children and adolescents with autism (Carod et al. 1995; Olsson et al. 1988; Tuchman et al. 1991). In autism, tonic–clonic seizures may be associated with other types of seizures, either as sequellae after infantile spasms or immediately following complex partial seizures (Gillberg and Steffenburg, 1987; Olsson et al. 1988).

5.7  Early onset epilepsy syndromes with developmental regression

We now review specific early onset epilepsy syndrome in which developmental regression occurs. This may be on the basis of normal early development or in some lesional cases in which early development may be slow. Some are strongly genetic and regression may theoretically be epileptically driven or genetic.

5.7.1  Infantile spasms and hypsarrhythmia (West syndrome)

Infantile spasms begin in early infancy with runs of spasms. The EEG changes have a characteristic picture of abundant spike and polyspikes along with high voltage slowing. The association of infantile spasms with this EEG picture of ‘hypsarrhythmia’ has become known as West syndrome, referring to the physician who first described the features in his own son. At the time of presentation eye contact and verbalisation are commonly lost.

Despite effective treatment of infantile spasms in many with corticosteroids and vigabatrin, the child is often left with cognitive impairment and autistic symptoms. The percentage of patients with infantile spasms who later show the symptoms of autism varies in different studies from 2% (Prats et al. 1991) to 16%
Autism and epilepsy (Riikonen and Amnell, 1981). Looking at the problem from a different perspective, one could ask what percentage of patients with autism with all forms of epilepsy have infantile spasms? In the large series of 302 patients with autism studied by Tuchman et al. (1991), infantile spasms occurred in 12% of those patients with autism who also had epilepsy.

Patients with infantile spasms who later develop an autistic syndrome may have one of a number of different disease entities, which include tuberous sclerosis, neurofibromatosis 1, Down syndrome, phenylketonuria and minor hydrocephalus. Tuberous Sclerosis is one of the more common aetiologies underlying autism in epilepsy. In a study of 38 patients with tuberous sclerosis and epilepsy, 17 had infantile spasms (Ohtuska et al. 1998). A number of patients with neurofibromatosis 1 also have been reported with infantile spasms (Millichap, 1997). Saemundsen in an Icelandic study found that the odds of developing autism was about 5–6 times raised after infantile spasms, but that much of this risk was associated with a symptomatic origin of the seizures (Saemundsen et al. 2008).

One study suggests that both temporal lobes often appear to be involved in those patients with infantile spasms who will later develop autism (Chugani et al. 1996). This follow-up study of 14 babies with infantile spasms and a PET study which showed bitemporal hypometabolism revealed that 10 had developed autism. We also have ERP evidence of delay and blunting of responses to novelty stimuli in the temporal lobe (Werner et al. 2005).

5.7.2 Landau-Kleffner (acquired epileptic aphasia) syndrome and ESES (electric status epilepticus in slow sleep)

Landau-Kleffner syndrome is an acquired epileptic aphasia or verbal auditory agnosia affecting children between 2 and 5 years of age who already have developed speech. There are seizures and/or an often bilateral paroxysmal EEG pattern. In the classical Landau-Kleffner syndrome, aphasia is acquired and other higher cortical functions usually do not deteriorate. In a variation of the syndrome called ‘epilepsy with continuous spike-waves during slow wave sleep’ (CSWS) or Electric Status Epilepticus in Slow Sleep (ESES), speech is disturbed in 50% of the cases and intellectual deterioration occurs with psychiatric symptoms, often reminiscent of autism, developing. According to Hirsch et al. (1990), they are probably variations of a single syndrome. Corticosteroids are usually tried in this patient group and may have at least a temporary – sometimes dramatic – beneficial effect. There is also an experimental surgical therapy called subpial intracortical transection (Cross and Neville, 2009; Morrell et al. 1995; Nass et al. 1998).

5.7.3 Dravet syndrome (severe myoclonic epilepsy in infancy)

Dravet syndrome is a catastrophic form of epilepsy which begins with seizures, often hemiclonic status epilepticus with fever, during the first year of
life (Nolan et al. 2008). Development remains normal during the first year and until the onset of habitual seizures, usually in the second year. These seizures include myoclonic, atypical absences, partial and secondarily generalised. Psychomotor retardation, autistic features often satisfying full criteria for autism, hyperactivity and other neurological deficits occur in affected children, and are usually obvious in the second to fourth year of life. A considerable proportion of all affected individuals have missense or truncated mutation of the sodium channel gene SCN1A. Seizures are often triggered by fever and children with very early onset, long-lasting (> 10 mins) ‘febrile seizures’ should always be suspected of Dravet syndrome. Unfortunately, most treatments for seizures in Dravet syndrome have been relatively unsuccessful, although stiripentol combined with sodium valproate and sometimes a benzodiazepine appears to hold promise (Chiron et al. 2000). During the first year of normal development the interictal EEG is usually normal but becomes abnormal during the second phase of regression.

In addition to these specific epilepsy syndromes at high risk of autism and cognitive impairment there is a generally higher rate of autism in unselected series of children with active epilepsy. Specialist referral units for childhood epilepsy are accustomed to autism and ADHD being unrecognised for several years despite obvious problems at home and school. It is therefore clear that all children with intractable epilepsy should be screened for these problems including ASD so that they can be fully diagnosed and managed. The simplest broad screen is the Strengths and Difficulties questionnaire (Goodman, 1999). The Autism Spectrum Screening questionnaire can be used for more precise identification (Ehlers and Gillberg, 1993).

5.8 The phenotype of ASD with epilepsy

Until recently the issue of whether the ASD associated with epilepsy is the same as that without epilepsy had not been addressed. We already know that cognitive level was lower with epilepsy. A study of this subject is difficult for several reasons:

- The two quite separate pathways outlined above may not be included in the study design
- The criteria for the diagnosis of ASD will influence the phenotype as an outcome measure
- The co-existence of other behavioural characteristics (e.g. of attention, impulsivity, obsessive and manipulative behaviour) will have to be handled in the study design in a way which answers the question. This is difficult because of the arbitrary nature of the definitions of ASD used.
In a recent study comparing the features of autism between those with and without epilepsy there were difficulties in controlling for IQ (Turk et al. 2009). The factors that were more evident in those with epilepsy were a relatively greater proportion of girls, more motor difficulties but no difference in aloofness and passivity, but the writers acknowledge the difficulties of this type of study.

One method of dealing with this would be a description of the elements of behaviour in children with epilepsy at different cognitive levels without attempting to control data.

5.9 Investigation and management

In early onset epilepsies with regression an urgent EEG including sleep is essential with a view to treatment particularly of sub-clinical seizure activity with benzodiazepine and corticosteroids. It is important that response to such treatment is monitored using standardised measures of verbal and non-verbal abilities and autism features. Details of the medical management of epilepsy are outside the remit of this text. It is important, however, that the epilepsy and psychiatric management are integrated. Neurological regression requires neurological investigation which will include MRI scanning and biochemical investigation.

5.10 Place of EEG in the investigation of autism

Despite the evidence of higher than expected rates of epileptic activity in autism without seizures no studies have shown that routine EEGs, waking or sleep, help in diagnosis or management of the patient and it may be quite testing to obtain a good record. In the main this conclusion also applies to those who show typical autistic regression in the second year of life. If, however, the regression is atypical or occurs with seizures EEG monitoring is indicated as it is with children with autism and seizures. Treatment with antiepilepsy drugs in the latter situation aims to reduce or stop seizures and no change in autism features is expected. There are, however, situations where clear features of autism recede with intensive treatment:

- In Landau-Kleffner syndrome obvious features of autism may remit with medical or surgical treatment.
- Early onset lesional epilepsy particularly dysembryoplastic temporal lobe lesions showing autistic regression which may remit with early effective surgery (Gillberg et al. 1996; Neville et al. 1997).
Pathogenesis of autistic regression in epilepsy

There are several strands of evidence that support the view that the developing temporal lobe is not able to make appropriate language and social communication connections in the presence of high rates of epileptic discharges. This evidence includes:

- West syndrome caused by tuberous sclerosis shows a relationship between temporal lobe tubers and autism (Bolton and Griffiths, 1997).
- Abnormal temporal lobe generator ERPs to novelty (Thivierge et al. 1990).
- A high rate of autistic features in LKS which is predominantly a disturbance of function and structure in the superior temporal gyrus.
- Strong association between temporal lobe lesions, particularly right sided, and autism in patients coming for epilepsy surgery (Taylor et al. 1999).
- Interestingly, as well as acute regression at about 4 months with infantile spasms and tuberous sclerosis, this regression with the appearance of autism has occurred with recurrence of seizures in the second year of life (Humphrey et al. 2006).

This evidence, however, only applies to autistic regression which is led by a severe early onset epilepsy syndrome. We have no current explanation for the high rates of epilepsy and epileptic EEG abnormality in developmental autism. Stating that in autism generally there appears to be a reduced threshold for epilepsy may be doing no more than repeating the above evidence.

References


Biochemistry of autism: changes in serotonin, reelin and oxytocin

ELIZABETA B. MUKAETOVA-LADINSA, JODIE WESTWOOD AND ELAINE PERRY

Autism is a neurodevelopmental disorder characterised by impaired social skills, communication deficits and repetitive behaviours. Alterations in a number of neurotransmitter signalling systems and neuroregulatory proteins have been reported in individuals with autism spectrum disorders (ASD). The most compelling evidence seems to suggest an imbalance in excitatory and inhibitory impulses in the premature autistic brain, combined with defects in secondary neurotransmitter systems, resulting in autistic traits. Serotonin, known to be disrupted in ASD, facilitates the release of both reelin and oxytocin, with excessive levels of serotonin resulting in a decrease in reelin and oxytocin. Deficits in developmental growth factors, such as reelin, may regulate or be regulated by oxytocin, thus contributing to both neurodevelopmental arrest and altered social behaviour, characteristic for the autistic spectrum. In this review we therefore concentrate on the role of the serotonin neurotransmitter and the two neuroregulatory proteins (reelin and oxytocin), and evaluate the pharmacological interventions available at the moment, associated with the latter neurochemical changes in autism.

6.1 Introduction

Autism is regarded as a heterogeneous neurodevelopmental disorder, characterised by a spectrum of impaired social skills, communication deficits, repetitive behaviour and frequently associated with co-morbid disorders (e.g. obsessive compulsive disorder, epilepsy, Tourette syndrome, attention deficit hyperactivity disorder, tuberous sclerosis and Fragile X syndrome, among others; Gillberg and Billstedt, 2000). A significant number of individuals with autism also show...
hyperactivity, anxiety and self-injurious behaviours. The degree of the characteristic symptoms can vary profoundly, from an extremely affected individual with significant learning difficulties, to a high functioning individual with Asperger syndrome, giving rise to the ‘autism spectrum’. The onset of the symptoms can also vary: some children have developmental delay within the first 18 months of life, whereas 25–40% of children (Goldberg et al. 2003) will have a ‘regressive’ phenotype, characterised by near-normal development until 18–24 months, following which they regress. Autism incidence rates are currently predicted as 1:150 births (Centers for Disease Control and Prevention, CDCP USA, 2007), with an overall prevalence estimate of 1:100 children (see Chapter 1), and a three- to four-fold higher prevalence in males.

The diversity and degree of severity of the various symptoms associated with ASD contribute to difficulties in studying these conditions. Similarly, the use of different diagnostic criteria limits continuity between studies. The heterogeneity of the autism spectrum is further supported by the various alterations in neurochemicals (signalling molecules in the nervous system) and neurotransmitters (molecules that travel across a synapse between pre- and post-synaptic nerve terminals). Thus, deficits in serotonergic, cholinergic, glutamatergic, gamma-aminobutyric acid (GABA)-ergic and oxytocin systems (McNamara et al. 2008), as well as reelin and N-acetylaspartate, have been documented (Blaylock and Strunecka, 2009; Fatemi et al. 2005; Martin-Ruiz et al. 2004; McNamara et al. 2008; Oblak et al. 2009).

Serotonin, a neurotransmitter shown to be disrupted in ASD, facilitates the release of both reelin and oxytocin. Thus, excessive levels of serotonin result in decreased reelin levels (Janusonis et al. 2004) and oxytocin-containing neurons (McNamara et al. 2008). Furthermore, deficits in developmental growth factors, such as reelin, may regulate or be regulated by oxytocin (Carter, 2007; Liu et al. 2005), and contribute towards altered social behaviours associated with the autism spectrum. Changes in the expression of serotonin, reelin and oxytocin may underlie altered neurodevelopment in autism. In this review we will concentrate on the role of serotonin and these two neuroregulatory proteins (reelin and oxytocin), and evaluate the pharmacological interventions that are currently available, targeting these latter neurochemical changes in autism.

6.2 Serotonin neurochemistry in autism

Serotonin, or 5-hydroxytryptamine (5-HT), is a signalling molecule found throughout the body (transported by platelets; Anderson et al. 1987), and in the brain where it acts as a neurotransmitter. It is derived from the amino acid tryptophan, hydroxylated by tryptophan hydroxylase (TPH) to form 5-hydroxytryptophan (5-HTT), the rate limiting step in the production of serotonin. An aromatic amino
acid decarboxylase then catalyses the conversion of 5-HTT to serotonin. Serotonin has many physiological functions and impacts on many human behaviours, including eating, sleeping, mood, hostility, temperament, body temperature and hormone release (reviewed by Keltikangas-Järvinen and Salo, 2009)).

6.2.1 Serotonin dysfunction

It has long been established that serotonin plays a role in autism. Acting as a developmental signal in the immature brain, prior to the time it assumes the role as a neurotransmitter, serotonin influences a range of brain developmental changes, including inhibition of serotonergic neurons (in an autocrine manner), promotion of neurite outgrowth, synaptogenesis, neurogenesis in target neurons, differentiation and organisation of the brain network (reviewed by McNamara et al. 2008). The impact of serotonin on atypical neurodevelopment in autism may be reflected, therefore, in brain overgrowth, poor cortical lamination, smaller neuronal cell size, as well as poor dendritic arborisation and synaptic expression (Amaral et al. 2008; Mukaetova-Ladinska et al. 2004).

Acute depletion of dietary tryptophan increases the symptoms of autism (McDougle et al. 1996a). Children exposed in utero to drugs that increase serotonin levels, such as cocaine, are reported to have a higher incidence of autism than is normally expected (Davis et al. 1992; Kramer et al. 1994). These findings have led to the development of a rat ‘hyperserotonaeemia’ model of autism, in which high levels of serotonin in the blood precede loss of serotonin terminals within the brain, acting through a negative feedback process. Serotonergic functions are consequently disrupted, with widespread changes affecting the hypothalamus and amygdala (McNamara et al. 2008). This animal model has much in common with several social and behavioural changes inherent in autism, e.g. lack of maternal and sibling bonding, diminution of adult pro-social behaviours in the social interactions and stereotyped behaviour and with certain neuropathological changes observed at post-mortem within the brain of individuals with ASD (Adolphs et al. 2002; Howard et al. 2000). Interestingly, post-mortem analysis in an animal model also found loss of oxytocin-containing neurons within the paraventricular nucleus of the hypothalamus (McNamara et al. 2007). These results may correspond to the hypothalamic and amygdalar changes in the human ASD and suggest that the hyperserotonaeemia model of autism may be a valid model which produces many of the social, behavioral and peptide changes inherent to autism. However, these findings need to be examined further in human neuropathological studies in ASD.

Dysfunction of the serotonin system may also arise from abnormal cholesterol metabolism, which could in turn lead to the range of social and behavioural problems associated with individuals with ASD (reviewed by Aneja and Tierney, 2008). Cholesterol is a constituent of the lipid rafts of the serotonin transporter (Allen et al. 2007), and disruption of lipid rafts by cholesterol-interfering agents
can lead to as much as a 50% reduction in the rate of GABA, 5-HT and glutamate transporters (Saher et al. 2005). A role for cholesterol in abnormal serotonergic neuronal development associated with ASD is further supported by a mouse model of Smith-Lemli-Opitz syndrome (Waage-Baudet et al. 2003). Furthermore, bioinformatics and gene ontological analyses of available data in ASD implicate a number of genes involved in nervous system development, inflammation and cytoskeletal organisation, in addition to genes relevant to gastrointestinal or other physiological symptoms often associated with autism. Most importantly, these processes appear to be modulated by cholesterol/steroid metabolism, especially at the level of androgenic hormones (Hu et al. 2009), and may thus explain the greater susceptibility to ASD in male subjects.

6.2.2 Positron emission tomography (PET) studies

PET studies have been used to determine serotonin synthesis in the brain, using an $\alpha^{[11]}$C methyl-L-tryptophan ($[^{11}C]$AMT) tracer. In a study by Chugani et al. (1997), seven boys with autism were analysed using PET and compared to their unaffected siblings. In autism, areas with unusual serotonin synthesis levels included the frontal cortex (decreased synthesis), cerebellar dentate nucleus (increased synthesis) and the thalamus (decreased synthesis), all connected via the dentatothalamocortical pathway, thought to be involved in speech production and sensory integration. Typically developing children have 200% higher serotonin synthesis levels than adults up to the age of five, with the levels then gradually decreasing with age to normal adult levels (Chugani et al. 1999). Similar findings of decreased cortical serotonin 5-HT$_2A$ receptor binding in a number of cortical areas (associated with impaired social communication) were reported in adults with Asperger syndrome using SPECT (Murphy et al. 2006). However, in ASD, serotonin synthesis capacity gradually increases from 2 years of age up to 15 years, being 1.5 times greater than typical adult levels (Chugani et al. 1999). This suggests that high brain serotonin synthesis occurs during childhood, but this developmental mechanism could be significantly altered in children with ASD. Lower cortical 5-HT$_2$ receptor density is also present in parents of children with autism (Goldberg et al. 2008), suggesting an underlying association.

6.2.3 Plasma blood serotonin levels in autism

Hyperserotonenaemia (elevated blood serotonin levels) has been shown to consistently occur in 25–33% of individuals with autism (Mulder et al. 2004; Takahashi et al. 1976; Table 6.1). The disequilibrium in the peripheral and central turnover of serotonin, accompanied by an increase in neurotoxic glucocorticoids (Croonenberghs et al. 2008), appears to play an important role in autism. Despite efforts to link hyperserotonenaemia to a possible clinical sub-group of autism, results have varied. Interestingly, about 20% of individuals with ASD also have
Table 6.1 *Hyperserotonema studies with autistic patients*

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Limitations</th>
<th>Criteria for diagnosis of autism</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi, <em>et al.</em> (1976)</td>
<td>30 children with early infantile autism, 30 age matched control children, 45 children with various neurological disorders (age range unknown)</td>
<td>Sample sizes; lack of accuracy of diagnosis</td>
<td>Kanner’s criteria</td>
<td>Platelet serotonin levels higher in children with autism. Elevated in some of the other groups with hyperactivity. Higher levels observed in under school age children with autism</td>
</tr>
<tr>
<td>McBride <em>et al.</em> (1998)</td>
<td>77 (aged 2–37 years) with autistic disorder, 22 with ID or otherwise cognitively impaired children. 65 controls</td>
<td>Lack of accuracy of diagnosis; sample sizes</td>
<td>DSM-III-R ADOS-G ABC</td>
<td>Platelet serotonin levels were higher in pre-pubertal children with autism, compared to controls. Hyperserotonema only evident in individuals with autistic features (not ID)</td>
</tr>
<tr>
<td>Mulder <em>et al.</em> (2004)</td>
<td>81 (aged 3–20 years) with autism, Asperger syndrome or PDD-NOS. 54 with ID, 60 controls</td>
<td>Medication; sample sizes; lack of accuracy of diagnosis</td>
<td>ADI-R ADOS DSM-IV-R ABC</td>
<td>Platelet serotonin levels higher in ASD group. Not found in majority of individuals with ID. No behavioural correlates</td>
</tr>
<tr>
<td>Hranilovic <em>et al.</em> (2007)</td>
<td>53 with ASDs (aged 16–45 years) of whom 48 were diagnosed with autism, 1 Asperger, 4 PDD-NOS. 45 controls (aged 20–55 years)</td>
<td>Most with ASD were medicated (those taking SSRIs were excluded); male to female ratio and mean age were lower in ASD group; lack of accuracy of diagnosis</td>
<td>DSM-IV Speech development was clinically evaluated</td>
<td>Platelet serotonin levels were significantly higher in the ASD group. Negative correlation between platelet serotonin levels and language development</td>
</tr>
</tbody>
</table>

hypocholesterolaemia, and this is not due to gastrointestinal disturbances or abnormal diets, but is a result of decreased cholesterol synthesis (Aneja and Tierney, 2008).

6.2.4 Genetics and serotonin

As blood hyperserotonemia is evident in many people with autism, candidate genes among the serotonin pathways have been identified and studied. The most extensively studied gene is SLC6A4, which encodes the serotonin transporter (chromosomal location 17q12). Several polymorphisms have been identified in this gene, the most significant so far being 5-HTTLPR, a functional polymorphism in the 5’ promoter region of the gene. The two forms of this polymorphism can be identified by the insertion or deletion of 44 base pairs, resulting in the short (‘s’) or the long (‘l’) allele (the ‘s’ allele being the dominant of the two). Over-transmission of either the ‘s’ or ‘l’ allele has varied among different studies (Table 6.2). Possible reasons for these differences include ethnic differences, since they are one of the most probable explanations for the variability of the serotonergic polymorphisms in ASD, as well as the genetic heterogeneity of autism (reviewed by Cho et al. 2007).

More recent studies have attempted to link the serotonin genotype and phenotype in ASD. In a study by Brune et al. (2006), the participants were analysed according to their genotype groups (s/s, s/l and l/l) and were then clinically studied and assessed using the autism diagnostic interview (ADI-R) and autism diagnostic observation schedule (ADOS) methods. Participants with the s/s or s/l phenotype scored significantly more severely than the l/l genotype in the B1 (failure to use non-verbal behaviours to regulate social interaction) subdomain of the ADI-R (Figure 6.1). The l/l genotype group was more impaired in the ADI-R D3 (stereotyped and repetitive motor mannerisms) subdomain. Parents of the participants in both genotypic groups confirmed that these behaviours (specific to their child’s genotype) were what first caused them concern about their child’s development. These results need to be repeated on a larger sample to be further validated.

Since platelets are considered to be a good model for neurons, a study by Cross et al. (2008) investigated the relationship between platelet serotonin levels and polymorphisms in various autism candidate genes. The participants were categorised into three groups. Group one was homozygous for haplotypes containing the T allele at both SLC6A4 single nucleotide polymorphism (SNP) 10 and SNP 11 (5-HTTLPR s/s and s/l). The second group consisted of individuals who were homozygous for the 5-HTTLPR long allele polymorphism, and group three had combinations of other haplotypes. Differences were observed between different haplotype groups at SLC6A4 for transporter $K_m$ and $V_{max}$. Participants with the s/s and s/l genotypes (TT/TT) were shown to have higher transporter $K_m$ and $V_{max}$
### Table 6.2 Serotonin transporter SLC6A4 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Criteria for diagnosis of autism</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klauck et al. (1997)</td>
<td>Probands with autistic disorder and both parents, 65 trios</td>
<td>ADI-R, ADOS</td>
<td>Preferential transmission of the long allele</td>
</tr>
<tr>
<td>Cook et al. (1997)</td>
<td>Probands with autistic disorder and both parents, 86 trios</td>
<td>Not disclosed</td>
<td>Preferential transmission of the short allele</td>
</tr>
<tr>
<td>Conroy et al. (2004)</td>
<td>84 trios</td>
<td>Not disclosed</td>
<td>Preferential transmission of the short allele</td>
</tr>
<tr>
<td>Guhathakurta et al. (2006)</td>
<td>61 trios, 18 duos</td>
<td>DSM-IV CARS</td>
<td>Preferential transmission of the short allele</td>
</tr>
<tr>
<td>Ramoz et al. (2006)</td>
<td>272 multiplex families and 80 simplex families, with 645 affected subjects</td>
<td>ADI-R</td>
<td>No association of the 5-HTTLPR locus with autism</td>
</tr>
<tr>
<td>Cho et al. (2007)</td>
<td>126 trios</td>
<td>DSM-IV K-CARS</td>
<td>Preferential transmission of the long allele</td>
</tr>
</tbody>
</table>

Duos: one parent with one affected child; trios: two parents with one affected child; multiplex families: families with multiple affected children; simplex families: families with only one affected child.


than the other two haplotypes. This is in contrast to previous studies which found that the s/s and s/l genotype is associated with lower serotonin transporter $V_{\text{max}}$ than other haplotypes (Anderson et al. 2002; Greenburg et al. 1999). The TT haplotype may be associated with functional variants elsewhere in the gene, or it may have an unknown function, for example altering gene expression or protein trafficking. Despite the correlation between the TT phenotype and the transporter kinetics, this group was not associated with a change in whole blood serotonin, which suggests that hyperseronaemia in autism has a heterogeneous aetiology. This theory is further validated by other results from the study with regards to tryptophan hydroxylase 1 (TPH1), as different polymorphisms in this gene were found to have different levels of whole blood serotonin (Cross et al. 2008).
Biochemistry of autism: changes in serotonin, reelin and oxytocin

Another candidate gene is ITGB3 (chromosomal location 17q21.32), which encodes the integrin β3 substrate (a subunit of the platelet heterodimeric fibrinogen receptor). ITGB3 is associated with high blood serotonin levels in ASD. While these variants in ITGB3 do not explain hyperserotonemia, it is very possible that they contribute to it (Weiss et al. 2006a). Selective serotonin reuptake inhibitor (SSRI) medications are found to be effective in 50% of patients with autism (McDougle et al. 1996b), despite only 25–33% of affected individuals showing hyperserotonemia (Table 6.1). It is therefore possible that variations in the ITGB3 gene could still be present in an individual with autism, and affect the broader serotonin system, despite normal platelet serotonin levels, thus providing further evidence for the heterogeneity underlying the phenomenon of hyperserotonemia in ASD.

While it is established that β3 integrin has a function within platelets, it also has a role in synapse maturation within the hippocampus (Chavis and Westbrook,
Both ITGB3 and SLC6A4 have been identified as male quantitative trait loci (QTL) and both are implicated in autism. This has spurred investigation of epistasis between the two genes (Coutinho et al. 2007; Weiss et al. 2006b). Specifically, Weiss et al. (2006a) hypothesised that genetic variation at ITGB3 may influence the expression of SLC6A4. They showed that expression levels of ITGB3 and SLC6A4 are correlated in several tissues in humans and mice (including the brain). Furthermore, a non-coding ITGB3 single nucleotide polymorphism (SNP) previously implicated in autism (via association with serotonin levels) may genetically interact with the SLC6A4 5-HTTPLR polymorphism to increase the risk of autism (Weiss et al. 2006b). Although these findings are not conclusive they do offer an insight into possible genetic factors for autism susceptibility, linked to serotonin.

6.2.5 Serotonergic interventions in autism

Selective serotonin reuptake inhibitors (SSRIs)

There are currently no effective medical remedies for autism, though there are some medications which may serve to alleviate certain symptoms associated with autism. Moreover, many if not most of these medications have potentially serious side effects, which must be taken into account in evaluating them.

Many individuals with autism, as well as their first- and second-degree relatives (Veenstra-VanderWeele et al. 2000) are treated with and respond well to selective serotonin reuptake inhibitors (SSRIs). SSRIs are found to be effective in around 50% of individuals with ASD (McDougle et al. 1996b). Their site of action is the serotonin transporter, and the drugs function by increasing the amount of serotonin available in the synaptic cleft. SSRIs can be therapeutic in ASD by reducing a range of symptoms, including anxiety, aggression and stereotypical/repetitive behaviours. However, the variable extent of improvement of mood and mood-associated behaviours even in the responders is also associated with a high incidence of a number of side effects (occurring in up to 50% of treated individuals with ASD) (reviewed by West et al. 2009a).

Fluoxetine and fluvoxamine have been highlighted as SSRIs which are particularly useful (Kolevzon et al. 2006). A double-blind, placebo controlled, crossover study of 44 children and adolescents with autism highlighted the usefulness of fluoxetine in reducing repetitive behaviours (Hollander et al. 2005), with some increase in hyperactivity, irritability, insomnia and lethargy described as adverse effects (Fatemi et al. 1998; Hollander et al. 2005). In a 10-week open labelled clinical study involving 18 children and adolescents with autism, fluvoxamine was shown to significantly improve obsessive-compulsive or anxiety-related symptoms in only 3 children, whereas 5 had only partial responses, with akathisia, behavioural activation and agitation reported as adverse effects (Martin et al. 2003). In contrast, a
A double-blind, placebo-controlled study of fluvoxamine in 30 adults with autistic disorder reported that half of the treated group were responders, showing significant reduction of repetitive thoughts, behaviour and aggression (McDougle et al. 2000). The findings of these two studies raise the possibility that fluvoxamine might have a better efficacy in older individuals with ASD.

Another SSRI, sertraline, was found to produce a similar rate of reduction in repetitive and aggressive behaviours to fluvoxamine in an open trial, with adult autistic individuals with Prader-Willi syndrome responding better than those with a clinical diagnosis of Asperger syndrome (Hellings et al. 1996). The efficacy of other SSRIs – paroxetine, citalopram and escitalopram – needs to be further investigated in larger studies.

Serotonin and noradrenaline reuptake inhibitors (SNRIs)

A recent case report on the use of another type of antidepressant, mirtazepine (a selective serotonin and noradrenaline reuptake inhibitor, SNRI), also points towards the usefulness of these types of antidepressants in adjusting sexual behaviour in ASD (Coskun and Mukaddes, 2008; Nguyen and Murphy, 2001). The benefits of SNRIs for improving inattention and hyperactivity in autism have been documented in a series of case reports (Carminati et al. 2006; Hollander et al. 2000).

Pharmacological manipulation of serotonin levels using SSRIs and SNRIs can affect distinct neuroregulatory proteins (e.g. increase plasma levels of oxytocin; Magalhães-Nunes et al. 2008) and neuronal signalling mechanisms, including glycogen synthetase kinase 3β (GSK3β) signalling. Inhibition of GSK3β appears to inhibit some behaviours, especially aggression (Beaulieu et al. 2008). This raises the possibility of developing further therapies that target GSK3β and its related signalling events to manage behavioural changes related to serotonin deficiency.

Tryptophan

Using tryptophan as a supplement has also been considered to enhance serotonin release and/or reuptake inhibition. Reduction in tryptophan has been documented to cause significant deterioration in people with autism (Cook and Leventhal, 1996). Although there is evidence for differences between individuals with autism and controls with respect to peripheral metabolism of 5-hydroxytryptophan after an oral challenge (Croonenberghs et al. 2005), the clinical efficacy of this intervention still needs to be assessed. Similarly, the cofactor tetrahydrobiopterin, which plays a role in the biosynthesis of catecholamines and serotonin, and enhances synaptic release of various neurotransmitters, showed a small, but statistically significant improvement in the ability of participants to interact socially, and in their IQs in a small double-blind, placebo-controlled, crossover study involving 12 children with autism (Danfors et al. 2005).
Risperidone

Risperidone is an atypical antipsychotic drug that blocks serotonergic 2A (5HT$_{2A}$) receptors and dopaminergic D2 receptors post-synaptically. Although predominantly used in schizophrenia, it has found its place in the treatment of certain symptoms in autism, thus providing further evidence for the role of 5-HT and dopamine in autism. Thus, short-term risperidone intervention is effective for ameliorating/improving a variety of behaviours associated with ASD, including aggression, hyperactivity, social skills and self-injurious behaviour (Capone et al. 2008; Nagaraj et al. 2006). About 66–83% of autistic children treated with risperidone will have substantial improvements in compulsive and stereotypic behaviour, affective reactions, sensory response and motor behaviours; with 68% of them maintaining a positive response during a 4-month drug maintenance phase (reviewed in West et al. 2009b). However, variable response to treatment between individuals and for distinct core symptoms of autism has also been noted (West et al. 2009b). An 18-month-long randomised, placebo-controlled, double-blind study also showed the benefits of risperidone intervention for children with autism (2–9 years of age), with improvement in social responsiveness and non-verbal communication, reduction of hyperactivity and aggression (Nagaraj et al. 2006). Improvement in social withdrawal was noted as early as 3 months after starting treatment (Capone et al. 2008).

Studies examining long term treatment (6 and 18 months) with risperidone report mild to substantial weight gain in patients (Martin et al. 2000; 2004; Nagaraj et al. 2006). Although risperidone appears to ameliorate some autistic symptoms, and it has been proven to be one of the rare interventions with which results can be replicated in intervention studies (reviewed in Parikh et al. 2008), the weight gain, alongside somnolence and hyperglycaemia (reviewed in Scott and Dhillon, 2007), may be too large an adverse effect to consider it as a long term intervention, and further studies are needed to establish the clinical relevance of this intervention for ASD.

6.3 Reelin

Reelin is a serine protease glycoprotein, essential for normal brain development (Quattrocchi et al. 2002). It has three receptors: α3β1 integrin, very low density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2). Disabled 1 (Dab-1) is a cytoplasmic adapter associated with reelin. In the prenatal brain, reelin is secreted by Cajal Retzius cells, interacting with other proteins to ensure correct laminar organisation in the neocortex, hippocampus and cerebellum (Ogawa et al. 1995). In adults, reelin is secreted from GABAergic interneurons.
throughout the brain (Pesold et al. 1998; Roberts et al. 2005), neurons which are believed to be disrupted in autism (Oblak et al. 2009).

Reelin is not only essential during development; it is also utilised for memory formation and higher cognitive function (D’Arcangelo, 2005; Krueger et al. 2006), which can be affected in autism. Serotonin, shown to be disrupted in ASD, facilitates the release of reelin. However, excessive levels of serotonin (as discussed above, see Table 6.1) may also decrease reelin levels, and could alter neurodevelopment (Janusonis et al. 2004).

6.3.1 Reelin animal models

Studies with reelin knockout (KO) mice (reeler mice) have shown the importance of reelin in neurodevelopment, with the KO mice displaying severe deficiencies in social behaviour and cognitive impairments, reminiscent of autism (Falconer 1951). Reelin KO mice have reduced numbers of cerebellar Purkinje cells—a finding that is common in post-mortem studies on autism. When reelin was ectopically expressed in developing reeler mice, some of the expected behavioural impairments (also noted in ASD) were avoided, especially the ataxic gait and deficiency in positional cue (Magdaleno et al. 2002), thus proving the importance of reelin in cognitive function in mice.

6.3.2 Reelin and autism

In a study examining blood reelin levels in 28 autistic twins, unprocessed reelin (410 KDa) was decreased by 70%. Levels were also decreased in their parents (mothers 72%, fathers 62%) and normal siblings (70%) compared to controls (Fatemi, 2002). Similar findings have been reported in related neurodevelopmental conditions, such as schizophrenia and mood disorders (Fatemi et al. 2001a). A later post-mortem study compared cerebellar cortices from five adults with ASD and eight age-matched controls, using SDS-gel electrophoresis and Western blotting. Reelin was found to be reduced by 43% in the ASD group (Fatemi et al. 2001b). These data suggest that the reelin blood decrease may reflect the reelin brain abnormalities. However, to date there are no comparative studies on blood and brain reelin expression.

In a more recent study, these authors examined various sections of the brain at post-mortem from 7 adult individuals with ASD (19–56 years of age at death) and 10 age-matched controls (20–36 years of age at death) (Fatemi et al. 2005). In the ASD group, levels of full-length reelin within the superior frontal cortices were 71% lower than controls. In the cerebellum in ASD, reelin levels were 39% lower, and in the parietal cortex levels of reelin were 72% lower than controls (Fatemi et al. 2005). mRNA levels were measured for reelin, VLDLR, Dab-1 and GSK3 (found downstream in the reelin signalling pathway, see Table 6.3 and Figure 6.2).
Table 6.3 mRNA levels for Reelin, VLDLR, Dab-1, and GSK3β in autism. Abbreviations: M, male; F, female; GOI, gene of interest (adapted from Fatemi et al. 2005)

<table>
<thead>
<tr>
<th>Brain area</th>
<th>GOI relative to age</th>
<th>GOI mRNA</th>
<th>matched control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal cortex</td>
<td>VLDLR</td>
<td>+14.2</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>(Brodmann Area 9) 6M controls and 7 ASD (6M, 1F)</td>
<td>GSK3β</td>
<td>+1.9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reelin</td>
<td>−4.7</td>
<td>&lt;0.035</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dab-1</td>
<td>−5.4</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Cerebellum 9 controls (8M, 1F) and 7 ASD (6M, 1F)</td>
<td>VLDLR</td>
<td>+2.8</td>
<td>&lt;0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GSK3β</td>
<td>+1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reelin</td>
<td>−3.9</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dab-1</td>
<td>−3.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Levels of reelin and Dab-1 mRNA were significantly decreased within the superior frontal cortex (Brodmann Area 9 in the dorsolateral part of the frontal lobe) and cerebellum in the ASD group compared to controls, whereas the levels of VLDLR were significantly increased.

These studies suggest that reelin signalling is impaired in autism (Figure 6.2). Thus, lower production of reelin (Fatemi et al. 2001b; Fatemi, 2002) and reduction in reelin mRNA levels (Fatemi et al. 2005) will result in lower activation of receptors. The increase in VLDLR mRNA in the ASD group may possibly reflect a response to lowered reelin levels – the body attempts to adapt by providing more receptors for the ligand to bind to. Dab-1 mRNA levels were also reduced – either due to the lack of positive feedback from reduced levels of reelin, or increased negative feedback from the upregulated VLDLR (Fatemi et al. 2005). However, these findings
are somewhat difficult to interpret in the light of not being replicated since, and although the decrease in reelin mRNA seems to parallel the protein decrease, their relationship was not addressed directly in the latter study (Fatemi et al. 2005). It is of interest to note that the GSK3β mRNA levels were not significantly different between ASD and control group, and one of the explanations for this may be that levels of phosphorylated GSK3β are altered in autism similar to the same phenomenon reported in schizophrenia (Emamian et al. 2004).

### 6.3.3 Reelin and genetic studies

Abnormalities affecting reelin and its signalling pathway have been associated with autism. Taken together with the behavioural deficits (highlighted above) observed in reeler mice, these findings suggest a role for reelin in the aetiology of autism. Various studies have implicated the RELN gene (chromosomal location 7q22) as a susceptibility gene for autism (Serajee et al. 2006; Skaar et al. 2005; Zhang et al. 2002). However, other studies have shown no association between polymorphisms in the RELN gene and autism (Devlin et al. 2004; Dutta et al. 2008; Krebs et al. 2002; Li et al. 2004). It may be that RELN polymorphisms are only present in a subset of the autistic population.

### 6.4 Oxytocin neurochemistry in autism

Oxytocin (OT) is a nine amino acid neuropeptide and hormone, synthesised in the paraventricular nucleus and the supraoptic nucleus in the brain, and is the product of a series of cleavage events from a prohormone. The last step in the process is the cleavage of C-terminal extended peptides, OT-Gly, OT-Gly-Lys and OT-Gly-Lys-Arg (or OT-X) to oxytocin. Receptors for oxytocin are found throughout the limbic system, forebrain and autonomic centres in the brainstem. The function of oxytocin receptors is modulated by cholesterol (Gimpl et al. 2002). Low levels of cholesterol are thought to perturb oxytocin receptors and may contribute to problems in social functioning in autism (Aneja and Tierney, 2008).

#### 6.4.1 Oxytocin and animal studies

Several animal studies have implicated oxytocin in social affiliative behaviours, such as mating, pair-bond formation, parental/maternal behaviour, social memory and recognition, separation distress and various other forms of attachments (reviewed by Tom and Assinder, 2010). Differences in behavioural profile in these animal models are due largely to different mouse strains being used, as well as different techniques to disrupt the OT gene or its receptor. Thus, oxytocin knockout (KO) mouse pups are less vocal when separated from the dam, and adult oxytocin KO mice are unable to recognise familiar peers even after
several social encounters (Winslow and Insel, 2002). However, after oxytocin is administered this social deficit is reversed. A recent study extended these findings, using them to separate OT KO mouse strains, and showed that the lack of OT does not alter general prosocial behaviour in the mutant, neither does it confer an anxiety-related phenotype, but selectively impairs the ability to remember having previously met a novel mate (Crawley et al. 2007). Increased aggressive behaviour has also been reported in OT KO mice (Ragnauth et al. 2005).

6.4.2 Oxytocin in humans

There is a relationship between oxytocin and human social behaviour. A person’s willingness to trust another individual (accepting social risks; Kosfeld et al. 2005) and the ability to interpret subtle social cues (Domes et al. 2007) have been shown to increase following oxytocin administration. In another study, participants administered oxytocin were found to be more generous when deciding how to split a sum of money than those on the placebo (Zak et al. 2007).

Altered oxytocin levels have been documented in certain neuropsychiatric conditions. People with obsessive-compulsive disorder (OCD), a condition with repetitive behaviours, have elevated levels of oxytocin in their cerebrospinal fluid (Leckman et al. 1994). Similarly, schizophrenic patients have decreased levels of plasma oxytocin, relating to the affected individual’s ability to identify facial emotions – a process that is also impaired in individuals with ASD (Goldman et al. 2008). Although not specific to a particular disorder, these findings could relate to neurobiological mechanisms underlying clinical symptoms that are shared in various psychiatric conditions, including autism, OCD and schizophrenia.

6.4.3 Oxytocin and autism

Plasma oxytocin levels were measured in 29 boys with autism (aged 6 to 11) and compared to 30 age matched controls (Modahl et al. 1998). All of the ASD participants were diagnosed using DSM-IV criteria. The boys all completed three cognitive tests, and additionally the parents of the autistic children were given two interview questionnaires (the Vineland Adaptive Behaviour Scales and a background questionnaire) and interviewed about their child’s behaviour. Despite a considerable overlap of values, the ASD group showed on average lower plasma oxytocin levels than the controls. A number of children ($N = 10$) with autism had undetectable levels of oxytocin. The lower levels of oxytocin in ASD children were not associated with the medication the children were taking. In the control but not the ASD group, there was a positive correlation between levels of plasma oxytocin and age. In contrast to the controls who had positive correlation between plasma oxytocin levels and social skills (except in expressive language), children with autism showed negative association (Modahl et al. 1998). These results suggest that
there may be deficits in oxytocin receptors or upstream regulators in children with ASD. The low expression of oxytocin is hypothesised to contribute to the delay in brain maturation in autism (Campbell et al. 1980). Similar observations were made in an independent study involving Saudi Arabian children with autism (Al-Ayadhi, 2005).

To further investigate plasma oxytocin levels in boys with autism, participants recruited in the previous study (Modahl et al. 1998) were examined to see whether isoforms of oxytocin were present at different levels in the ASD group when compared to controls (Green et al. 2001). OT antisera which react with either oxytocin or the C-terminal extended oxytocin (OT-X) isoforms were used. Similar to previous findings, the ASD group showed lower levels of oxytocin than the control group. However, OT-X levels were higher in the group with autism, with a more than two-fold higher OT-X to OT ratio. OT-X levels were also positively associated with age in the ASD group, but not the controls (Green et al. 2001). These results suggest that children with autism may have deficits in oxytocin processing.

An inability to completely process mature oxytocin may result in elevated amounts of OT-X. Studies examining the function of OT-X have shown that it is not an effective agonist at OT receptor sites (Mitchell et al. 1998), meaning that OT-X is not an adequate substitute for decreased levels of oxytocin in children with autism. In contrast to the studies conducted in children, a study in adults with ASD reported higher plasma levels of oxytocin (Jansen et al. 2006), suggesting that the maturation process may affect the level of oxytocin expression. However, the variations in oxytocin levels were large, and the participant groups were small (10 ASD and 14 controls). This study (Jansen et al. 2006) was also conducted on high functioning ASD adults, in contrast to previous studies conducted on children with variable cognitive functioning (Modahl et al. 1998). However, further studies are needed to elucidate the reasons for the differences between the young and adult autistic populations.

6.4.4 Oxytocin and genetic studies in autism

A study screening the Autism Genetic Resource Exchange (AGRE) samples and a Finnish autism sample identified the oxytocin receptor gene, OXTR, as a candidate susceptibility gene in autism (Ylisaukko-oja et al. 2005). The OXTR gene is located on 3p25.3, within the 3p25–27 loci identified in the study. Two single nucleotide polymorphisms (SNP) located within the OXTR gene in 195 Chinese Han autism trios (two parents with one affected child) were found to be significantly associated with autism (Wu et al. 2005), further implicating OXTR in the condition. In contrast to the Chinese Han population, Caucasian children and adolescents with autism have overtransmission of the G allele, rather than the reported overtransmission of the A allele (Jacob et al. 2007). This discrepancy may be due to a
different pattern of linkage disequilibrium between the genetic marker and the susceptibility variant in the OXTR gene. An additional study has again shown a significant association between SNPs on the OXTR gene and autism susceptibility, also analysing any linkage between the SNPs and cognition (Lerer et al. 2007). The study reports that there is an association between IQ and Vineland Adaptive Behaviour Scales and OXTR, suggesting that the OXTR gene affects skills such as communication and daily living skills.

6.4.5 Oxytocin as a therapeutic agent

The deficit of oxytocin in oxytocin KO mice, in which impairments in social recognition and discrimination have been demonstrated, can be reversed by infusion of oxytocin within the amygdala (Ferguson et al. 2001). In a clinical study, Hollander et al. (2003) administered synthetic oxytocin (pitocin) or placebo to six adults with autism (diagnosed according to DSM-IV and ADI-R criteria) and nine adults with Asperger disorder (aged 19–55 years). Repetitive behaviours were significantly reduced over time, as well as the number of different types of repetitive behaviours, after pitocin had been administered. In a later study, these authors reported that intervention with oxytocin led to improvements in ‘appropriate use of emotional intonations’ in the speech within a group of individuals with ASD (Hollander et al. 2007). In this study, six adults with autism and nine adults with Asperger syndrome were enrolled, and they all showed improvement in comprehension of affective speech (e.g. happy, indifferent, angry and sad). A recent functional imaging study showed that intervention with oxytocin reduced activation within the amygdala, and also reduced ‘coupling’ of amygdala to brainstem regions that are implicated in autonomic and behavioural manifestations of fear (Kirsch et al. 2005).

The results of these studies reinforce the notion that the oxytocin system is affected in autism, and may contribute towards repetitive and emotional behaviours. Although these studies have been carried out on only a very small number of individuals, the potential therapeutic use of oxytocin for treating some of the symptoms of autism seems promising. However, this intervention may have some restrictions in a clinical setting – pitocin is administered intravenously, and monitoring social behaviour would require involvement of a number of people (family members, teachers, carers).

An interesting theory that has been proposed recently is that high levels of oxytocin which are released during childbirth in the mother (i.e. during labour), and the use of oxytocin in inducing labour, could also influence brain development in the infant. Thus, elevated oxytocin levels may be transferred to the infant via the maternal–fetal circulation during this critical period, and cross over from the blood into the infant brain (which lacks a fully developed blood–brain barrier at this stage) (reviewed by Rojas Wahl, 2004). The hypothesis is that raised levels
of oxytocin can lead to desensitisation of oxytocin receptors within key areas of the infant brain. In vitro studies have shown that within 5–10 minutes following agonist stimulation, more than 60% of the oxytocin receptor is internalised, thus becoming unavailable for further oxytocin binding and corresponding signal transduction cascades (reviewed by Zingg and Laporte (2003)). The excess of oxytocin, in turn, downregulates oxytocin receptor mRNA (Jo and Fortune, 2002). According to a study in 1998, about 61% of children with autism were reported to have had a history of induced labour (Hollander et al. 1998), three-fold higher than the national average. However, an independent study found similar rates of pitocin-induced labour among ASD and matched control children (Gale et al. 2003). This hypothesis needs to be explored in further prospective studies to determine whether oxytocin-induced labour may indeed influence the incidence of autism.

6.5 Conclusions

In this review we have discussed alterations in serotonergic neurotransmitters and two neuroregulatory proteins, reelin and oxytocin, in ASD. The studies predominantly come from reports on people with autism from 5 years old and upward. The reasons for this are manifold; e.g. children younger than five (with or without ASD) often prove more difficult to study clinically because of their inattention and lower IQ (Mayes and Calhoun, 2003); post-mortem samples from infants are limited. However, discovering the causes of ASD may ultimately depend on data obtained from infants between 2 and 4 years (age range at which autism is usually diagnosed) and even younger, when symptoms first become apparent.

The heterogeneity of the autism spectrum, alongside the lack of well characterised clinico-pathological and biochemical studies, small sample sizes, and lack of coverage of the various developmental stages of the spectrum, all contribute to difficulties in understanding the neurobiology of autism. It is difficult to be conclusive in allocating distinct neurotransmitter alterations to a distinct clinical symptom. Although a number of neurotransmitter systems have been investigated and found to be altered in autism, the resultant pharmacological interventions on their own do not appear to regulate all the characteristic clinical symptoms of the syndrome. Due to the percentage of autistic patients found to be hyperserotonenaemic (25–33%, see Table 6.1), and compelling evidence from genetic studies implicating the serotonin transporter gene, SLC6A4, in ASD (Table 6.2), the serotonergic system appears to be significantly involved in ASD. Although perhaps not a cause, disruptions to the serotonergic system may worsen the behavioural phenotype of an individual with autism. As serotonin facilitates the release of reelin, and excess serotonin may decrease reelin levels (Janusonis et al. 2004), an individual with ASD who is hyperserotonenaemic may also have reelin deficits. Since these factors are among the most consistent biochemical changes reported in
autism, it would be of interest to explore further their contribution towards the aetiology of ASD.

Oxytocin is involved in human social behaviour (Kosfeld et al. 2005; Zak et al. 2007). It is, therefore, not surprising that altered levels of oxytocin are reported in autism, and correlate with the altered social behaviour, one of the core symptoms. Various genetic studies also implicate the oxytocin receptor gene in autism (Jacob et al. 2007; Lerer et al. 2007), suggesting that deficits in the oxytocin system contribute towards the clinical phenotype. Intravenous administration of oxytocin has had some success as a pharmacological trial for certain symptoms associated with autism (Hollander et al. 2003; 2007). Improvements noted in repetitive behaviours and expressive speech may be beneficial, and the potential for oxytocin to improve social behaviour, a trait associated with autism that has not been targeted by drug therapy, looks promising from animal studies (Winslow and Insel, 2002), as well as human trials (Kosfeld et al. 2005).

Although oxytocin replacement therapy, as well as SSRI/SNRI, appears to be useful in regulating some of the clinical features of autism, larger clinical and neuropathological studies are now needed not only to replicate these findings, but also to put together the distinct neurotransmitter and neurochemical profiles in autism, and relate them to distinct (or group of distinct) clinical symptoms. This will help in understanding the neurobiochemical changes behind the clinical phenotype of autism, and will contribute to novel development of symptom-targeted medical interventions.

While the heterogeneity of ‘autism’ is accepted, we are still far from understanding the specific causes of the condition and subsequently developing appropriate pharmacological interventions that would be of benefit to individuals on the autism spectrum, especially those with significantly altered behaviour and cognition. Further evidence is needed from larger, multi-centre clinical studies that can be replicated, in order to accept such medical interventions within a clinical setting.

6.6 Acknowledgement

We would like to thank Mrs Christine Bohanan for secretarial support.

6.7 References


Biochemistry of autism: changes in serotonin, reelin and oxytocin


Psychological models of autism: an overview

ELIZABETH PELLICANO

Autism is currently defined in terms of a core set of behaviours, including difficulties in social reciprocity and communication, and limitations in behavioural flexibility. In the past three decades, considerable efforts have been directed towards understanding the neurocognitive atypicalities that underlie these core behaviours. This chapter provides an overview of the major theoretical accounts of autism, especially the theory of mind hypothesis, the executive dysfunction hypothesis, and weak central coherence theory, each of which has aimed to explain autism in terms of a single underlying cognitive atypicality. Some of the reasons why researchers have become dissatisfied with these so-called ‘single-deficit’ accounts as explanatory models of autism will be analysed, before turning to more recent ‘multiple-deficits’ models to begin the task of outlining the additional challenges faced by such models. The chapter concludes by stressing the need to situate explanatory accounts of autism – single or multiple-deficit models – within a developmental context.

7.1 Introduction

Since the seminal experimental work of psychologists such as Hermelin and O’Connor (1970) and Frith (1970, 1972), considerable research efforts have been directed towards elucidating the psychological mechanisms underpinning the behavioural manifestations of autism spectrum disorder (hereafter ‘autism’),

1 The term ‘autism spectrum disorder’ includes Autistic Disorder, Asperger’s Syndrome, Pervasive Developmental Disorder – Not Otherwise Specified and Atypical Autism, and has been adopted by clinicians and researchers to reflect the variability of these disorders in terms of intellectual functioning, language ability and degree of symptomatology.
Figure 7.1 Causal model showing three levels of explanation: genetics/biology, cognition and behaviour (adapted from Frith et al. (1991)) encompassing a single primary cognitive deficit. In addition to interactions with the environment, there is likely to be a complex interplay between these explanatory levels, as the arrows indicate. For example, atypicalities in early cognitive development could have profound secondary effects on later brain and psychological development. Likewise, the premise of early behavioural intervention is that it should capitalise on the plasticity of the developing brain to alter underlying (atypical) brain processes.

including the often profound difficulties in social reciprocity and communication, and stereotyped, repetitive interests and activities. Historically, in the interests of parsimony, researchers focused their efforts on isolating a single primary cognitive deficit that could provide a unifying explanation for the constellation of symptoms that are unlikely to co-occur by chance (Morton and Frith, 1995) (see also Rutter, 1968; 1983). In the absence of specific genes or biological markers for autism, cognitive accounts of autism sought to further our understanding of autism by pinpointing the ‘intervening variable’ between biology and behaviour (Frith et al. 1991; Morton and Frith, 1995; 2001; Figure 7.1). Identification of a core cognitive marker could not only inform research at the genetic level by the discovery of ‘endophenotypes’ or vulnerability markers (Gottesman and Gould, 2003), but also provide insight into the brain bases of autism (Hill and Frith, 2003), and form the basis for intervention programmes.

The past few decades have witnessed researchers fervently pursuing the notion of a primary cognitive marker for autism, generating as they have done so numerous hypotheses concerning the nature of the cognitive deficit in autism, some of which have included atypical ‘central’ processes such as sequencing, concept formation and abstraction (Hermelin and O’Connor, 1970), core problems in language (Rutter, 1968), sensory and perceptual atypicalities (Ornitz and Ritvo, 1968), disruption of ‘complex’ information processing (Minshew et al. 1992;
Psychological models of autism: an overview

Minshew et al. 1997), poor social responsiveness (Klin and Volkmar, 1993; Mundy and Sigman, 1989) and impairments in interpersonal relatedness (Hobson, 1989; 1993) (see also Hobson, 2002). Three additional theories have been particularly influential in the field largely due to their potential to explain autism in terms of a single underlying cognitive atypicality. These include: (1) the theory of mind hypothesis, which claimed that autism is caused primarily by a specific inability to impute mental states to oneself and to others (Baron-Cohen et al. 1985) (see Baron-Cohen et al. (2000) and Tager-Flusberg (2007), for reviews); (2) the executive dysfunction hypothesis, which proposed that the symptoms of autism are a result of a dysexecutive syndrome – a primary problem in the executive control of action (Hughes and Russell, 1993; Ozonoff et al. 1991), (see Hill (2004) and Russo et al. (2007) for reviews); and (3) ‘weak’ central coherence theory, which posited that individuals with autism have a tendency to focus on individual elements rather than wholes combined with an inability to integrate information into context (Frith, 1989; Frith and Happé, 1994) (see Happé and Booth (2008) and Happé and Frith (2006), for reviews).

These so-called ‘single-deficit’ theories have generated a huge amount of research, and, as a result, have brought autism research to the attention of mainstream developmental and cognitive neuroscience. Nevertheless, the notion of a single cause at the cognitive level of analysis has been challenged repeatedly by empirical investigations, which have cast considerable doubt on the validity of several of the theories’ central claims. Consequently, there has been a recent shift from single-deficit accounts towards those espousing ‘multiple deficits’. Proponents of these latter accounts argue that they could in principle provide a more adequate explanation of the diverse set of symptoms defining autism.

The goal of this chapter is to present an overview of each of the major single-deficit theories in turn, detailing the empirical reasons why researchers have become dissatisfied with these accounts as potential causal explanations of autism. In so doing, the often sophisticated conceptual accounts on which the theories depend will be introduced initially, before reviewing the extensive empirical literature that puts those theories to the test in such a way as to allow the reader direct access to the relevant results. The chapter also considers more recent multiple-deficits models, and begins the task of outlining the additional challenges faced by such models.

The chapter thus provides the reader with a comprehensive (although not, of course, exhaustive) survey and analysis of the most influential cognitive accounts of autism. Before it begins, however, it is necessary to outline the criteria specified by researchers, which have been used not only to guide and constrain single-deficit models of autism, but also to assess the veracity of these models’ claims.
7.2 Criteria for explanatory accounts of autism

Michael Rutter (1983) first advocated the notion of a primary deficit for which he outlined several indicators, including universal manifestation, early appearance, prognostic significance, and the capacity to explain performance on a variety of tasks. Researchers have since refined the notion of a primary cognitive deficit as one which is ‘universal, specific, and necessary and sufficient to cause the symptoms of the disorder… in other words, the proximal cognitive cause of the behavioural symptoms of the disorder’ (Pennington and Ozonoff, 1996, page 57). Similar to Rutter (1983), several authors have emphasised that the primary cognitive marker should also show causal priority; that is, it should have the capacity to explain the earliest-emerging features of autism (Boucher, 1996; Happé, 1994b; Tager-Flusberg, 2001).

The putative cognitive deficit should therefore:

1. Be universal, or near universal, among individuals with autism
2. Be unique to individuals with autism (i.e. not present in individuals with other developmental conditions)
3. Show causal precedence
4. Show explanatory power (i.e. the incidence and severity of the deficit should be directly related to the behavioural symptoms in each of the three domains)

These four criteria have been echoed in subsequent empirical and theoretical work (e.g. Bailey et al. 1996; Ozonoff and McEvoy, 1994; Turner, 1997), and will be used to evaluate each of the major theoretical accounts in the following sections. This set of criteria is by no means exhaustive. Additional criteria have been cited by several researchers, including presence of the putative deficit in the broader autism phenotype (individuals with a genetic liability for autism, who display autistic behaviours, albeit of a lesser degree than in autism itself) (Bailey et al., 1996; Bailey and Parr, 2003; Hughes, 2001), and persistence or stability over time (Ozonoff and McEvoy, 1994; Rutter, 1983).

7.3 The Theory of Mind Hypothesis

The first major cognitive theory of autism focused on deficits in theory of mind (ToM) or ‘mentalizing’: the ability to attribute mental states to oneself and to others, which allows one successfully to predict and interpret others’ behaviour (Dennett, 1978). A central focus of such work has been on children’s understanding of beliefs, which often involves mistaken representations of reality, and is therefore held to signal the emergence of a representational understanding of
mind (Wimmer and Perner, 1983). In a landmark study conducted more than two
decades ago, Baron-Cohen et al. (1985) showed that 80% of their sample of chil-
dren with autism displayed difficulties on the now classic false-belief task, despite
the fact that the verbal mental age of these children was well beyond the 4- to
5-year-old level, when success on this task typically occurs. This evidence led to the
proposal that the core features of autism could be explained by a single primary
cognitive deficit in the ability to understand other minds (Baron-Cohen, 1993;
1991) and Leslie and Thaiss (1992) argued strongly that individuals with autism
specifically lack the modular Theory of Mind Mechanism (ToMM), which in the
typically developing child enables the formation of propositional attitudes (e.g. of
the form, ‘X believes that ( . . . )’), and provides insight into others’ behaviour.

In support of this position, a multitude of studies has since demonstrated
that many persons with autism fail tasks that require a representational under-
standing of other minds (see Baron-Cohen et al. 2000, and Tager-Flusberg, 2001,
2007, for reviews), including those tapping the understanding of deception (Baron-
Cohen, 1992; Russell et al. 1991; Sodian and Frith, 1992), knowledge (Baron-Cohen
and Goodhart, 1994; Leslie and Frith, 1988), complex emotions, such as surprise
(Baron-Cohen et al. 1993), intention (Phillips et al. 1998), in addition to recognition,
comprehension and expression of mental state terms (Baron-Cohen et al. 1994;
Tager-Flusberg, 1992; Ziatas et al. 1998).

The theory of mind hypothesis seemed to capture what Kanner (1943) first
described as ‘autistic aloneness’. Certainly, the inability to realise fully what it
means to have a mind and to think, know, believe and feel differently from others
should affect one’s capacity to relate to others socially, and also should influence
one’s ability to communicate effectively (see Happé, 1993). Indeed, links were
made between successful theory of mind task performance and pragmatic skills
(Eisenmajer and Prior, 1991), in addition to ‘real-life’ social difficulties, including
the ability to make or keep secrets, offer important information, and recognise
surprise and embarrassment (Frith et al. 1994; Hughes et al. 1997; Tager-Flusberg,
2000). Furthermore, Leslie (1987, 1991) argued that a core ‘metarepresentational’
impairment in autism could also account for the lack of imaginative or pretend
play in autism. The prospect that a core cognitive impairment in theory of mind
could provide a causal explanation for autism caused a flurry of research. Yet it
was soon met with various criticisms, which are outlined below.

7.3.1 Universality

Initial research showed that not all individuals with autism fail false belief
tasks. In Baron-Cohen et al.’s (1985) original study, 20% of children with autism
passed the critical false belief question. In subsequent studies, this percentage varied from 15% (e.g. Reed and Peterson, 1990) to 55% (e.g. Prior et al. 1990), with 90% of participants with autism passing in one study (Dahlgren and Trillingsgaard, 1996). The presence of a theory of mind difficulties in some, but not all, individuals with the condition cast doubt over whether these difficulties played a causal role in the development of autism.

Proponents of the theory of mind hypothesis responded to this initial criticism by showing that although some individuals with autism could pass first-order false-belief tasks, they nevertheless failed more difficult second-order false-belief attributions (i.e. of the form ‘Mary thinks that John thinks the ice cream van is in the park’; Perner and Wimmer, 1985) despite being significantly older than the age at which such tasks are typically passed (6–7 years) (Baron-Cohen, 1989a; Perner et al. 1987; but see Bowler, 1992). These findings led Baron-Cohen (1989a) to suggest that the development of theory of mind is specifically delayed in autism rather than completely absent. Support for this view came from reports of a link between theory of mind success and autistic children’s language skills (e.g. Charman and Baron-Cohen, 1992; Leekam and Perner, 1991) (see also Fisher et al. 2005 and Tager-Flusberg and Joseph, 2005). Indeed, in her review, Happé (1995) showed that the level of verbal ability necessary to pass standard false-belief tasks was considerably higher in children with autism (mental age (MA) of at least 12 years) than in typically developing children (MA of 4 years).

Some authors argued, however, that success by older individuals with autism on false-belief tasks did not provide unequivocal evidence that these individuals had in fact developed a theory of mind. Instead, these ‘passers’ could be using alternative compensatory routes to task success (Eisenmajer and Prior, 1991; Frith et al. 1991; Happé, 1995; Holroyd and Baron-Cohen, 1993; Ozonoff et al. 1991). Subsequent studies have provided indirect support for this idea. Behavioural studies have shown that older individuals with autism who pass standard false-belief tasks nevertheless show poor performance on more naturalistic tests of theory of mind, including understanding of irony (Happé, 1994a), and the attribution of mental states of moving geometric figures (Castelli et al. 2002; Klin, 2000). Neuroimaging studies have further shown that, while typical adults activate regions of the so-called social brain network (e.g. medial pre-frontal cortex and temporoparietal junction; Frith and Frith, 2003; Saxe et al. 2004) when solving theory of mind tasks, cognitively able adults with autism who pass such tasks show significantly less activation in these regions (e.g. Castelli et al. 2002) and may instead recruit

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2 Given the use of only two test trials in this study, it is plausible that the four children with autism who passed both trials may have done so due to random responding rather than a true understanding of other minds.
neural regions associated with general problem-solving skills (e.g. Happé et al. 1996), suggesting they might be using non-mentalistic strategies to help them reason about other peoples’ behaviour.

Although more direct support for this proposal is still needed, a recent elegant study provides the most conclusive evidence to date that individuals with autism may genuinely show atypicalities in mentalising. Senju et al. (2009) used eye-tracking methodology to reveal the on-line processing of adults with Asperger syndrome as they watched an actor and puppet enact the classic false belief scenario. In an earlier study, the same authors had shown that, after having observed the puppet move a ball from one box to another unbeknown to the actor, typical 2-year-olds immediately looked to the empty box that the actor believes still holds the ball (Southgate et al. 2007). In their new study, adults with Asperger syndrome – who previously had passed standard versions of the false belief task – failed to anticipate accurately the box in which the actor will look for the ball, instead looking almost equally at the two boxes. Although older and more able individuals with autism may be able to solve standard false belief tasks, these findings strongly indicate that there may be less spontaneous mentalising in autism, the sort of processes automatically used by typical infants, children and toddlers to navigate everyday social interactions successfully. Future research using eye-tracking and functional imaging will help determine precisely what processes give rise to an implicit, intuitive theory of mind, and whether such additional processes might be atypical in autism.

7.3.2 Uniqueness

Researchers also showed that problems with theory of mind were not specific to autism. Researchers reported that a significant proportion of children with moderate learning difficulties without a diagnosis of autism also showed difficulties on false belief tasks (Benson et al. 1993; Yirmiya et al. 1996; Zelazo et al. 1996), and that problems with false belief understanding were present in children with other developmental disorders, such as oral deafness (Peterson and Siegal, 1995; 1999; Russell et al. 1998), congenital blindness (Brown et al. 1997; Green et al. 2004; Minter et al. 1998), and children with specific language impairment (Miller, 2001; but see Colle et al. 2007; Perner et al. 1989). This evidence called into question whether a specific deficit in theory of mind was necessary and sufficient to cause the behavioural symptoms of autism per se.

Proponents of the hypothesis have defended their position by claiming that it may be the severity of the impairment rather than the impairment itself that is unique to autism (e.g. Green et al. 2004; Yirmiya et al. 1998), or that the failure of the non-autistic clinical groups on false belief tasks might be due to reasons other than a genuine representational deficit (Baron-Cohen, 2000; Tager-Flusberg, 2001). For
example, theory of mind difficulties might be the result of reduced conversational opportunities in the case of late or non-signing deaf children (Peterson and Siegal, 1999; 2000), or an inability to use visual cues, such as eye gaze or pointing gestures to ‘read’ other minds in the case of children with congenital blindness (Minter et al. 1998; Tager-Flusberg, 2001).

7.3.3 Causal precedence

One additional challenge for the theory of mind hypothesis was to account for how an impairment in theory of mind – as indexed by failure on false belief tasks usually passed by typically developing 4-year-olds – could explain the earliest symptoms of autism including atypicalities in social responsiveness and reciprocity, gaze behaviour, joint attention, and imitation often detected during infancy (e.g. Dawson and Adams, 1984; Klin et al. 1992; Mundy and Sigman, 1989; Volkmar et al. 1987). Leslie (1987) argued that pretence may be the earliest manifestation of theory of mind, emerging at around 18 months, and later authors suggested that earlier behaviours such as pointing to share interest in something (protodeclarative pointing) and joint attention may be precursors to a theory of mind (Baron-Cohen, 1989b; 1991) (see also see Leslie and Happé (1989)). Nevertheless, studies pointed towards early autistic symptoms that were non-representational in nature, including a failure to ‘show anticipation of being picked up by a caregiver’ or ‘reach for familiar person’ (Klin et al. 1992), which were interpreted instead as evidence in favour of a more primary affective, emotional or intersubjective impairment in autism (e.g. Hobson, 1993; Klin and Volkmar, 1993; Mundy et al. 1993).

Subsequent theoretical accounts have broadened the definition of theory of mind to respond to this challenge. Baron-Cohen (1994; 1995) proposed a more extensive ‘mindreading’ system, which included not only a module for understanding mental states, such as think, believe, know, but also other early-emerging ‘precursor’ modules, which include innate mechanisms for eye-gaze detection and shared attention. He proposed that one of these modules – the Shared Attention Mechanism – is specifically damaged in autism, which, as a result, fails to trigger the subsequent development of the Theory of Mind Module. Other theorists have proposed alternative models. Tager-Flusberg (2001) has interpreted the earliest symptoms of autism within a componental account of theory of mind, which encompasses a socio-cognitive system that allows for mental-state reasoning, and also a socio-perceptual system that includes eye-gaze perception, face recognition and emotion recognition, and imitation. Both systems are held to be impaired in autism, and dissociations among systems may be present in other neurodevelopmental conditions (e.g. William’s syndrome; Tager-Flusberg and Sullivan, 2000). Others have postulated further that the social impairments in
autism extend beyond the processing of mental state stimuli to include the online processing of social stimuli, including faces, voices and gestures (e.g. Klin et al. 2003). These broader theory of mind accounts represent attempts to provide a causal explanation of the development of autism. Nevertheless, it is important to note here that by broadening the definition of theory of mind to extend beyond false-belief understanding, these accounts introduce a degree of circularity in which the first signs of autism (poor gaze monitoring, failure to orient towards social stimuli) are, by definition, components of poor theory of mind (see Hughes and Leekam (2004) for discussion).

7.3.4 Explanatory power

Although the theory of mind hypothesis provides an intuitively appealing explanation of the core socio-communicative symptoms of autism, there has been limited direct evidence showing that the degree of theory of mind difficulties are linked to the nature and severity of the symptoms they purport to explain. Tager-Flusberg (2007) has attributed the series of negative findings (e.g. Pellicano et al. 2006; Travis et al. 2001) to the small numbers of individuals with autism included in these studies. Indeed, in the most comprehensive assessment thus far of the explanatory power of theory of mind difficulties, Tager-Flusberg (2003) reported significant longitudinal associations between performance on multiple theory of mind tasks and several behavioural outcome measures in 69 children with autism aged between 4 and 14 years. Early theory of mind performance emerged as a significant predictor of social and communicative functioning one year later, including real-life social functioning (as assessed by the Vineland Adaptive Behaviour Scales; Sparrow et al. 1984), conversational discourse (during a parent–child interaction) and degree of socio-communicative symptoms (as indexed by scores on the Autism Diagnostic Observation Schedules – Generic (ADOS-G); Lord et al. 2000) independent of age and verbal ability. Her findings suggest that the degree of impairments in theory of mind could explain in part the wide variation in socio-communicative symptoms in autism.

Despite such positive analysis, the theory of mind hypothesis has failed to address adequately the distinctive non-social symptoms in autism, particularly the repetitive behaviours and stereotyped interests also characteristic of the condition. Baron-Cohen (1989b) argued that the restricted repertoire of behaviours and interests are merely secondary consequences of a core mindreading deficit – the defence mechanisms that emerge to cope with the unpredictability of the social world. Yet rigid and repetitive behaviours are seen in individuals across the autism spectrum and across all levels of functioning. Furthermore, contrary to Baron-Cohen’s (1989b) thesis, several early studies reported that individuals with
autism show fewer repetitive behaviours and motor stereotypies in interpersonal situations than in situations in which the social demands are limited (e.g. Clark and Rutter, 1981). Moreover, several researchers have failed to find any relationship between scores on false belief tasks and symptoms in the repetitive behaviours domain (Joseph and Tager-Flusberg, 2004; Pellicano et al. 2006; Turner, 1997), questioning whether these atypicalities in mindreading are capable of accounting for the development of all autistic behaviours.

Overall, the theory of mind hypothesis has struggled to satisfy the criteria for an explanatory model of autism. Indeed, critics (e.g. Bloom and German, 2000) have stressed that the success of the hypothesis has centred largely on the validity of the false belief task as an index of theory of mind. They highlighted that failure on such tasks can of course occur for many reasons, and that in the case of autism, could be explained not by a fundamental theory of mind deficit but by deficits in more domain-general processing in executive function (see Section 7.4) or language ability (Bruner and Feldman, 1993; Tager-Flusberg, 2000). Although it was shown initially that children with autism succeed on tasks which have equivalent structure and demands to false belief (or other theory of mind) tasks but do not have mentalistic content (e.g. tests involving false photographs, drawings and models; Charman and Baron-Cohen, 1992; 1995; Leekam and Perner, 1991; Leslie and Thaiss, 1992), more recent analysis of these tasks has questioned whether the structure is in fact identical to standard false belief tasks; see Perner and Leekam (2008), and Sabbagh et al. (2006). One study using a false signs task, in which a sign falsely represents the location of an object, found that the difficulties that children with autism display on false belief task extend to the analogous false signs task, casting doubt on whether the children’s difficulties on false belief tasks are due to a genuine difficulty in representing other minds (Bowler et al. 2005).

Although the theory's proponents have made some plausible arguments in defence of a single primary cognitive difficulty with theory of mind, which stretches beyond problems in false belief understanding, most authors would agree that autism in its entirety is not accounted for by theory of mind alone.

7.4 The Executive Dysfunction Hypothesis

Executive functions are a range of higher order functions, explicitly linked to the prefrontal cortex, which help guide flexible, goal-oriented behaviour, especially in novel circumstances (e.g. Lezak, 1995; Luria, 1966; Pennington and Ozonoff, 1996). Most theoretical models of executive function (e.g. Diamond, 2006; Miyake et al. 2000; Pennington, 1997; Shallice and Burgess, 1991) agree that the construct is componential in nature and includes inhibiting or resisting a
natural response, working memory or the ability to hold information 'on-line' (in the mind) and mentally work with it, and the ability to flexibly shift one's attentional focus.

In what could be interpreted as one of the first demonstrations of a possible executive function impairment in autism, Frith (1972) showed that individuals with autism produced more rule-bound, repetitive and less unique patterns in a task of spontaneous colour and tone sequence production than comparison individuals. It was not until 1978, however, that Damasio and Maurer published an influential paper noting the striking resemblance between individuals with autism and patients with frontal lobe damage, including inflexible, perseverative behaviours, and concreteness in thought and language (Damasio and Maurer, 1978). Subsequent investigations using neuropsychological tasks such as the Wisconsin Card Sort Test (WCST), a test of cognitive flexibility, and the Tower of Hanoi (ToH) task, a test of higher order planning ability, showed that individuals with autism did in fact display remarkably poor performance on such tasks (Prior and Hoffmann, 1990; Rumsey and Hamburger, 1988). Ozonoff et al. (1991) confirmed these findings in an important study comparing performance on theory of mind and executive function tasks in cognitively able or 'high-functioning' children and adolescents with autism and Asperger syndrome. Individuals with autism performed poorly relative to comparison individuals on the WCST and ToH tasks, and Ozonoff et al. (1991) showed that executive function variables rather than theory of mind variables were best able to distinguish between individuals with autism and comparison individuals. This evidence led to the hypothesis that executive deficits might represent a single primary cognitive deficit in autism (Hughes and Russell, 1993; Ozonoff et al. 1991; Russell, 1997), and that the inflexible, 'stuck in set' problem solving strategies might explain autistic individuals' failure on theory of mind tasks. Furthermore, Ozonoff et al. (1991) pointed towards damage to the prefrontal cortex as the possible neuroanatomical underpinnings of executive (and theory of mind) problems in autism.

The executive dysfunction hypothesis has since generated numerous studies largely because of its promise as a candidate for a core cognitive marker in autism; see Hill (2004), O’Hearn et al. (2008), and Russo et al. (2007) for reviews. Indeed, in their review of studies on executive function in autism, Pennington and Ozonoff (1996) reported that 13 out of the 14 existing studies found evidence of disrupted performance on at least one executive task in autism. They also examined the magnitude of the group differences, and estimated the average effect size on executive tasks to be 0.98, and as high as 2.07 on the ToH task. Despite such promise, the hypothesis has faced a series of challenges, and these are outlined below.
7.4.1 Universality

Testing the criterion of universality has been more difficult in the case of executive dysfunction compared with theory of mind, largely because performance on executive tasks, unlike theory of mind tasks, is normally not reducible to ‘pass’ or ‘fail’. Rather, typical executive variables include, for example, percent correct, time taken, number of perseverative responses, or number of rule violations. As a result, some researchers have used an arbitrary criterion of ‘impairment’ to determine the pervasiveness of executive deficits in autism. Ozonoff et al. (1991) calculated the proportion of individuals with autism who performed below the mean composite score of the comparison group for tasks of executive function. Remarkably, they found that impairments in executive function were almost universal in the autism group (96%). These authors, however, used quite a lenient criterion to determine the pervasiveness of executive difficulties. Indeed, if performance on the tasks was genuinely normally distributed, then one should expect to find half of the comparison group also showing ‘impairments’ in executive skills. When more conservative criteria are used, the proportions of individuals with autism demonstrating difficulties are not so striking. Liss et al. (2001) found that 57% of their group of high functioning autistic adolescents scored within 1 standard deviation of the mean number of perseverative errors of the comparison group on the WCST, and Pellicano (2007) reported that between 33% and 50% of her sample of cognitively able children with autism scored more than 1 standard deviation below the mean of the typically developing group on a range of executive function tasks. Other investigators have demonstrated that not all individuals with autism fail executive tasks (Hill and Bird, 2006; Hughes et al. 1994; Ozonoff and Jensen, 1999; Teunisse et al. 2001) (see also Guerts et al. 2009 for discussion), and have shown further that when task success does occur, it is usually in those individuals who are older (Ozonoff and Jensen, 1999) and/or have higher verbal ability (Liss et al. 2001; Ozonoff and McEvoy, 1994; Pellicano, 2007; but see Joseph et al. 2005).

7.4.2 Uniqueness

One other major challenge for the executive dysfunction hypothesis has been research showing that executive problems are not unique to autism but are present also in a variety of other developmental conditions, including, amongst others, conduct disorder, Attention Deficit Hyperactivity Disorder, early-treated phenylketonuria, and Tourette syndrome; see Hill (2004), and Pennington and Ozonoff (1996) for reviews. This so-called ‘discriminant validity problem’ (Pennington and Ozonoff, 1996) has called into question whether executive problems are necessary and sufficient to cause autistic symptomatology, and points
towards the possibility that executive problems might be secondary in autism and possibly some of the other conditions – that is, that executive difficulties are a general consequence of having a developmental condition.

Proponents of the executive dysfunction hypothesis of autism have proposed instead that the development of distinct psychopathology could be explained by different severity and age of onset of executive impairment, and in particular, specific profiles of impairment on the various components of executive function (Ozonoff, 1997; Ozonoff et al. 1994; Pennington and Ozonoff, 1996). Since executive functions cover a range of different component processes, identifying the exact nature of the executive atypicality in autism has been the focus of more recent research. Ozonoff (1995) advocated the use of an information processing approach, which more precisely targets particular executive functions. For example, Hughes et al. (1994) administered the Intradimensional-Extradimensional shift task, a computerised test of cognitive flexibility, to children with and without autism. This task begins with a discrimination learning task, which becomes progressively more challenging such that shifts in discrimination are required either within-set (intradimensional; i.e. to a new set of stimuli) or between-set (extradimensional; i.e. to a new set of stimuli and a new set of dimensions). Hughes et al. (1994) found significant group differences only on the extradimensional shift stage of the task, which involves shifting cognitive set to new categories or rules and which places the most demands on executive resources, indicating a specific difficulty with cognitive switching in autism.

More recent studies making crucial cross-condition comparisons have delineated a profile of difficulties specific to autism in cognitive flexibility and planning (Guerts et al. 2004; Happé et al. 2006a; Ozonoff and Jensen, 1999), but not generativity (Bishop and Norbury, 2005a). It is less clear whether problems in inhibition are included in this profile since some studies have found problems in inhibitory control (e.g. Christ et al. 2007; Hughes, 1996; Rinehart et al. 2002; Williams et al. 2002), while others have not (e.g. Russell et al. 1999). Also, it remains controversial whether working memory problems form part of this profile. While some studies have reported difficulties in verbal (Bennetto et al. 1996) and non-verbal (Dawson et al. 1998; McEvoy et al. 1993) working memory tasks in persons with autism, other studies have failed to demonstrate autism-specific working memory problems in autism (Griffith et al. 1999; Guerts et al. 2004; Ozonoff and Strayer, 2001; Russell et al. 1996). Some theorists (e.g. Russell, 1997) have argued that these atypicalities emerge only if the task involves both inhibitory and working memory requirements.

The challenges faced by the executive dysfunction hypothesis with respect to the criterion of uniqueness raise an important methodological issue. Although executive function has a theoretical definition, it has nevertheless been difficult to
operationalise for several reasons – see Hughes and Graham (2002) for discussion. First, unlike theory of mind, there is no ‘gold standard’ executive task (Burgess, 1997). Second, executive tasks are not process pure. Instead, ‘non-executive’ task factors are also likely to play a role in task performance, and these are notoriously difficult to disentangle from ‘executive’ factors. Third, since executive function tasks need to be sufficiently novel and demanding to engage controlled rather than automatic processing, their test–retest reliability is necessarily limited (Rabbitt, 1997). Indeed, since subsequent performance on the same tasks might be less challenging, it might not recruit the same executive processes as those involved in initial performance (e.g. Bishop et al. 2001). The lack of an operational definition for executive function (and for its component functions) therefore has made it difficult to pinpoint the precise profile of executive atypicalities which distinguish autism from other developmental conditions.

7.4.3 Causal precedence

If indeed executive functioning difficulties do play a causal role in autistic symptomatology, then it should be the case that deficits in these areas should be readily apparent in very young children with autism. McEvoy et al. (1993) administered a spatial reversal task to pre-schoolers with autism (mean age = 5 years 1 month). In this task, the child observes as the experimenter hides a reward in one of two identical containers placed to the left and right of the child’s midline, concealed behind a screen. After the screen is removed, the child searches for the reward. Once the child retrieves the reward successfully for several consecutive trials (and forms an arbitrary stimulus–response mapping), the side of hiding is reversed, and it is on these so-called ‘reversal’ trials that he/she must shift to a new stimulus–response set. Pre-schoolers with autism in the study by McEvoy et al. (1993) made significantly more perseverative errors on this spatial reversal task. Dawson et al. (1998) assessed young children with autism (mean age = 5 years 5 months) on a version of the A-not-B task (see Diamond, 2002). In this task, the child observes as the experimenter hides a desired object in one of two places (e.g. location A). Following a delay (e.g. 5 seconds), the child is encouraged to find the object. After several successful searches, the child is shown the object again but this time the side of hiding is reversed (e.g. to location B). Young children with autism committed significantly more errors on ‘reversal’ trials compared to children with Down syndrome or typically developing children (Dawson et al. 1998).

Subsequent studies have failed, however, to find autism-specific executive difficulties at a young age. Griffith et al. (1999) tested young children with autism (mean age = 4 years 4 months) and children with developmental delay on a range
of developmentally appropriate executive function tasks, including tasks measuring inhibition, set-shifting, spatial and object working memory, and action monitoring. Surprisingly, they found no group differences in performance on any executive function measure. Furthermore, a longitudinal follow-up of the same samples of children showed that autistic children’s performance on the spatial reversal task did improve over the one-year period, and still no group differences were found at age 5 years. More recent studies have supported this conclusion (Dawson \textit{et al.} 2002; Rutherford and Rogers, 2003; Stahl and Pry, 2002).

The apparently intact executive abilities of young children with autism suggest that executive difficulties cannot account for the earliest symptoms of autism, and instead suggest that executive problems may be acquired later, and could be a secondary consequence of other more primary cognitive atypicalities. If this were the case, then children with autism would show impaired performance on executive tasks compared with a group of typically developing children (rather than children with developmental delay; Griffith \textit{et al.} 1999), and the magnitude of these group differences would increase with age. A recent study by Yerys \textit{et al.} (2007) suggests, however, that this is not the case. They assessed the executive skills of the youngest autism sample to date (mean age = 2 years 11 months), and failed to find autism-specific difficulties on executive tasks when compared to either a group of children with developmental delay matched both in terms of mental and chronological age, or a group of chronological age-matched typically developing children. Yerys \textit{et al.} (2007) suggested that executive problems are therefore an unlikely candidate for a primary cognitive deficit in autism and instead might emerge as a consequence of having autism (though see Ozonoff \textit{et al.} (2004) for evidence of age-related increase in set-shifting problems in cognitively able adults with autism).

It remains possible that executive difficulties may have been missed in young children with autism because the tasks themselves are not sufficiently sensitive to detect what could be quite subtle difficulties in these young children with autism. Biró and Russell (2001) have noted that the tasks generally used with such young children do not invoke the use of arbitrary rules, which they assert is precisely the primary difficulty in autism. Also, executive problems might have been missed because researchers have not employed a thorough range of executive tasks. The past few years have seen the development of a range of reliable and valid tests to assess ‘fledgling’ executive skills in typically developing toddlers (Carlson \textit{et al.} 2004a; Hughes and Ensor, 2005). It remains to be seen whether young children with autism will show problems on these tasks. Most of the studies reporting unimpaired executive function in young children have used tasks that have been linked directly to the dorsolateral prefrontal cortex (e.g. A-not-B task). One
exception to this is work by Dawson et al. (1998; 2002) (see also Munson et al. 2008), which employed tasks that are known to activate the ventromedial prefrontal cortex, a region which has been linked to the processing of emotionally salient (rather than emotionally neutral) stimuli. Nevertheless, as it stands, this failure to demonstrate supporting evidence for an autism-specific problem in executive dysfunction at quite a young age challenges the idea that autistic symptomatology is a result of atypicalities in executive function.

7.4.4 Explanatory power

The executive dysfunction hypothesis has considerable face validity: it seems to easily explain the inherent rigidity and invariance of autistic behaviours, as a result of a reduced ability to generate novel, goal-directed behaviour. Indeed, evidence to support this claim has been reported for links between repetitive behaviours and measures of executive function. Turner (1997) showed that lower-level repetitive behaviours (e.g. motor stereotypies) were associated with perseverative responses on a set-shifting task, while higher-level repetitive behaviours (e.g. circumscribed interests) were related to the inability to switch cognitive set on the same task, and a reduced ability to generate new ideas. Similarly, López et al. (2005) found significant associations between restrictive and repetitive symptoms and indices of cognitive flexibility, inhibitory control and working memory, and, more recently, South et al. (2007) found a significant relationship between performance on the WCST and a measure of repetitive behaviour (see also Boyd et al. 2009; but see Pellicano et al. 2006; Joseph et al. 2005).

There have been less favourable findings, however, from studies investigating the strong version of the executive dysfunction hypothesis, that executive dysfunction has the power to explain also the persisting social handicaps in autism (Bennetto et al. 1996; Pennington et al. 1997; Rumsey, 1985; Russell, 1997; see section 7.6 below). There is some limited evidence for a link between performance on executive measures and measures of social functioning. McEvoy et al. (1993) found that performance on executive function tasks and joint attention behaviours were related in pre-school children with autism, and Griffith et al. (1999) demonstrated a significant association between early executive skills (performance on a spatial reversal task) and socio-communicative behaviour (bids for joint attention) in young children with autism, but not in children with developmental delay, both concurrently and longitudinally. Using more ecologically valid tests of executive function, Hill and Bird (2006) found that individual differences in performance on executive measures were significantly related to certain features of autistic symptomatology (specifically, pragmatic communication) in adults with Asperger syndrome. Joseph and Tager-Flusberg (2004) reported
evidence of significant associations between a planning measure and communicative symptoms in children with autism, although this correlation failed to remain significant once variation in children’s verbal ability was adjusted for (using partial correlations). Several other studies, however, have failed to find evidence of a link between executive function variables and specific features of autistic symptomatology (Bishop and Norbury, 2005b; Liss et al. 2001; Pellicano et al. 2006) when variance attributable to verbal and/or non-verbal ability was accounted for.

It is noteworthy that executive skills have been linked to a distinct aspect of outcome, adaptive functioning, typically measured by the Vineland Adaptive Behaviour Scales (Sparrow et al. 1984) in both cross-sectional and longitudinal work. Ozonoff et al. (2004) found a significant negative correlation between scores on a computerised version of the Tower of London task (the Stockings of Cambridge) and adaptive behaviour scores in a large group of adults with autism, in which poor executive skills were associated with fewer real-life adaptive skills (also see Gilotty et al. 2002). Happé et al. (2006a) reported significant links between certain executive measures and some aspects of concurrent adaptive functioning in adolescent boys with autism. In a 3-year follow-up study, Berger et al. (2003) found that, after controlling for verbal IQ, cognitive flexibility significantly predicted the social competence scores of high functioning young adults with autism in residential care. Similarly, in a long-term outcome study of cognitively able adults with autism, Szatmari et al. (1989) showed that a measure of cognitive flexibility, the WCST, upon initial testing was a strong predictor of adaptive functioning at follow-up between 11 and 27 years later. Although it remains unclear whether executive skills are a specific correlate of autistic symptomatology, these latter studies suggest that they may be one of a set of skills necessary for achieving later independence.

In sum, there have been numerous challenges to the executive dysfunction hypothesis in terms of its claims on universality, uniqueness, causal precedence and explanatory value, all of which are damaging to the notion that executive dysfunction plays a primary causal role in the development of autism. Critics of the executive dysfunction account have raised one other potential problem: if executive function difficulties are causally related to autistic symptomatology, then patients with acquired frontal lobe damage, who show executive function deficits, should meet diagnostic criteria for autism (see Bishop, 1993). A more appropriate comparison would be between children with autism and children who have sustained early damage to the prefrontal cortex, and therefore grown up with problems in executive function. Interestingly, these children do in fact show impairments in social interaction, spontaneous speech and pragmatic communication, and the production of novel, goal-directed behaviours but they do not actually go on to develop autism, more often displaying a condition resembling
psychopathy or conduct disorder (Anderson et al. 1999; Eslinger et al. 1992; 1997). These findings point to the possibility that executive problems might be necessary but not sufficient to cause the full range of autistic symptomatology (see Section 7.6 for further discussion).

7.5 Central Coherence Theory

Frith (1989) identified one problem fundamental to these and other theories of autism which construed the condition in terms of deficits: they failed to explain the preserved or superior areas of skill present in individuals with autism. Initial clinical observations by Kanner (1943) and Asperger (1944) emphasised that, despite their impairments, many of their children with autism displayed special talents or ‘islets of ability’. Indeed, the incidence of savant skills, that is, exceptional skills in the context of disability, in areas such as music, drawing, and mathematics, is much higher in individuals with autism than in those with intellectual difficulties (Heaton and Wallace, 2003; Hermelin, 2001; Rimland and Hill, 1984). Kanner (1943) highlighted other more common features, including excellent rote memory and a preoccupation with parts of objects, the latter of which has remained part of the current diagnostic criteria for autism (American Psychiatric Association, 1994; 2000). He also commented on children’s remarkable ability to detect rapidly very minor modifications to their environment, and this peculiar attention to detail was considered to be one manifestation of what he termed ‘insistence on sameness’.

Early empirical work also elucidated an unusual profile of performance on experimental tasks, where children with autism tended to do well on tasks where the stimuli were unarranged or devoid of meaning relative to tasks which entailed patterned or meaningful stimuli (Frith and Hermelin, 1969; Hermelin and O’Connor, 1967). Children were just as good, for example, at recalling jumbled sentences as coherent ones (Hermelin and O’Connor, 1967), and were as proficient at completing jigsaw puzzles upside-down as they were picture-side up (Frith and Hermelin, 1969). In an influential study, Shah and Frith (1983) tested children’s performance on the Embedded Figures Test (EFT) (Witkin et al. 1971), where one must find hidden figures (e.g. a triangle) within larger meaningful drawings (e.g. a clock) as quickly as possible. Remarkably, autistic children’s performance exceeded that of children with moderate learning difficulties (MLD), who were matched for non-verbal mental age.

The findings from these initial clinical and experimental reports led to Frith’s (1989) formulation of central coherence theory. She described how typical individuals display ‘central coherence’: the natural propensity to process stimuli as Gestalts, which predominates over a local or piecemeal style of processing. In
contrast, individuals with autism exhibit ‘weak’ central coherence – an inherent preference for processing local elements over the global whole. Frith (1989) and Frith and Happé (1994) argued that this local processing bias could effectively explain autistic children’s enhanced performance on tasks such as the EFT since it enables them to focus immediately on the individual elements of stimuli. In contrast, typically developing individuals take longer to find the embedded figure because they become captured by the global meaning and need perceptually to resist the Gestalt. Frith and Happé (1994) explained further how weak central coherence in autism could account for another often-cited ‘islet of ability’ – superior performance on the Block Design task (Happé, 1994c; Tymchuk et al. 1977). Shah and Frith (1993) showed that pre-segmenting the to-be-copied designs, such that the individual blocks were immediately apparent, benefited the performance of control participants but did not confer any advantage to participants with autism. Enhanced performance on the standard task by individuals with autism seemed to be attributable to a natural facility for perceiving the design in terms of its constituent parts (see also Caron et al. 2006).

Central coherence theory (Frith, 1989; Frith and Happé, 1994) has engendered a significant amount of research during the past two decades. It makes two clear predictions. First, since (weak) central coherence is considered to be a domain-general information processing style, this particular cognitive style in autism is expected to pervade all areas of an individual’s functioning, not just in the visuospatial domain. Second, the theory predicts that the relationship between local and global processing is reciprocal in nature. Accordingly, individuals with autism, who display weak central coherence, should demonstrate preserved or even enhanced performance on tasks where a local processing style is beneficial, but perform poorly on those tasks that necessitate the integration of information.

Several lines of evidence show support for this cognitive style in individuals with the condition for a variety of different stimuli across several levels of functioning, including visuospatial, perceptual (visual and auditory), and to a lesser extent, verbal-semantic levels (see Frith and Happé (1994), Happé (1999), Happé and Booth (2008), and Happé and Frith (2006) for reviews). Yet this evidence has been tempered by a series of inconsistent findings, largely driven by repeated demonstrations of intact global or contextual processing in autism (e.g. Caron et al. 2006; López and Leekam, 2003; Mottron et al. 1999; 2003; Norbury, 2004; 2005; Ozonoff et al. 1991; Plaisted et al. 1998; 1999; Ropar and Mitchell, 1999; 2001). Indeed, several elegant studies using a variety of task paradigms have shown that individuals with autism can in fact process information at the global level when they are instructed to do so (López et al. 2004; Plaisted et al. 1999; Snowling and Frith, 1986).

Happé and Frith’s (2006) review of existing empirical work led to a reappraisal of the notion of weak central coherence in autism. They asserted that ‘the original
suggestion of a core deficit in central processing, manifest in failure to extract
global form and meaning, has changed from a primary problem to a more sec-
ondary outcome – with greater emphasis on possible superiority in local or detail-
focused processing’ (Happé and Frith, 2006; page 6, but see Behrmann et al. 2006,
and Happé and Booth, 2008). Importantly, Happé and Frith (2006) stressed that this
default can be overridden in the event of explicit situational demands to permit
processing at the global level. Several researchers have responded to the shortfalls
of this particular aspect of central coherence theory with alternative explanations
of their own (Baron-Cohen, 2002; Baron-Cohen et al. 2005; Mottron and Burack,
2001; Mottron et al. 2006; Plaisted, 2000; 2001).

7.5.1 Universality

The theory predicts that a weak drive for coherence should be present in all individuals across the autism spectrum, regardless of age or ability (Happé, 1999). In support of this claim, weak central coherence has been demonstrated in autistic individuals with MLD (e.g. Hermelin and O’Connor, 1967; van Lang et al. 2006) and cognitively able individuals with autism (Happé, 1994c; 1997), and from early childhood (e.g. Morgan et al. 2003) to adulthood (e.g. Jolliffe and Baron-Cohen, 1997).

Numerous studies, however, have failed to find evidence in favour of weak central coherence in individuals with autism therefore questioning whether weak central coherence is in fact a universal feature of the condition (Bowler et al. 2000; Brian and Bryson, 1996; Burnette et al. 2005; López and Leekam, 2003; Norbury, 2004; 2005; Ozonoff et al. 1991; 1994; Ropar and Mitchell, 1999; 2001). An evaluation of these studies is beyond the scope of this overview but suffice to say that the studies vary considerably in terms of the populations sampled and the ages and abilities of the persons with autism, making it difficult to draw firm conclusions regarding the pervasiveness of the weak coherence bias. One alternative way to approach this issue is to examine the proportion of individuals who exhibit weak central coherence in those studies where supporting evidence has been reported. Happé demonstrated that almost all her sample of cognitively able children with autism exhibited a weak coherence bias as indexed by peak performance on the Block Design task (Happé, 1994c) or by poor use of context on the homograph task (Happé, 1997). Consistent with Happé, Pellicano et al. (2006) found that exceptional performance on three visuospatial coherence tasks (EFT, Block Design and Figure-Ground tasks) characterised between 78% and 92% of their group of young children with an ASD (aged 4 to 7 years).

Other findings, however, have indicated that weak coherence might be present in only a subset of individuals with autism. Teunisse et al. (2001) reported that 18 out of 35 of their sample of adolescents with autism exhibited this cognitive style.
Similarly, in a study on canonical counting, Jarrold and Russell (1997) showed that just under half of their sample of children with autism \((N = 22)\) failed to adopt a local strategy (in their study, counting dot by dot). More recently, Caron et al. (2006) reported that almost half (42\%) of their sample of adults with autism \((N = 92)\) displayed a relative peak in performance on the Block Design task compared with 2\% of their sample of typically developing individuals \((N = 112)\). Although superior local processing might be more prevalent in autism than in typically developing populations, this latter finding indicates that this superiority might not be universal in more able adolescents and adults with autism.

### 7.5.2 Uniqueness

The few studies that have examined the specificity of weak central coherence in autism have yielded mixed results. In a study designed to test directly the criterion of uniqueness, Booth et al. (2003) administered a drawing task to children with autism, children with ADHD, and typical children. Only the children with autism were found to display a detail-focused drawing style, suggesting that this style might be unique to autism. Several other findings, however, have been less definitive. A local processing strategy has also been reported on perceptual coherence tasks by children with MLD (Jarrold and Russell, 1997; van Lang et al. 2006). Weak central coherence at the verbal-semantic level has been demonstrated in children with specific language impairment. Using either figures of speech or homographs, Norbury (2004; 2005) found that, akin to a subgroup of children with autism who exhibited concomitant language impairments, children with isolated (specific) language impairments also failed to use surrounding contextual cues to abstract higher-level meaning.

Researchers have also pointed towards a local processing style in children with Williams syndrome (Bihrlle et al. 1989; though see Pani et al. 1999), casting further doubt on whether weak central coherence is specific to autism. Interestingly, unlike individuals with autism who demonstrate preserved or superior performance on the Block Design task due to a facility for segmentation (Shah and Frith, 1993), persons with Williams syndrome perform significantly worse on this task, relative to typically developing comparison individuals (Farran et al. 2001). These authors suggest that, for individuals with Williams syndrome the local bias most clearly hinders performance during the construction phase of the task, while for children with autism, the local bias seems to manifest itself at the initial segmentation or perceptual phase of the task, thus resulting in superior performance. It is surprising, however, that inferior and superior performance on the same task have been interpreted as reflecting a local processing bias; research designed to tease apart the different stages of processing for the Block Design task (e.g. Caron et al. 2006) across several developmental disorders is clearly desirable.
7.5.3 Explanatory power

In its strongest form (Frith, 1989), weak central coherence is held to play a primary causal role in the development of autistic symptoms. Frith described how an impaired ability to draw together complex information in the social environment in order to derive coherent and meaningful interpretations of social situations would result in ‘an incoherent world of fragmented experience’ (Frith, 1989; page 98). Similarly, she argued that an inability to extract meaning during a conversational exchange would impede an understanding of the ‘deeper intentional aspects of communication’ (Frith, 1989; page 124). She explained further that without the overriding drive for deriving coherence, automatic (maladaptive) behaviours could not be inhibited, thus resulting in rigidly structured and repetitive behaviour.

Very few studies have investigated whether indices of weak central coherence are related to autistic symptoms. One positive finding was reported by Briskman et al. (2001) in their investigation of weak central coherence in individuals with the broader autism phenotype. They demonstrated links between performance on coherence measures (e.g. un/segmented Block Design and EFT) and scores on a self-report questionnaire relating specifically to attention to detail in parents of children with autism (but not parents of children with dyslexia). Nevertheless there is limited evidence for a direct link between this cognitive style and behavioural symptoms (social or non-social) in individuals who meet diagnostic criteria for autism. Berger et al. (2003) investigated whether weak central coherence or executive dysfunction was best able to predict the functional outcomes of young adults with autism over a 3-year period. They found no support for a relationship between coherence measures and indices of social competence; instead, reduced set-shifting ability was significantly related to individuals’ prognosis. Also, Pellicano et al. (2006) failed to find a significant link between performance on central coherence and a measure of autistic symptomatology (scores on the Autism Diagnostic Interview–Revised; Lord et al., 1994) in their samples of children with autism (see also Burnette et al. (2005) and South et al. (2007)). These negative findings might be attributable to the rather crude measures of symptomatology used in these studies, and any such associations might be best elucidated by a more fine-grained assessment of behaviours of interest (e.g. insistence on sameness).

Although Frith (1989) originally considered weak central coherence to explain the non-social and the social symptoms of autism, subsequent findings led Frith and Happé (Frith and Happé, 1994; Happé and Frith, 2006) to no longer make strong claims about primacy. Initial findings revealed little association between weak central coherence and theory of mind in individuals with autism (Happé,
In one study, Happé (1994c) showed that superior performance on the Block Design task was characteristic of almost all individuals with autism in her sample, independent of theory of mind ability. Similarly, in a second study, the entire group of adults with autism displayed weak coherence on the homograph task, regardless of whether they were successful ‘mindreaders’ (Happé, 1997). In light of this evidence, Frith and Happé (1994) abandoned their earlier position, arguing that weak central coherence on its own was unable to provide a complete account of autism. In more recent work, they consider weak central coherence to be one of several primary cognitive atypicalities in autism, including problems in theory of mind and executive control (Happé and Frith, 2006) in which each atypicality is held to play a causal role in the development of some (but not all) symptoms.

7.5.4 Causal precedence

Very little attention has been paid to the development of a local processing bias either theoretically or empirically. The youngest age at which a local processing bias has been detected using common central coherence tasks comes from a study by Morgan et al. (2003). They reported superior performance on the Pre-school version of the EFT and Pattern Construction task (similar in nature to the Block Design task) in pre-schoolers with autism (mean age = 4 years 6 months) relative to typically developing children of similar age and non-verbal ability. Although Happé and Frith (2006) do not elaborate on what might be the earliest manifestations of weak central coherence in autism, one rival account, Mottron et al.’s (2006) Enhanced Perceptual Functioning model, says something about the developmental course of a local processing bias. Mottron et al. (2006) proposed that autistic individuals’ peaks in perceptual abilities derive from the overdevelopment of basic low-level perceptual processes, including local processing. Rather than being present from birth, enhanced local processing emerges early during the course of development and in response to diminished higher order processing operations. In a longitudinal study on children’s cognitive skills, Pellicano (2010a) found that children with autism were no quicker to find the hidden figure on the CEFT than they were 3 years earlier, and that they made no improvements on the Pattern Construction task over time. This lack of improvement was in striking contrast to the significant gains made by typically developing children on both visuospatial coherence tasks, which implies, rather paradoxically, that typical children develop a more pronounced local processing bias over time. Other factors, however, are more likely to be driving this developmental change. For example, typical children’s maturing executive skills might enable children to better resist interference from the overall Gestalt and therefore rapidly locate either the hidden figure (in the case of the CEFT) or the blocks necessary to reconstruct the design.
(in the case of the Pattern Construction task). For children with autism, local processing skills might be early-emerging and initially accelerated (cf. Mottron et al. 2006), and their concomitant problems in executive control might not limit performance on such tasks.

The notion of ‘weak’ central coherence in autism has been very influential. Not only has the theory generated a great deal of interest in local and global processing in autism, it also has forced researchers to reappraise their understanding of the condition as one with a specific pattern of weaknesses and strengths. In light of the significant challenges faced by the theory, the proponents no longer make strong claims about primacy. Rather than proposing that weak central coherence plays a unique causal role in the development of autism, the revised version of the theory espouses multiple cognitive atypicalities, including coexisting atypicalities in central coherence, theory of mind and executive function each of which might have their own distinctive causal pathways (see Section 7.6 for discussion) (Happé and Frith, 2006).

One putatively similar account that deserves mention here is Baron-Cohen’s notion of Systemising (Baron-Cohen, 2002; Baron-Cohen et al. 2005). Proposing that autism is a result of an ‘extreme male brain’, Baron-Cohen postulates that autism is characterised by dual atypicalities: an underdeveloped ability to empathise and, most relevant to this discussion, a hyper-developed ‘systemising’ brain. The latter term systemising is defined as the predominantly male drive to analyse and control non-social systems. He argued that superior systemising can account for the non-social strengths, including savant abilities and attention to detail, and weaknesses, circumscribed interests and repetitive behaviours, that are characteristic of autism. Baron-Cohen’s systemising–empathising theory distinguished itself from central coherence theory (Frith, 1989; Frith and Happé, 1994) by predicting superior local processing combined with intact (rather than impaired) integration in autism, the latter of which is essential to understanding both simple and complex rule-based systems. At present, the evidence for superior systemising is derived largely from self-ratings of preference and abilities (Baron-Cohen et al. 2002), though several authors have begun to establish links between behavioural task performance and scores on questionnaires tapping systemising and empathising (e.g. Brosnan et al. 2010; Lawson et al. 2004; see also Baron-Cohen et al. 2009). The theory has since been grounded in neurobiology (Baron-Cohen and Belmonte, 2005) – reduced functional connectivity to brain regions responsible for higher order social cognition combined with over-functioning of lower-level, perceptual processing. Although similar neural accounts have been proposed for weak central coherence in autism (see Happé and Frith, 2006), little has yet been said as to whether the account satisfies the criteria of universality, uniqueness and explanatory power.
7.6 Beyond single-deficit models of autism

It should be clear from the discussion above that all three cognitive accounts have struggled to meet the various criteria for primacy (particularly the criterion of explanatory power), which ultimately casts doubt on whether an atypicality in one of these domains alone is sufficient to cause such a complex behavioural phenotype. It remains possible of course that there might be other, as yet undiscovered candidates that could prove successful in explaining the full range of autistic symptoms. The shortcomings of these three cognitive accounts, together with emerging evidence that autism might not be a unitary construct, have led to a plea from some authors to ‘give up on a single explanation of autism’ (Happé et al. 2006b; page 1218) in favour of an explanation encompassing coexisting atypicalities in multiple cognitive domains.

The notion of ‘multiple deficits’ in autism is certainly not new. Wing and Wing (1971) first suggested that autism could arise due to multiple psychological deficits that were a result of multiple ‘insults’ at the neurological level. Subsequently, Goodman (1989) proposed that genetic and environmental insults could act upon distinct neural systems, which in turn could cause simultaneous ‘abnormalities’ at the cognitive level, each affecting a specific aspect of cognition. He suggested that it is ‘synergistic interactions’ between these cognitive ‘abnormalities’ that gives rise to the constellation of symptoms we call ‘autism’ (see also Bishop, 1989; Pennington et al. 1997).

Despite these early views, a multiple-deficits view has failed to capture the sustained attention of empirical researchers. This unwillingness to move beyond a single-deficit account is attributable largely to the fact that researchers and clinicians have traditionally assumed that the defining behavioural features of autism – both the socio-communicative symptoms and the non-social symptoms (repetitive behaviours and restricted activities) – occur together more often than what would be expected by chance, thus implicating a single underlying aetiology. Yet there is increasing agreement among researchers that this assumption may be unwarranted (see Boucher, 2006 and Mandy and Skuse, 2008 for discussion).

Two pieces of evidence argue against the traditional view. First, work on the broader phenotype of autism (Bailey et al. 1998) suggests that the relatives of people with autism do not tend to show a profile of symptoms that is qualitatively similar to (albeit milder than) autism in all three behavioural domains; instead, research suggests that the ‘triad of impairments’ may in fact be dissociable. While some relatives of people with autism display co-occurring behavioural symptoms (in the ‘triad of impairments’), which are milder but qualitatively similar to those found in autism proper, the majority of these individuals show behaviours in isolated symptom domains (e.g. social difficulties or repetitive activities alone) (e.g. Bolton
This evidence suggests that the ‘triad of impairments’ might be fractionable, and inherited separately.

Second, research examining autistic traits in the general population further suggests that the behavioural features of autism might only be weakly related (Mandy and Skuse, 2008). Findings from a population-based study investigating autism-related social, communicative and repetitive traits in over 3000 7- to 9-year-old typically developing twin-pairs found that, rather than clustering together, the cross-trait genetic correlations were surprisingly modest-to-low (ranging from 0.4 down to 0.2) both across the general population and in children lying at the extreme end of the distributions, suggesting that largely independent genes may be operating on each aspect of the triad of impairments in autism (Ronald et al. 2006; see also Ronald et al. 2005). Although the defining behavioural features of autism were found to occur together more often than would be expected by chance alone, these authors also showed that a considerable number of children displayed behavioural difficulties in isolation (e.g. social difficulties only, communication problems alone).

Both sets of findings provocatively suggest that the components of the triad might have distinct underlying causes. Indeed, together with the failure to discover a single core cognitive marker for autism, their work led Happé et al. (2006b) to argue that researchers ‘should abandon the attempt to find a single cognitive explanation, in favour of good accounts for each distinct aspect of the triad’ (page 1219). They offered one candidate account of their own: independent cognitive atypicalities in three core domains – theory of mind, executive function and central coherence – are jointly necessary to produce autism, with each atypicality underpinning distinct aspects of the behavioural phenotype. For example, weak central coherence might best account for the perceptual and visuospatial anomalies associated with the condition; executive dysfunction might relate directly to the nature and severity of the repetitive behaviours, stereotypies and circumscribed interests, while a theory of mind deficit might best capture the difficulties in social reciprocity and communication (Figure 7.2). Since these atypicalities are held to be largely independent of each other both at the phenotypic and genetic levels, autistic symptomatology is therefore viewed as the result of multiple and distinct cognitive atypicalities.

Recent evidence partially supports this candidate multiple-deficits account. Pellicano et al. (2006) found that young children with an autism spectrum disorder ($N = 40$) did in fact demonstrate the cognitive profile proposed by Happé and colleagues, including difficulties in aspects of theory of mind (false-belief understanding) and executive function (planning, cognitive flexibility) accompanied by weak central coherence (i.e. enhanced local information processing), relative to age- and ability-matched typically developing children. This support at the group
level was somewhat tempered, however, by a failure to demonstrate the presence of this specific cognitive profile in each child with autism. These initial attempts to test the validity of this candidate account raised an important question: are multiple-deficits accounts confronted by the same set of criteria used to assess the veracity of single-deficit accounts? It is worth considering briefly these criteria in turn.

Should this profile of cognitive atypicalities be present in all, or nearly all, individuals with autism? Issues of task measurement and problems equating task difficulty can of course cloud whether a particular atypicality, or in this case a profile of atypicalities, is universal in individuals with the condition. There are also significant challenges inherent in defining atypicality (see Section 7.4.1), especially when examining individuals with developmental conditions, whose cognitive skills are unlikely to be ‘all or none’. Rather than ‘atypicality’ being conceptualised categorically, Happé and colleagues (Happé et al. 2006b; Happé and Ronald, 2008) have conceived of the three cognitive domains as dimensions located (orthogonally) within a multivariate space. If one accepts a multidimensional version of this candidate multiple-deficits view, then the lack of universality of this particular cognitive profile may actually turn out to explain some of the heterogeneity in the condition. Indeed, the extent to which a person with autism shows a particular cognitive atypicality therefore should vary according to the place he/she occupies on that dimension, which in turn, should relate directly to the degree and nature of the behavioural symptoms it purports to explain.
It is easy to see how the criterion of uniqueness should apply to a multiple-deficits view. Since it is the co-occurrence of all three cognitive atypicalities that yields ‘autism’, one should expect that no other developmental condition should share all three atypicalities. It is plausible nevertheless that some conditions might show atypicalities in one or even two of the domains. For example, children with pragmatic language difficulties, who show similar socio-communicative symptoms to children with autism, show abnormalities in two putative cognitive dimensions – impairments in some aspects of executive function (generativity: Bishop and Norbury, 2005a) and difficulties understanding other minds (e.g. Shields et al. 1996).

It is also clear that the cognitive accounts held to explain each distinct aspect of the phenotype should show explanatory power. In a multidimensional model, one should expect that a cognitive atypicality should be shown by anyone displaying the relevant behavioural symptom, and that the degree of impairment within each dimension should be associated with the extent of symptomatology. Consideration of this issue in the sections above indicated, however, that there is limited evidence for a link between cognitive atypicality and behaviour for each of the three cognitive domains. A failure to establish links between performance on cognitive tasks and everyday behavioural symptoms in autism may be due to the difficulties inherent in acquiring a valid representation of the child’s current symptomatology (see Bishop and Norbury (2002) and Pellicano et al. (2006) for discussion). Or it may reflect the possibility that there is no simple or direct relationship between current cognitive functioning and behavioural symptoms (Karmiloff-Smith et al. 2002). Further still – and most damaging for Happé et al.’s candidate multiple deficits account – it could indicate that these particular cognitive atypicalities, that is, difficulties in theory of mind, executive function and central coherence, are not sufficient to cause the triad of impairments. Establishing links between performance on cognitive tasks and everyday behavioural symptoms in autism is clearly a key challenge for future research.

In addition to satisfying these criteria, there are several additional challenges faced by a multiple deficit view. Current thinking assumes that these atypicalities in autism are largely independent of each other, and that different genes might contribute to each aspect of cognition (Happé et al. 2006b). These authors hint at the possibility that there might be interactions between cognitive functions but do not discuss the extent or nature of potential interactions between domains. This view is sharply contrasted with the developmental approach championed by several authors (e.g. Bishop, 1997; Karmiloff-Smith, 1998), which emphasises the dynamic nature of developing systems, where interactions between domains are likely to be the norm and where a selective difficulty at an early point during development
is likely to have substantial knock-on effects on the subsequent development of
other cognitive functions (see also Oliver et al., 2000). On this view, the different
cognitive atypicalities might be seen to occupy different positions in a causal
chain.

In direct contrast to Happé et al.’s (2006) suggestion, significant associations
have in fact been demonstrated between cognitive domains in both autism and in
typical development (e.g. Carlson and Moses, 2001; Hughes, 1998a; 1998b; Jarrold
et al. 2000; Ozonoff et al., 1991; Pellicano, 2007; 2010b). Indeed, research on the
typical development of theory of mind and executive function has consistently
demonstrated a robust relationship between individual differences in tasks tapping
theory of mind and tasks tapping several components of executive function,
including mental flexibility, inhibitory control and working memory (but not
planning ability), independent of age and IQ, in pre-schoolers (e.g. Carlson and
Moses, 2001; Carlson et al. 2004b; Frye et al. 1995; Hughes, 1998a; 1998b), and more
recently, in toddlers (Carlson et al. 2004a; Hughes and Ensor, 2007). These findings
have prompted fervent theoretical discussion surrounding the functional link
between these cognitive domains. For example, some theorists (e.g. Perner, 1998;
Perner and Lang, 1999; see also Carruthers, 1996) argue that theory of mind is a
prerequisite for the later development of executive control, while others (Moses,
2001; Russell, 1997) argue that the causal direction is reversed, such that executive
function is a necessary precondition for understanding others’ mental states. Find-
ings from several longitudinal studies (e.g. Carlson et al. 2004a; 2004b; Flynn et al.
2004; Hughes, 1998b; Hughes and Ensor, 2007) demonstrate a functional relation-
ship in one direction only, such that performance on executive function measures
predicts developmental changes in performance on false-belief measures but not
vice versa, therefore providing compelling evidence that early executive function
plays a critical role in the emergence of theory of mind in typical development
(cf. Moses, 2001; Russell, 1997).

There are fewer studies on the association between theory of mind and exec-
utive function in autism, although the very co-occurrence of such difficulties
is suggestive of a link between domains. Significant theory of mind-executive
function correlations have been documented, independent of age, verbal ability
and non-verbal ability (e.g. Joseph and Tager-Flusberg, 2004; Ozonoff et al. 1991;
Pellicano, 2007), and one cross-sectional study provided clues to developmental pri-
macy, indicating that executive abilities might be especially important for theory

Links between other cognitive domains are less clear. While some researchers
have found evidence for the independence of theory of mind difficulties and weak
central coherence in individuals with autism (Happé, 1997; Pellicano et al. 2006),
others have not (Baron-Cohen and Hammer, 1997; Jarrold et al. 2000). Also, there
is some evidence for a significant link between central coherence and executive function in children with autism (Pellicano et al. 2006; though see Booth et al. 2003), with some authors suggesting that one domain-general account could potentially be subsumed by the other (cf. Pennington et al. 1997).

Given the evidence for a significant link between some (though not all) of these domains, it might therefore be more plausible to expect that the dimensions within this candidate multiple-deficits model might not be orthogonal. Crucially, devising a theory that can take account of the interrelationships between aspects of cognition can only be accomplished within a developmental framework. At present, there are very few longitudinal studies examining the development of specific cognitive functions rendering it uncertain as to how this specific profile of cognitive atypicalities might manifest themselves during development. Remarkably, out of the multitude of studies published on autism every year, only five longitudinal investigations have traced developmental changes in theory of mind (Holroyd and Baron-Cohen, 1993; Ozonoff and McEvoy, 1994; Pellicano, 2010a; Serra et al. 2002; Steele et al. 2003), a mere three studies have charted changes in executive function (Griffith et al. 1999; Ozonoff and McEvoy, 1994; Pellicano, 2010a), and only one study has examined longitudinally changes in local processing in autism (Pellicano, 2010a). Consequently, there is very little knowledge about the development of these functions in individuals with autism. Does the full set of atypicalities co-exist at birth or do the different cognitive atypicalities emerge at different points during development? Moreover, how are these atypicalities related throughout development? This latter point raises the issue of developmental causal links between the three cognitive domains: do the three co-occurring cognitive atypicalities develop independently from one another or does one atypicality take precedence over another during development? It is possible that difficulties in one area (executive function, for example) might cause problems in another area (theory of mind, for example) during development, in which case we may come full circle to the notion of a ‘single primary deficit’. Preliminary evidence suggests that this might be the case. In a 3-year follow-up study, Pellicano (2010b) found that individual differences in children’s early skills in executive function and central coherence (Time 1) were longitudinally predictive of later theory of mind skills (Time 2), independent of age, language, non-verbal intelligence and early theory of mind skills. Predictive relations in the opposite direction, however, were not significant, and there were no developmental links between executive function and central coherence. Rather than viewing problems in these three domains as co-occurring, independent and predominantly static atypicalities in autism, these findings suggest that early domain-general skills might play a critical role in shaping the developmental trajectory of other functions (in this case, theory of mind). Since variation in both
intellectual functioning and language ability plays a significant role in the development of the condition, attention should be directed towards elucidating the precise nature of this role, and how it relates to the cognitive capabilities in local processing and co-existing difficulties in theory of mind and executive function.

Traditionally, research was targeted towards specifying the single primary cognitive ‘abnormality’ to explain the development of autism. The field has since rejected this view in favour of a multiple-deficits account, which may be a more plausible explanation of autism given the extant heterogeneity evident at genetic, neurobiological and behavioural levels. It should be clear from this discussion that a multiple-deficits view of autism is confronted by a set of questions similar to those asked of a single-deficit account, as well as additional challenges, which require the analysis of concurrent and predictive relationships between cognitive functions. Teasing apart the complex (cognitive) mechanisms underlying the diverse set of autistic symptoms must be addressed longitudinally if we are to appreciate fully how these multiple atypicalities emerge during the development of the condition.

7.7 References


Cognitive flexibility in autism: a social-developmental account

PETER HOBSON AND JESSICA HOBSON

There are important social-developmental contributions to the acquisition of flexible, generative, context-sensitive thinking and engagement with the world. We highlight how among individuals with autism, limitations in the propensity to identify with the attitudes of other people might lead to a paucity of movement across alternative ‘takes’ on the world, and with this, specific forms of cognitive restriction and rigidity.

8.1 Introduction

Consider this condensed version of a classic description of a person with autism called L (Scheerer et al. 1945). L was first seen at the age of 11 with a history of severe learning difficulties. He was said never to have shown interest in his social surroundings. Although he had an IQ of only 50 on a standardised test of intelligence, L could recount the day and date of his first visit to a place, and could usually give the names and birthdays of all the people he met there. He could spell forwards and backwards.

L’s background history included the fact that in his fourth and fifth years he rarely offered spontaneous observations or reasons for any actions or perceived event. Nor would he imitate an action of others spontaneously. He was unable to understand or create an imaginary situation. He did not play with toys, nor did he show any conception of make-believe games. He was unable to converse in give-and-take language. He barely noticed the presence of other children, and was said to have ‘little emotionality of normal depth and coherence’.

Up to 15 years of age, L was unable to define the properties of objects except in terms relating to his own use of the objects or to specific situations. For example, he defined orange as ‘that I squeeze with’, and an envelope as ‘something I put in with’. He could neither grasp nor formulate similarities, differences or absurdities, nor could he understand metaphor. At the age of 15 he defined the difference between an egg and a stone as ‘I eat an egg and I throw a stone’. Once, when the doctor said ‘Goodbye my son’, L replied: ‘I am not your son’. When asked ‘What would happen if you shot a person?’, L replied: ‘He goes to the hospital’. He showed no shame in parading naked through the house.

We begin with this case description, for two reasons. First, it captures something of the quality of rigid thinking that typifies autism – a ‘stuckness’ that does not extend to all kinds of thought. Second, it sets L’s cognitive limitations in a broader context (also Kanner, 1943). Not only do we see that there is specificity to L’s impairments, indeed that in some respects he has exceptional cognitive abilities as well as disabilities, but also our attention is drawn to aspects of L’s communicative and social-emotional relations that might bear an intimate relation to the nature of his thinking disorder. For example, L would rarely see someone else’s actions and make those his own through imitation, he seemed not to engage with others’ feelings or perspectives in either verbal or non-verbal give-and-take exchanges, and he seemed unselfconscious. If we were to focus too narrowly on data from children’s performance on standardised cognitive tests, revealing though these can be for what is characteristic of children, we might overlook developmentally important links among the children’s impairments across different domains of functioning.

It remains the case that a hallmark of the syndrome of autism is the children’s lack of flexibility in acting, thinking and relating to the world. Why should this be? It is not self-evident why individuals who are limited in their engagement with other people should also be restricted in thinking about things in one way and then another, nor that they should appear insensitive to context in adjusting their thought and language, nor that they should become preoccupied with certain narrow topics to the exclusion of others. If we could explain these coincidences in the case of autism – and we shall suggest the explanation is not far beneath the surface of case descriptions such as that of L – then this might lead us to deeper understanding of the foundations for and/or implications of thinking itself.

Our aim in this chapter, then, is not to present a comprehensive account of the sources of inflexibility in thinking among persons with autism. Partly this is because there may be several causes (both aetiological and developmental) to this aspect of the disorder, some of which operate in only a proportion of affected children. Yet despite such heterogeneity, we consider that one important source of restrictions in thinking among most if not all individuals with autism is their difficulty in engaging with, and being moved by, the bodily expressed attitudes of
other people towards a shared world. If, as Vygotsky (1978, p. 57) argued, ‘All the higher functions originate as actual relations between human individuals’, then no wonder if the children’s failure to interiorise their experience of other people’s relatedness to the environment leads to impoverishment in their own ability to generate and adopt multiple ‘takes’ on the world.

At present, evidence for or against the thesis we shall be propounding is inconclusive. Indeed, one reason we believe it may be worthwhile to articulate our position on these matters is that this may provoke researchers to seek evidence that it is mistaken. Yet our hunch is that it will prove to be important in explaining cognitive deficits that characterise autism.

8.2 Frameworks of understanding

In the spirit of developmental psychopathology, the challenge of understanding why children with autism are limited in the flexibility of their thinking is linked with another challenge, namely that of characterising the nature and basis of flexible thinking among children who do not have autism. From a complementary perspective, if we can both conceptualise and account for the development of thinking among typically developing children, this should stand us in good stead when we try to pinpoint factors that impair the development of thinking in the atypical case. Indeed, the way we think about thinking makes a big difference to the probability of success in explaining its development and pathology. Here it may be helpful to consider two contrasting approaches to the cognitive abnormalities in autism, presented in oversimplified but not unfamiliar guises for the sake of argument.

8.2.1 A ‘hardware’ approach

One might start by considering paradigmatic cases of flexible thinking among adults as manifest in tests of executive functioning, and then note how neurological conditions such as frontal lobe pathology can interfere with such performance (see Hill, 2004 and Pellicano (Chapter 7) this volume, for detailed discussion and overview of studies we shall not be citing here). In this case there seems to be little problem in identifying what is ‘cognitive’, and every reason to analyse how localised neurological dysfunction – problems with the hardware needed for thinking – can compromise cognitive abilities. Then we can transpose similar principles to the case of children with autism, and examine their abilities on appropriately styled tests of executive functioning from a neuropsychological perspective.

Yet this strategy is not without its hazards. Early in the life of typically as well as atypically developing children, the organisation of cognitive abilities such as those entailed in executive function tests, as well as the organisation of the brain subserving the abilities in question, may be quite different to what pertains in
adulthood. Moreover, autism is a developmental disorder with early onset. This means that even in comparison with typically developing young children, the basis and organisation of affected children’s cognitive and/or neurological functioning may be unusual.

In order to establish that when children with and without autism achieve similar levels of performance on particular tests, this reflects similar underlying mental processes, one needs to accumulate evidence that the patterning of these abilities in relation to other abilities and disabilities is also similar. Evidence for unusual profiles of executive ability among children with autism (reviewed in Geurts et al. 2009; Hill, 2004; also Lind and Williams, 2010), for improvements in performance when tests are administered by computers rather than human beings (Kenworthy et al. 2008) and for a lack of expected dysfunction among those who are very young (e.g. Griffith et al. 1999) has punctured early enthusiasm for explaining executive dysfunction in autism as the product of primary frontal lobe disorder. Such evidence highlights the need to justify both the ascription of ‘executive dysfunction’ (as commonly understood) to children with autism – without such justification, it is difficult to see how the approach has the status of a major cognitive theory of autism (Hill and Frith, 2003) – and the assumption that it maps on to specific brain pathology.

If one were to establish a correlation between an autism-specific atypicality in neurological functioning and a pattern of cognitive dysfunction, it would remain open to question whether the neurological side of the correlation is primary and not secondary to abnormality in thinking. Brains are structured by experience and by neural functioning earlier in life, so we should not presume that neurofunctional atypicalities detected among, say, adolescents with autism, play a causative role in determining their profiles of psychological disability. Although a hardware approach is going to feature in any valid explanation of autism, then, for the present purposes the critical question is whether it explains the children’s inflexibility in thinking – and if so, whether it does so without the need for further levels of psychological, and developmental, explanation.

8.2.2 A ‘software’ approach

A ‘software’ approach to cognitive dysfunction in autism does not dispense with the idea that neuropathology is important in causing very many cases of the syndrome (perhaps not all, as we shall illustrate with the case of congenital blindness), nor does it underestimate the need for a neurodevelopmental story to complement and interpenetrate an account of the children’s atypical psychological development. In the present context, what it may offer is a way of seeing how those qualities of cognitive inflexibility that characterise autism could arise out of the children’s limitations in social experience. The software analogy is meant to capture how even to the extent that the brain regions subserving cognitive flexibility
might be intact (in the sense of available for performing the relevant functions, at least early in development), still children with autism might be at risk for thinking in rigid, context-insensitive ways. To repeat: This approach still admits that in most cases, neurological disorder will feature as a necessary part of the explanation of the children’s dysfunction. It is the level at which this operates that is critical. In particular, neurological disorder (perhaps of various kinds) might explain impairments in the children’s social-affective relations, and such impaired social relatedness account for their partial failure to develop flexible thinking.

We have suggested that the very concept of thinking may need revisiting. So where is our point of embarkation for a more detailed specification of a software approach? It is with typically developing infants, and with the construction of the means (software) to think according to one perspective and then another, with sensitivity to context. It is with a theory that grounds creative, generative thinking in communication between and among persons. Communication arises on the basis of modes of interpersonal engagement and role-shifting that are non-inferential and affectively configured (which does not make them ‘non-cognitive’). From this starting-point, we distinguish between those forms of thinking that depend upon social perspective-taking, and those forms of (prototypically, sensorimotor) thinking for which social role-taking is relatively unimportant. We arrive at a view of the cognitive impairments characteristic of autism in which the children’s relative failure to engage with the psychological stances of other people is critical for their own limited abilities to generate fresh context-sensitive ideas, as well as their difficulties in shifting from one communicative stance to another.

At this point, an aside is in order. It may be considered that much of the previous paragraph goes over ground already covered by ‘theory of mind’ approaches to the communicative and cognitive deficits of autism (e.g. as articulated in Baron-Cohen et al. 2000). We acknowledge that our account, first presented some years ago (especially Hobson, 1989; 1993), has points of overlap with theory of mind theorising, and there is no doubt that research from a theory of mind perspective has been fruitful and important in furthering our understanding of the relations among communication, interpersonal understanding and thought (e.g. Baron-Cohen, 2000; Frith, 2003; Happé, 1995; Tager-Flusberg, 2000). Yet there are many fundamental contrasts between the two theoretical perspectives (e.g. Hobson, 1990; 1991). A bedrock of theory of mind theorising has been children’s mental representations of people’s mental states, and computations that are performed upon these postulated units of psychological functioning. We stress how such representations are a developmental achievement founded upon ‘qualities of relatedness’ between the growing child and his or her social and non-social environment. These social relations have affective and motivational as well as
cognitive aspects. Aspects are not components, and if basic forms of personal relatedness are not decomposable into cognitive, affective and motivational parts out of which they are constructed (Hobson, 2008), then it may be a mistake to divorce the foundations of ‘thinking about’ from (for example) ‘feeling towards’ objects, events and people.

We can illustrate what this means by considering the development of symbolic functioning. According to at least one influential theory of mind account, that of Leslie (e.g. Leslie, 1987), symbolising takes place through the operation of a computational mechanism that comes on line in the second year of life. Our view is that the kinds of symbolic representation and symbolic functioning that are impaired among children with autism, as well as the kinds of pragmatic linguistic adjustment that are compromised, are those that have a developmental grounding in affectively configured relations and non-verbal communication between a child and other people (e.g. Hobson, 2000). One implication is that creative symbolising bears the stamp of the social-relational matrix out of which it has emerged. In particular, the creativity, flexibility and context-sensitivity of symbolising reflect the creativity, flexibility and context-sensitivity of engaging with, relating to and moving among person-anchored perspectives. By ‘person-anchored’ perspectives we mean not the perspectives of particular other people, even though adopting the mental orientations of actual people sets this form of role-taking in motion, but perspectives taken from the position of ‘virtual’ stances in the mind – where those stances are created as ‘software’ for the hardware of the brain through an infant identifying with the attitudes of other embodied people. As Vygotsky (1978) described, what happens between people – in this case, adopting the stances and orientations of others towards a shared world – is interiorised to become a feature of the individual’s own propensity to move through alternative stances all by him/herself. So . . . how does this happen?

8.3 A social-developmental account of flexible, creative symbolic thinking

Over the first two-thirds or so of the first year of life, infants relate with persons on the one hand, and things on the other (Trevarthen, 1979). Then towards the end of the first year, in what Trevarthen and Hubley (1978) called the stage of secondary intersubjectivity, they relate to others’ relations towards a shared world, for example in episodes of joint attention in which they bring objects to show to someone else, apparently with the aim of sharing experiences (Bretherton et al. 1981; Carpenter et al. 1998). Yet it is only in the middle of the second year of life that the child, now moving out of infancy, comes to conceptualise self and other as separate individuals who have their own takes on the world. This is
manifest in toddlers’ growing propensity to comply and co-operate with others, and to engage in co-ordinated role-responsive interactions (e.g. Kaler and Kopp, 1990). From around the age of 18 months, moreover, toddlers not only make self-descriptive utterances such as ‘my book’ or ‘Mary eat’ (Kagan, 1982), but they also show silly or coy behavior in front of a mirror (Lewis and Brooks-Gunn, 1979) – and there is evidence that personal pronoun usage and self-recognition may reflect development in self-concepts that are also relevant for advanced pretend play (Lewis and Ramsay, 2004). More or less explicit forms of emotional understanding and self-reflective awareness, together with a capacity to symbolise, appear to have emerged hand-in-hand.

We suggest that critical for the transition to thinking of self and other as discrete persons who live in a shared world, and with this to thinking about the world from multiple points of view, is the fact that from around nine or ten months of age, infants are moved in responding to the attitudes of others. The nature of this movement is what matters. Take the case of social referencing, where an infant is confronted with an emotionally ambiguous object or event – in one well-known early study (Sorce et al. 1985), this was what seemed like a ‘cliff’ that prevented the child reaching a goal – and the infant looks towards and then responds to the affective expression of a parent, as this has directedness to the object or event in question. In the ‘visual cliff’ experiment, 14 out of 19 12-month-olds who perceived that their mothers were looking to the cliff with smiles tentatively proceeded towards their goal, whereas none of those who witnessed their mothers showing fear did so. Here we see how the infant is able to identify with the attitudes of the other as ‘other’ – which also accounts for why the infant shows things to others, and is interested in the other’s reactions – such that the world comes to have meaning according-to-oneself-as-identified-with-the-other, and therefore (potentially at least) a new meaning-according-to-oneself.

Such movements in affective stance establish a framework within which a child can, over the next nine months or so of life, come to conceptualise – that is, think about – how different persons have different takes on the same shared world. The critical element in this is that in the child’s own experience, even prior to conceptualizing another person as a person, some of the otherness of the other-person-anchored attitude is registered. The structure of such social co-orientation in relation to a given object or event is such as to establish the possibility of the infant coming to differentiate how two person-anchored attitudes can be brought to bear on the same object or event in the environment. In addition, from around the end of the first year the infant begins to adopt the stance of the other towards his or her own attitudes, which as Mead (1934) described, is important for at least some forms of reflective self-awareness. The reversibility of communication – that what X means when you use it to communicate something to me is what X means
when I use it to communicate to you – and the emancipation of meanings from the objects in which those meanings reside paves the way for symbolic thought.

Therefore we propose that among typically developing human beings from infancy onwards – but not in the same way for most children with autism – there is a natural propensity to identify with other people’s attitudes, and that this plays a pivotal role in shaping subsequent cognitive as well as social development. It is critical that this process cannot be classified as simply affective, nor as simply motivational, nor as simply cognitive; rather, it is a process with affective, motivational and cognitive aspects. We are drawn to identify with others, identifying-with is a feature of our affective responsiveness, and the social-communicative transactions configured by identification are critical for the acquisition of special qualities of thinking. So, too, according to our account, much of the flexibility, creativity and fecundity of thinking derive from these characteristics of the social relations on the basis of which symbolic thinking (of a particular kind) is founded. As Vygotsky (1962, p. 8) wrote, what we need to envisage is ‘…a dynamic system of meaning in which the affective and the intellectual unite. It shows that every idea contains a transmuted affective attitude toward the bit of reality to which it refers’.

8.4 Studies in autism: flexibility in attitude and stance

It is well known that children with autism have limitations in joint attention and other kinds of person-with-person engagement well before they could be expected to conceptualise minds (e.g. Charman et al. 1997). Perhaps most relevant for the present purposes, they are atypical in their relative lack of engaging in ‘sharing’ forms of joint attention and in social referencing (Sigman et al. 1992). All this makes it plausible that, as one of us argued some years ago (e.g. Hobson, 1989; 1990; 1993), it is in the children’s limited engagement with other people’s attitudes, both in one-to-one mutual exchanges and in person-person-world interactions such as those of joint attention and social referencing, that we find the source of later deficits in interpersonal understanding (so-called Theory of Mind). More specifically, we propose, the final common pathway to autism is a limitation in the children’s propensity to identify with the attitudes of others (originally Hobson, 1993, but more recently Hobson, 2002; Hobson et al. 2006; 2008; Hobson and Hobson, 2007; Hobson and Lee, 1999; Hobson et al. 2007).

What is the evidence in support of this thesis and how does it bear on the issue of cognitive flexibility? One part of what it means to identify with someone else is that one individual apprehends and responds to the other-person-centred source of attitudes. In other words, one is affectively engaged with and cares about the other person’s feelings as the other’s. In a recent programme of research on social emotions among children and adolescents with autism (Hobson et al. 2006), we
interviewed parents of matched children with and without autism. Parents felt they could recognise in their children with autism not only emotions such as anger and fear and emotional responsiveness to other people’s mood states, but also pride and jealousy. Yet in contrast with parents of children without autism, rarely were they able to report that their children with autism showed more person-focused emotions or qualities of relatedness, for example guilt or empathic concern. Several remarked on the absence of specifically person-directed displays of pride, even though they felt confident their children could feel proud. This points to a specific impairment in the children’s abilities not only to think about other people’s emotional states, but also to feel for and relate to the people whose states they are.

Here we can see that what it means to understand minds involves more than thought. If to think were enough to cause a sea-change in personal relations, then children’s acquisition of seemingly coherent thoughts about people’s feelings, wishes, and so on – and many children with autism do acquire such thoughts – would be the harbinger of radical changes in clinical features of autism. Yet such alterations are often modest. The fact is that feelings are constitutive of the kinds of thought about minds (or more fundamentally, persons) that really make a difference. Here is one particular, and particularly important, expression of cognitive flexibility – movement to thinking about other people as centres of consciousness.

Now consider a study of communication that focuses upon the kind of immediate, unreflective (and arguably, unconceptualised) role-taking that characterises the process of identifying with the attitudes of someone else. Hobson and Meyer (2005) presented a ‘sticker test’ in which children needed to communicate to another person where on her body she should place her sticker-badge. The majority of children without autism pointed to a site on their own bodies to indicate the tester’s body, that is, anticipating that the other person would identify with their act of identifying with her body. The children with autism rarely communicated in this way; instead, most pointed to the body of the investigator to indicate where the sticker should be placed. Although it is possible that this style of flexible self-other communication depends upon thinking or understanding other people’s minds, we consider it more likely that such seemingly effortless and natural stance-shifting reflects a more basic form of self-other connectedness and differentiation that has a cognitive aspect – not as a cause, but as an essential property of such relations – and affective and motivational aspects, too.

Affective as well as motivational concomitants to what might be considered ‘cognitive’ communication were brought out in a further study. Hobson et al. (2007) created a setting in which participants had the task of observing an investigator
who demonstrated an action, and then communicating to another tester who only subsequently entered the room that he should complete the same action. There were six actions demonstrated, and for each in turn, the demonstrator’s instruction was: ‘Get Pete to do this’. Three actions involved goal-directed use of objects (e.g. using a mechanical arm to place a cloth frog into a waste-bin), two were non-goal-directed involving the body (e.g. raising hands above head), and three included a form of expressive style (e.g. placing hands on hips in proud, assertive stance). As predicted, the results were that participants with autism contrasted with matched participants without autism in showing lesser degrees of (a) emotional engagement with the testers, (b) joint attention that implicated sharing of experiences, (c) communication of expressive styles of action and (d) role-shifting from that of the learner to that of the teacher. When these measures were combined in a composite index of identifying with someone else, the two groups were almost completely distinct. Apart from a single individual with autism who achieved a score equal to the lowest-scoring three participants without autism, there was complete separation of the two groups.

The question arises whether in one-to-one interpersonal communicative exchanges – the kinds of exchange familiar between typically developing young infants and their caregivers – the structure of communication is shaped by processes of identification. Hobson and Hobson (2007) invited independent raters to watch videotapes of participants interacting (one at a time) with an adult whose actions they had been asked to imitate, and to judge the quality of each look they made to the adult’s face. The actions could be imitated either as seen from the participant’s point of view, or as adopted from the point of view of the demonstrator (Meyer and Hobson, 2004). There was a significant group difference, in that participants with autism were less likely to adopt the tester’s orientation-to-herself as an orientation-to-themselves. For example, if they saw the tester rolling a wheel far-from-herself and close-to-participant, they were less likely than participants without autism to roll the wheel far-from-themselves and close-to-tester. More important for the issue of sharing was that those participants who imitated the tester’s self/other-orientation (a relatively rare event among those with autism) also tended to be those most likely to manifest ‘sharing looks’ towards the tester in the imitation task itself. This relation did not hold for looks in which participants were judged to be checking out, or responding to prompts from, the tester. The result applied within each group of participants, and had been predicted on the basis that both the imitation of self/other-orientation, and qualities of person-with-person engagement reflected in sharing looks, are structured by processes of identification. Once again, to think about other human beings’ states of mind and to adjust communication in relation to those states implicates feelings in relation
to those others, and it is also to be *motivated* (or ‘moved’) to act and communicate accordingly. This is hardly surprising, if such thinking is a developmental implication of identifying with others.

### 8.5 Symbolic thinking in autism

Symbolic play is an especially clear manifestation of children’s ability knowingly to apply alternative meanings to materials that do not usually have these meanings. There is substantial evidence that children with autism are limited in their creative representational play, especially in their spontaneous play (e.g. Lewis and Boucher, 1988; Ungerer and Sigman, 1981; Wing *et al.* 1977). On the other hand, many children with autism do achieve some ability to make one thing stand for another, so it is difficult to argue that as a group, they completely lack the ability to ‘represent representations’. The really important question here is whether the developmental underpinnings of the play they achieve, and therefore the qualities and creativity of this play, are the same as in the case of typically developing children.

Again we encounter a debate in the literature (Jarrold *et al.* 1993), as to whether the children have limited potential to engage in symbolic play, or whether they are less motivated to do so. According to the present approach, the reason they are less motivated is the same reason that their ability to engage in symbolic play is restricted: lacking the usual interpersonal sources of symbolic functioning, they also lack the kinds of motivation and investment that come with engaging with other people’s stances. Just as they are limited in their propensity to be moved among alternative person-anchored perspectives, so, too, they are limited in the spontaneous impetus to move among alternative symbolic meanings. From the complementary viewpoint of typical early development, the pull for children to adopt this and then that perspective is derived from the pull, through identification, to take other-person-centred stances.

Is there evidence in support of such a thesis? In a recent study we compared two matched groups of children, one with and one without autism, for their ability to engage in symbolic play (Hobson *et al.* 2009). As it turned out, these two groups were similar in the mechanics of play, that is, on ratings of whether they were able to make one thing stand for another, or represent absent properties, or pretend that something was present when it was not. Yet there were significant group differences insofar as in ‘subjective’ judgements that had acceptable inter-rater reliability, the children with autism were rated as showing less creativity and fun, they were less invested in the new meanings of the play, and they were less aware of themselves as initiators of the new meanings. Of course, these results might be interpreted as demonstrating that the children with autism were perfectly able
to symbolise in play, but as a separate matter, they showed little affective and motivational investment. In our view, by contrast, these very qualities of affective and motivational investment betrayed what it meant for the children without autism to symbolise. The investment and fun that accompanied their play was intrinsic to their symbolic thinking, and reflected the interpersonal transactions from which this form of thinking was derived.

8.6 The case of congenital blindness

Features of autism are prevalent among congenitally blind children. Brown et al. (1997) reported that approximately one half of such children between the ages of 4 and 8 in special schools for the blind (this was not an epidemiological study) who were without obvious neurological impairment met the criteria for the full syndrome of autism, and many of those who did not have the diagnosis displayed some features of autism. This at-risk status had been predicted on the basis of reasoning that children who are congenitally blind are deprived of being moved by the attitudes of embodied other people towards a visually specified world, in such a way as to be lifted out of their own viewpoint and to experience ‘takes’ on the world that are registered as having their source in someone else. An extension of this study by Hobson et al. (1999) confirmed that the syndrome of autism among blind children was closely comparable to that manifest in matched sighted children with autism, except that among the former group, the social impairment tended to be less severe.

What is most important about this for the present purposes is that congenitally blind children show restriction in creative symbolic play, and manifest other forms of restricted communication and activity that appear to have similarities with those seen among sighted children with autism (e.g. Hobson and Bishop, 2003). In a study specifically concerned with symbolic play among congenitally blind children who did not have the syndrome of autism (Bishop et al. 2005), we compared socially impaired with more socially able children who were matched for mental age and chronological age. This matching procedure meant that group differences in play could not be attributed to disparities in general intellectual functioning. The results were that the socially impaired children were limited in the attribution of symbolic meanings to play materials, the ascription of individual roles to play figures, and the anchorage of play in the scenario as presented by the adult. Within this at-risk sample, therefore, those children who were able to establish interpersonal engagement (the principal criterion for social ability) were also those who showed more elaborate symbolic play – as we had predicted on the basis of a hypothesis concerning the social-developmental bases for this kind of flexible thinking.
8.7 Executive dysfunction reconsidered

In this chapter we have chosen to focus upon a particular way of approaching the topic of cognitive flexibility, as well as limitations in flexibility in the thinking of individuals with autism. We have not reviewed, nor attempted to reinterpret, the substantial evidence that has accrued from administering tests of executive functioning and/or creativity to children, adolescents and adults with autism (for such reviews, see Geurts et al. 2009; Kenworthy et al. 2008; Hill, 2004). However, it may be appropriate to illustrate how this might be achieved by citing two important studies in this tradition, and returning to the case of L with which we began.

Minshew et al. (2002) administered a battery of executive function tests to 90 individuals with autism and of normal IQ, and over 100 control participants without autism. Through a factor analysis of the data, they were led to the conclusion that the participants with autism were relatively able to complete tests of concept identification such as the Halstead Category Test of rule-following, or the Wisconsin Card Sorting Test where groupings were inherent in the test materials and the task was to identify attributes such as form or colour. When it came to tests of concept formation, on the other hand, for example the Gold-Scheerer object sorting test or the 20 Questions Task, when alternative, self-generated shifts in sorting strategy were needed, they were far less able. In an overview of these and other results, the authors suggested that there is a changing pattern of deficits among the children with autism, depending upon levels of ability: ‘the most impaired individuals with autism have neither rule learning nor concept formation abilities, less impaired individuals have rule learning abilities but inflexibility in applying them, and the highest ability individuals can discern and flexibly apply rules but not formulate original concepts’ (Minshew et al. 2002; page 327). The authors’ interpretation of these findings was neuropsychological, for example in their suggestion that individuals with autism might have abnormalities in the neural processes involved in self-initiating a schema for problem solving, but this is not the only theoretical option for explaining the results.

Before considering an alternative perspective, we turn to a second study in which Craig and Baron-Cohen (1999) administered the Torrance Creativity Tests to groups of children with autism and Asperger syndrome, and others showing typical development. The results were that the former two groups tended to generate fewer novel ideas of changes to objects when asked to do so, and most interestingly, they also generated more reality-based suggestions for what ambiguous shapes could be, rather than coming up with the kinds of imaginative idea (especially those involving ascriptions of animacy) that were frequent among typically developing children. As the authors considered from a theory of mind perspective (citing Leslie, 1987), this imaginative deficit among the individuals with autism
and Asperger syndrome was more than a matter of failing to generate ideas, and might reflect a difficulty in representing mental attitudes towards a proposition, as in 'I can pretend that...'. We fully agree that this form of creativity and flexibility is grounded in imaginative activity that arises from self-conscious shifting among alternative attitudes and ‘takes’ on the world – but of course, we also believe that this has a developmental grounding in a child’s affectively configured engagement with others.

At this point it may be worth returning to the original passage in which Scheerer et al. (1945) summarised what they meant by L’s impairment in abstract attitude (a formulation which Minshew et al. 2002 cited with approval), in order to see whether one might encompass their formulation within a social-developmental account. These authors considered the abstract attitude to be a ‘common functional basis’ for the following (amongst other things): ‘to behold simultaneously different aspects of the same situation or object, to shift from one aspect to another; to understand a general frame of reference, a symbolic meaning as relation between a given specific percep and a general idea; to evolve common denominators, to reason in concepts, categories, principles; to assume different mental states... to plan ahead ideationally... to behave symbolically (e.g. demonstrating, make belief, etc); to reflect upon oneself, giving verbal account of acts; to detach one’s ego from a given situation or inner experience; to think in terms of the “mere possible”, to transcend the immediate reality and uniqueness of a given situation, a specific aspect or sense impression’ (Scheerer et al. 1945; page 37).

It is our contention that the forms of abstract attitude and ‘detachment’ that are missing in autism are precisely those for which appropriately patterned intersubjective experience is necessary. Note how in the formulation by Scheerer et al., as well as in the case illustration of L with which we began, there is a close connection between aspects of self-reflective awareness and thinking. In particular, L had difficulty reflecting on himself, detaching himself from a situation or inner experience, and transcending immediate reality. The story we have sketched about young children’s conceptual development in differentiating between self and other with their distinct and yet connected attitudes to a shared world is also a story about the growth in infants’ understanding of the differentiation between people’s takes and attitudes towards objects or events, and those objects or events as foci for such attitudes. In accordance with the ideas of Mead (1934) as well as Werner and Kaplan (1984), the achievement of self-reflective awareness and the ability to think about self and other appears to be one side of a coin, of which the other face is the ability to grasp how symbols can function as the means to thought. One could not think about self and other without symbols, but one could not achieve the requisite ability to use symbols without grasping how symbolic vehicles and their referents are linked and yet differentiated – something that requires an understanding
of what it means to take alternative person-anchored perspectives on a shared world.

Self/other awareness and role-shifting, with the movement among alternative perspectives that these entail, are intrinsic to a certain mode of flexibility in thinking. We have suggested that these features of mental functioning are structured and motivated by the social-developmental process of identifying with other people’s attitudes. If certain forms of difficulty in generating ideas are linked with communicative impairments in autism (and see Bishop and Norbury, 2005, for additional evidence), this may be explained by the importance of communicative transactions for establishing the capacity to generate new perspectives within an individual’s own mind. If this is so, then it is not difficult to see why children with autism, with their profound impairments in engaging and identifying with the attitudes of others, can also become stuck in one orientation within their own minds, and thereby constrained in generating and applying alternative perspectives in a flexible and context-sensitive manner.

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8.9 References


9

Language in autism spectrum disorders

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Studies of structural language in individuals with autistic spectrum disorder (ASD) are reviewed, and theories of the causes of structural language anomalies and impairments in ASD are presented and discussed. It is concluded that the factors that may contribute to language impairment in individuals with ASD are many and various; that impaired mindreading is always implicated, but that some additional and critical causal factor remains to be conclusively identified.

9.1 Introduction

Languages, defined in formal or structural terms, are systems of mainly arbitrary items (e.g. sounds, signs or written letters; morphemes; words) with rules for combining items to convey meaning to others with shared knowledge of the language. Language can be analysed and characterised at the level of grammar (morphology and syntax) and meaning (semantics); and, in the case of spoken language, phonology1.

Communication, on the other hand, involves the use of language in social interaction, whether directly in face-to-face talk, or indirectly as in, for example, a recorded phone message or a Last Will and Testament. Thus, language is a means, or method, of communicating. Non-linguistic, or non-verbal, signals including

1 Expressive use of phonological knowledge is sometimes referred to as ‘articulation’. ‘Articulation’ in this sense should not be confused with the ability to produce speech. Speech is the output channel for spoken language, just as writing is the output channel for written language, and hand, face and body postures and movements constitute the output channel for signed language.

facial expression, gesture, and body language also provide means, or methods, of communicating. Prosody, which involves the use of vocal tone, pitch, rhythm and inflexion during speech also comes under the heading of non-verbal communication. Factors influencing the communicative use of language and non-verbal communication signals in specific instances can be analysed and characterised in the study of pragmatics.

All individuals with an autistic spectrum disorder (ASD) have impaired communication, this being one of the necessary diagnostic features of all forms of ASD (American Psychiatric Association, 2000; World Health Organisation, 1992). Thus, all individuals with ASD have impaired pragmatics, and most also have impaired prosody. Some individuals with ASD also have clinically significant structural language impairments. Others, however, do not. This chapter is about structural language and language impairment in people with ASD; it is not centrally about communication. The first part of the chapter describes and discusses the patterns of linguistic abilities, anomalies and impairments that occur across the spectrum. The second part of the chapter reviews theories of the causes of the patterns of linguistic strengths and weaknesses that have been described.

9.2 Patterns of language abilities and impairments across the spectrum

Patterns of language ability across the spectrum are discussed below under the following sub-headings:

- Asperger syndrome (AS – strictly defined in terms of ASD plus normal IQ and language with no history of language delay)
- Narrowly-defined High-Functioning Autism (HFA – referring to individuals with ASD, normal IQ and currently normal language following an early history of abnormality or delay)
- Broadly-defined High-Functioning Autism (referring to individuals with ASD, normal IQ and currently normal language regardless of early history, thus comprising individuals with a strict diagnosis of AS plus those with ‘narrowly-defined HFA’)
- Autistic Spectrum Disorder with Language Impairment (ASD-LI)

It is worth stressing that the terms do not identify mutually exclusive categories, but rather those ‘different ways of cutting the cake’ that have been used in studies designed to investigate different profiles of language ability that may emerge.

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2 Structural language, non-verbal communication signals including prosody, and pragmatics are indissolubly linked in reality. The sharp distinction made here is intended to focus attention solely on structural language in ASD, rather than to deny the interconnectedness of language, its expression and its uses.
9.2.1 Asperger syndrome

According to DSM-IV (American Psychiatric Association, 2000) and ICD-10 (World Health Organisation, 1992) criteria, Asperger syndrome should be diagnosed only in individuals with the triad of behavioural impairments characteristic of individuals with ASD who have normal intelligence and language, and no history of delay or abnormality of language development. Asperger syndrome thus represents the purest form of ASD, with the pathognomic behaviours occurring in the absence of intellectual or clinically significant linguistic impairment either past or present.

Asperger himself described the language used by the children he originally studied as being idiosyncratic and pedantic, but normal or superior in terms of breadth of vocabulary and grammatical correctness (Asperger, 1944; translated in Frith, 1991). So, for example, language used by an 11-year-old boy quoted by Asperger included the following: ‘I can’t do this orally, only headily’ (meaning he knew what he wanted to say but couldn’t express it); ‘I wouldn’t like to say I’m unreligious, but I just don’t have any proof of God’. Other examples of idiosyncratic and pedantic language are: ‘Missage’ (meaning ‘going to sleep when your favourite person is away’); ‘fonding’ (meaning ‘affection’); and ‘tammer’ (‘getting involved’) used by an adult with AS (Tantam, 1991); and ‘May I extract a biscuit from the container?’ and ‘I wish to thank you for the hospitality extended to me this afternoon’ said by children with AS (Wing, 1996).

Asperger considered that the oddities of expressive language in the children he studied were associated with their social impairments, constituting a problem of the communicative use of language rather than of language itself. Subsequent studies of language comprehension in people with AS largely confirm this interpretation, demonstrating impaired ability to understand non-literal uses of language where the speaker’s intention must be taken into account, as in the comprehension of irony, metaphor, sarcasm and some forms of humour (Happé, 1995; Martin and McDonald, 2004; Rajendran et al. 2005). An interpretation of linguistic anomalies in AS in terms of communication impairment is also consistent with the conspicuous abnormalities of pragmatics and of prosody that have been noted from Asperger onwards (Asperger, 1944; Baltaxe, 1977; McCann and Peppé, 2003; Shriberg et al. 2001).

There is, however, some evidence suggesting that people with AS process the structural components of language differently from neurotypical individuals. For example, Kamio et al. (2007) showed a relative lack of semantic priming effects for written words in a group of individuals with AS. Similarly, in a detailed single-case study, Worth and Reynolds (2008) showed that a boy with AS with normal language on most standardised measures performed strikingly poorly on a semantic
decision-making task. Consistent with these observations, Ring et al. (2007) showed atypical EEG responses in a group of participants with AS when reading sentences containing semantic incongruities.

Language ability overall has also been shown to be somewhat below average in individuals with AS despite the impression given by the tendency to use pedantic words and phrases. Thus, Koning and Magill-Evans (2001) reported that language as measured by the Clinical Evaluation of Language Fundamentals – Revised (CELF-R) (Semel et al. 1987) was below average overall in a group of boys with AS, with a significant impairment of receptive language relative to a comparison group (see also Saalasti et al. 2008). Similarly, Howlin (2003) found below average language abilities in a group of young adults with AS, although scores were within the normal range.

In sum, most of the evidence is consistent with the broad statement that structural language is normal in individuals with AS. However, across groups of adolescents and young adults with AS, mean levels of spoken language are somewhat below average, especially in terms of comprehension. There is no evidence of impaired phonology, and little evidence of impaired grammar. There is, however, some evidence of anomalous semantic processing.

9.2.2 Narrowly defined high functioning autism

The issues to be considered in the present section concern whether or not language in individuals with narrowly defined HFA (see the second bullet point above) resembles language in AS, despite the difference in early history; and, related to this, whether or not language in people with narrowly defined HFA is, in fact, completely normal.

Three studies have shown that language in individuals with narrowly defined HFA normalises to levels comparable to those achieved by individuals with AS. Mayes and Calhoun (2001) compared expressive language in children between the ages of 2 years 8 months and 12 years 9 months, 24 of whom qualified for a diagnosis of AS whereas 23 had narrowly defined HFA. They found no significant differences between the expressive language abilities of the two groups. Similarly, Howlin (2003) assessed language in 76 young adults divided into two groups on the basis of whether or not they had a history of language delay. The groups were equated for age and non-verbal IQ. Howlin found no significant differences in language ability as assessed using vocabulary tests, and language was within the normal range in both groups, although slightly below average as noted above. Seung (2007) carried out more detailed assessment of language used by adolescents and adults with either AS or narrowly defined HFA, equated for age and non-verbal ability, and found no significant differences between language in the two groups, although some non-significant differences in uses of verb tense markers were
reported. All three of these studies included, in addition to assessment of language, assessment of specifically ASD-related behaviours. No significant differences were found between individuals with AS or HFA in terms of ASD-related behaviours; nor were there differences in relationships between language and ASD-related behaviours in the groups studied.

People with narrowly-defined HFA also share with individuals with AS subclinical anomalies of semantic processing, as indicated by studies of brain activity. Dunn and Bates (2005) assessed brain activity using EEG in two groups of high-functioning children with currently normal language following initial delay, one aged 8–9 years and one aged 11–12 years. Children in both HFA groups performed similarly to age and ability matched comparison groups on the behavioural task, but showed atypical brain responses to semantically related as compared to unrelated words. Similarly, Gaffrey et al. (2007) assessed brain activity during a semantic decision task in two adult males with AS and eight with narrowly-defined HFA all of whom had clinically normal language, comparing findings in this combined group with findings on an age and non-verbal ability matched group of neurotypical males. Abnormal brain activity in the combined AS–HFA group was observed. No differences between the participants with a diagnosis of AS as opposed to a diagnosis of HFA were reported.

The above evidence all tends to show that the early language problems that may be used to differentiate narrowly-defined HFA from strictly defined AS tend to resolve leaving only subclinical abnormalities of lexical-semantic processing. In contrast, one study suggests that individuals diagnosed with AS or narrowly-defined HFA differ in terms of grammatical competence when assessed in adolescence (Ghaziuddin et al. 2000). The participants with AS in this study tended to produce longer sentences than the HFA group, and their sentences were significantly more complex and also more grammatically correct than those produced by the HFA group. The two latter findings remained significant when differences in verbal IQ were taken into account.

A longitudinal study by Bennett et al. (2008) also suggests that the persistence of grammatical impairments may be critical in determining where children with ASD and normal non-verbal IQ eventually fall on a continuum of language abilities, and therefore on a continuum of diagnostic or descriptive terms. Bennett et al. (2008) studied 19 children with AS and 45 high-functioning children with early language problems, from pre-school age (4–6 years) through to adolescence (15–17 years), assessing each child on five different occasions. All the children in the study had non-verbal IQ > 70 at the outset of the study, with mean quotients of 100 in the AS group and 87 in the group with early language delay. The children’s grammatical abilities were assessed at Time 1 (4–6 years) and at Time 2 (6–8 years). At Times 3–5
broader outcome measures were used, subsuming structural language under the heading of ‘communication’.

The main finding from this study was that the best predictor of outcome in terms of autism-related behaviours and general developmental attainments at Times 4 and 5 (up to late teenage) was grammatical competence at Time 2 (6–8 years). Notably, the presence or absence of grammatical impairments at Time 2 was a better predictor of outcome than either language impairments at Time 1, or the diagnosis of AS or HFA based on whether or not there was a reported history of language delay. Information is not given by Bennett et al. (2008) concerning structural language abilities at Times 4 and 5. However, the authors’ suggestion that language abilities at age 6–8 years might be used diagnostically to distinguish between AS and ‘autism’ implies that children with significant grammatical impairments at this age remain language impaired, and only those with relatively normal grammar at this age fall into the narrowly-defined HFA subgroup in later childhood.

In sum, most studies of language in older children and adults with narrowly-defined HFA show that language attainment resembles that of individuals with AS in being within the normal range although slightly below average levels. Individuals with narrowly-defined HFA may also resemble those with AS in that semantic meaning may be mediated by non-typical brain systems. However, one study has reported that individuals with narrowly-defined HFA differ from those with AS in having poorer grammatical outcomes, and another study suggests that grammatical competence at age 6–8 years predicts whether a child with initial language delay may or may not at a later age be described as having narrowly-defined HFA, as opposed to ASD with language impairment, highlighting the possible significance of grammatical development.

9.2.3 Broadly defined high functioning autism

Results of studies such as those of Mayes and Calhoun (2001), Howlin (2003) and Seung (2007), cited in the previous section, are consistent with other evidence that has failed to find reliable behavioural differences between AS and narrowly-defined HFA (for reviews see Frith, 2004; Macintosh and Dissanayake, 2004; Prior, 2003; Volkmar and Klin, 2000). The accumulation of negative evidence is sometimes used to justify use of the term ‘HFA’ to refer to all individuals with the triad of impairments, normal intellectual ability and currently normal language (i.e. no distinction is made between individuals with a strict diagnosis of AS as opposed to those who may be described as having narrowly-defined HFA). Findings from studies of this undifferentiated group, referred to here as having ‘broadly-defined HFA’, are considered next.
A behavioural study by Kelley et al. (2006) of children with broadly-defined HFA strengthens the finding of Kamio et al. (2007) on children with AS (see above) showing that even high-functioning individuals with ostensibly ‘normal’ language, have subtle semantic processing impairments. Kelley et al. (2006) reported residual semantic impairments in the absence of any abnormalities of phonology or syntax in young children with an early diagnosis of ASD who were at the time of testing considered to be functioning normally.

These findings are consistent with some of the evidence from behavioural studies not designed to assess language directly, but rather to probe the acquisition and use of conceptual-semantic and lexical-semantic knowledge. For example, in addition to well-known demonstrations of failure to utilise semantic relatedness in tests of verbal memory (Bowler et al. 1997; Minshew et al. 1992; Tager-Flusberg, 1991; Toichi and Kamio, 2002) abnormalities of concept acquisition and categorical knowledge have been shown in some studies (Bott et al. 2006; Dunn et al. 1996) and impaired semantic priming in others (Kamio et al. 2007). However, other findings from this broad group of studies indicate relatively intact semantic abilities in high-functioning individuals with normal language (Hala et al. 2007; Toichi and Kamio, 2001; Walenski et al. 2008; Whitehouse et al. 2007a).

Dunn and Bates (2005) review this discrepant evidence and conclude that ‘Although there is significant evidence that individuals with autism comprehend basic concepts and word meanings, they do not appear to extract and apply commonalities among category members’. Minshew and colleagues suggest that semantic impairments in individuals with broadly-defined HFA are restricted to tasks involving ‘complex material’ (Minshew et al. 1997; Williams et al. 2006). Toichi and Kamio (2001) suggested that discrepancies relating to semantic processing by people with broadly-defined HFA may be explained in terms of specific difficulties with spoken as opposed to written inputs. However, in a later publication Toichi (2008) suggests that the discrepant findings may be explained in terms of impaired relationships between episodic and semantic memory.

The above findings are consistent with the results of studies assessing brain activity during semantic processing. Thus, Dunn and Bates (2005) reported atypical patterns of EEG during semantic processing in children with broadly-defined HFA. Similarly, Harris et al. (2006) reported anomalous distribution of brain activity as assessed using fMRI in adult males with broadly-defined HFA, during semantic processing. The results of these studies are consistent with those of the studies by Ring et al. (2007) and by Gaffrey et al. (2007) cited in Sections 9.2.1 and 9.2.2 (on AS and on narrowly-defined HFA), respectively.

Numerous other studies of broadly-defined HFA have investigated anatomy and function of brain regions involved in language processing more generally, reporting a wide range of differences between HFA groups and neurotypical controls.
Many of these studies report abnormalities of language lateralisation. However, these abnormalities vary in kind, with reversed asymmetry being reported in some studies (e.g. Boucher et al. 2005; Herbert et al. 2002; 2005) and lack of the normal asymmetry in other studies (e.g. Schmidt et al. 2009). Other studies suggest that specific structures or brain regions mediating language in neurotypical populations develop and function differently in individuals with broadly defined HFA (for reviews see Groen et al. (2008); Herbert and Kenet (2007); Kleinhans et al. (2008)).

In sum, behavioural findings from studies of language in broadly defined HFA add to evidence already cited in the sections on language in AS and in narrowly-defined HFA, in that they indicate subtle anomalies in the processing of semantic meaning accompanied by atypical brain activity in individuals with clinically normal language. However, the observation of minor grammatical anomalies in cases of narrowly-defined HFA but not in children with AS, as reported by Ghaziuddin et al. (2000) (see above), suggests that it may be premature to conclude that grammar is completely unaffected in all individuals within the broadly-defined HFA group. In addition, the considerable body of evidence showing that language in this group is subserved by partially different, or differently lateralised, brain structures shows that language has been acquired differently, and is processed atypically, by this group. Nevertheless, the most striking observation, overall, is that despite the differences in brain representation, language in people with broadly-defined HFA is so very little affected.

9.2.4 Autistic spectrum disorder with language impairment (ASD-LI)

Until the early 1980s, ‘early childhood autism’ was diagnosed only in individuals with clinically significant language impairment, the large majority of whom were low-functioning, where low-functioning is taken to mean non-verbal IQ or full-scale IQ < 70. Much of what is known about structural language in ASD-LI comes from studies carried out during this early period, and these studies are reviewed first.

Early studies showed that 50–75% of the individuals with this diagnosis never acquired useful language in any modality (Rapin, 1991). With the expansion of the definition of ASD to include people with AS or HFA, the proportion of mute individuals within the group of all individuals with ASD has reduced. However, the absolute numbers of individuals with ASD who are non-verbal have not changed, even if they constitute a smaller proportion than previously of the total population diagnosed with ASD.

Most non-verbal individuals are severely or profoundly intellectually disabled, often with multiple handicaps. However, this is not invariably the case, some having adaptive abilities significantly in advance of their communication skills.
Researching the Autism Spectrum

and discrepant with their complete lack of expressive language (Carter et al. 1998; Kraijer, 2000). Language in these individuals has been little researched except within the context of the intervention method known as Facilitated Communication, a method that has been widely criticised on the grounds that claimed ‘miracle cures’ are an artefact of the methods used (see Mostert, 2004 for a review). This is unfortunate in that it obscures the fact that research is needed to investigate the nature and causes of language impairment in mute individuals who are not overall profoundly intellectually disabled. If, for example, language comprehension were found to be only moderately impaired in some individuals with a complete lack of intentional communicative output, this would be of considerable theoretical and practical interest and importance.

Early studies of language in those individuals with ASD-LI who do acquire some useful language were widely interpreted as showing a pattern of delay rather than deviance, at least in the acquisition of phonology and grammar (see reviews by Swisher and Demetras, 1985 and Tager-Flusberg, 1981; 1989). In other words, it was concluded that although language development begins late and progresses slowly, reaching a plateau beyond which further development does not occur, the stages through which language develops resemble those observed in young typically developing children, and are mental-age appropriate.

For example, studies of articulation in children with ASD-LI demonstrated that articulatory errors were similar to those made by younger, typically developing children (Bartolucci et al. 1976) and comparable to errors made by children with intellectual disabilities without autism (Boucher, 1976a). A detailed study by Tager-Flusberg et al. (1990) appeared to demonstrate conclusively that grammatical competence is delayed, rather than deviant, settling a controversy concerning these children’s acquisition of articles and verb tense endings (Bartolucci et al. 1980; Howlin, 1984; see also Bartak et al. 1975).

The area of language development that appeared to be more deviant than simply delayed concerned the acquisition of lexical meaning, as evident from tests of comprehension and also from the study of expressive uses of words and phrases by children with ASD-LI. Both Kanner (1943; 1946) and Asperger (1944) had noted a characteristic tendency amongst children across the whole spectrum of autism-related disorders to use stereotyped language, idiosyncratic words and phrases including neologisms, and to make errors in the use of personal pronouns. A detailed study by Rutter and colleagues comparing patterns of language impairments in children with ASD-LI and children with specific language impairment (SLI) underlined the fact that the major difference between the language of the two groups was in the area of unusual or bizarre utterances by the ASD-LI group (Bartak et al. 1975; 1977; Cantwell et al. 1978). However, these researchers also noted that comprehension impairment was more severe in the ASD-LI than in the SLI group despite the fact that both groups were selected using receptive language.
impairment as a criterion, and despite the fact that the groups were equated for single word picture-naming ability.

Other researchers emphasised the fact that echolalia is common and persistent in less able individuals with ASD-LI, associated with a tendency to reproduce whole sentences or phrases in contexts closely similar to those in which they were originally heard, and often with functional though idiosyncratic meaning (Fay and Schuler, 1980; Kanner, 1946; Prizant and Duchan, 1981). In their fascinating and insightful book on language in autism, Fay and Schuler (1980) remarked:

> If there is one pervasive theme in the study of the language of childhood autism it is the permanence of the initial learning situation. How can speech be brought into line with adult models if the only associations are first associations that are tenaciously stored and recycled as if they were cast in concrete? (pp. 77–78; italics as in the original).

Fay and Schuler go on to suggest that as a result of the paucity and rigidity of the associations to words or phrases learned by a child with autism, language for these individuals denotes but does not connote. Thus, at least for young or less able individuals with limited language, words and phrases are used like proper names, having a single referent rather than having a rich and generalisable network of associations and meaning.

Evidence from some early experimental studies including those of Hermelin and O’Connor (1967) further suggested that the ability to utilise word meanings in, for example, tests of memory, is impaired. This kind of evidence led some influential researchers to propose that children with autism, as then diagnosed, have a fundamental impairment in the acquisition of conceptual knowledge and hence lexical-semantic meaning (Fay and Schuler, 1980; Hermelin and O’Connor, 1970; Menyuk, 1978; Menyuk and Quill, 1985). However, tests of knowledge of basic and superordinate categories failed to confirm this hypothesis, the children with autism performing appropriately for mental age (Tager-Flusberg, 1985; Ungerer and Sigman, 1987). These observations prefigured observations of a similar discrepancy in high functioning individuals with normal language (noted in a previous section) between unimpaired comprehension of basic concepts and word meanings but impaired use of semantic knowledge in cognitive tasks.

The view that language development in individuals with ASD-LI is predominantly delayed rather than deviant, and most commonly characterised by normal or mental age appropriate phonology and grammar, with oddities of word usage, remained current until the end of the last century (see for example the review by Lord and Paul, 1997). However, a rather different picture of the pattern of language impairment associated with ASD-LI began to emerge towards the end of the
century, especially from some large-scale studies of younger children than those previously investigated.

Thus, through the 1990s Rapin and colleagues collected a wide variety of data on hundreds of children with ASD referred to specialist clinics for assessment, diagnosis and treatment. Data relating to language in the group as a whole were reported during the 1990s (Tuchman et al. 1991; Rapin, 1996) and findings on those children with clinically significant LI are summarised in a review by Rapin and Dunn (2003). The conclusions from this review were: that children with ASD-LI aged between 3 and 6 years invariably have impaired language comprehension; approximately 35% have the kind of ‘higher order processing’ problems that relate most clearly to linguistic meaning; while approximately 65% fall into the clinical category of ‘mixed receptive/expressive language disorder’ that includes grammatical and phonological impairments. In their most recent follow-up of language in the whole cohort, Rapin et al. (2009) report that by ages 7 to 9 years, 73% of those children with clinically significant LI had poor comprehension but intact phonology; and 27% had moderately or mildly impaired comprehension with ‘severe and persistent’ phonological impairments. Because most of the children in the latter subgroup were low-functioning, and a non-autistic low-functioning comparison group was not included, it is not possible to conclude whether or not the phonological impairments were typical of intellectually disabled children at this age, or autism-specific in kind.

Deviant rather than simply delayed language development was also reported in two large-scale studies of unselected groups of pre-school children with ASD, using information from parental report (Charman et al. 2003; Luyster et al. 2007). The children studied understood more words and phrases than they spontaneously used, following the normal pattern. However, whereas the discrepancy between comprehension and production is large in typically developing children, it was much smaller in the ASD groups in both studies, consistent with Rapin and Dunn’s (2003) observation that comprehension is invariably and markedly impaired in young children with ASD-LI.

A smaller-scale but detailed study by Eigsti et al. (2007) confirmed Rapin and Dunn’s report of significant impairments of productive morphology and syntax in young children with ASD and initial language delay. In this study spontaneous language used by a mixed ability group of 16 children with ASD aged 3–6 years was compared with spontaneous language produced by an ability-matched group of children with developmental delay without ASD and a group of younger typically developing children. The main findings were that the children with ASD had shorter mean length of utterance (MLU) than the developmentally delayed group, and somewhat shorter MLU than the younger typically developing group. The children with ASD were also significantly impaired in their use of various
grammatical constituents and forms as measured using the Index of Productive Syntax (IPSyn) (Scarborough, 1990). Moreover the pattern of syntactic development in the ASD group differed from that in either of the other groups, and was thus deviant rather than simply delayed. Most strikingly, the abnormalities of grammatical development occurred in children the majority of whom had non-verbal IQ > 70 and single word comprehension within the normal range. Consistent with their relatively good lexical ability on single-word testing, the ASD group produced as many and as varied words as the two other groups. However, the ASD group produced significantly more jargon words than either of the other groups.

A study by Condouris et al. (2003) of 44 children who were somewhat older than those assessed in the studies described above also showed that children with ASD-LI have reduced MLU and impaired syntax as measured using the IPSyn. The number of different word roots used in spontaneous speech was also below age-related norms. The main purpose of this study was, however, to compare the results of language assessment based on spontaneous speech as compared with assessment based on the results of standardised clinical language tests. The two sets of measures were correlated in predicted ways: for example, scores on clinical tests of vocabulary correlated with the number of word roots used in spontaneous speech. However, measures of spontaneous speech, and especially the IPSyn, produced results indicative of a considerably greater degree of language impairment than did the standardised tests, an observation that is relevant to interpreting Eigsti et al.’s (2006) findings described above. Subsequent experimental tests of verb tense marking by 19 of the ASD-LI children studied by Condouris et al. (2003) confirmed the presence of grammatical abnormalities similar to those originally reported in 1980 by Bartolucci et al. (Roberts et al. 2004).

All the above findings suggest that clinically significant grammatical and phonological impairments are more common in children with ASD-LI than was widely thought to be the case up until the late 1990s. Rapin and Dunn (2003) suggest two possible explanations of discrepancies between the results of earlier and later studies.

Their first suggestion was that earlier studies focused on relatively high functioning children excluding those with moderate or severe language impairment and significant intellectual disability, and that patterns of language impairment differ across lower- and higher-functioning language impaired groups. However, early studies did not, in fact, focus mainly on more able individuals with ASD-LI; moreover, many studies over several decades have shown that grammatical impairments can occur alongside higher-order lexical impairments in individuals with non-verbal IQ within the normal range, although significant phonological impairments are rarely noted (e.g. Bartak et al. 1975; Bennett et al. 2008; Eigsti et al. 2007; Kjelgaard and Tager-Flusberg, 2001).
Rapin and Dunn’s (2003) second suggested explanation of the discrepancies between the traditional profile of language strengths and weaknesses and their own findings concerns the ages of the groups assessed. Rapin and Dunn point out that most early studies focused on older children and adolescents, whereas children included in the studies they reviewed were all below the age of 6 years. Children studied by Eigsti et al. (2007) (also by Charman et al. 2003, and by Luyster et al. 2007) were also below age 6.

Rapin and Dunn (2003) provide evidence consistent with this explanation, some of which is amplified in the latest evidence from follow-up assessments of children from the original cohort (Rapin et al. 2009, see above). In these reviews, Rapin and colleagues note that the prevalence of grammatical and especially phonological impairments declines with age, leaving a predominance of higher-order processing impairments marked in particular by impaired language comprehension. Nevertheless, a minority of predominantly low-functioning children have grammatical and especially phonological impairments that persist beyond the age of 6.

Twelve of the 19 children initially investigated by Bartak et al. (1975; 1977), and reported to have some phonological and syntactic immaturities were also reassessed in a follow-up study two years after their initial assessment (Cantwell et al. 1978). Detailed analysis of spontaneous language produced by these children, then aged between 6 and 11 years (mean age 9 years 2 months) showed ‘generally correct usage’ of a majority of grammatical forms (excluding personal pronouns). In addition, a reduced percentage of children had phonological errors. However, high rates of stereotypic or echolalic utterances remained. This trend towards reduced grammatical and phonological impairment with persistent abnormalities of word use and meaning brings the group profile closer to the traditional profile of linguistic strengths and weaknesses than had been the case two years previously.

Bartak et al.’s group was followed up again in early adulthood (Mawhood et al. 2000). Severe problems of language comprehension and production remained even on measures of single word comprehension and use. However, gains in absolute language levels had been made across the group as a whole, and eight individuals were judged to be using ‘good sentence speech’ and five individuals were described as having ‘immature speech’. By contrast, six individuals were predominantly mute or echolalic. Thus the trend towards the more traditional profile of language abilities appears to continue into adulthood in a majority but not all individuals with ASD-LI, some of whom actually regress.

In sum, the discrepancy between the traditional picture of language impairments in children with ASD-LI and findings such as those reviewed by Rapin and Dunn (2003) cannot be explained in terms of differences in intellectual ability of the individuals studied. Indeed, the studies of language impairment in high
functioning individuals reviewed above might suggest that this subset of individuals with ASD-LI is particularly prone to grammatical impairments (e.g. Bennett et al. 2008; Eigsti et al. 2007; Kjelgaard and Tager-Flusberg, 2001). However, the discrepancy between the older and more recent literatures may be at least partly explained in terms of differences in the ages of the children studied. Specifically, it appears that the phonological/articulatory impairments and grammatical impairments common in children with ASD-LI under the age of 6 years tend to decline with age, leaving a predominance of problems associated with the processing of lexical-semantic meaning. Phonological impairments persist only in a minority of less able children and may be mental age appropriate.

A study of spontaneous language produced by adults with ASD-LI underlines the pervasiveness and persistence of lexical-semantic abnormalities in ASD-LI (Perkins et al. 2006). In this study, seven adults with ASD-LI, only one of whom was high-functioning and none of whom lived independently, but who were all described by their carers as ‘quite voluble’, were recorded in one-to-one conversation with a familiar adult. Corpora of language from each participant were analysed linguistically and it was concluded that all seven adults were relying to an abnormal extent on using certain preferred lexical items, phrases or grammatical frames within their conversation, and in some cases on reproducing words or phrases recently used by the interlocutor. It also became clear that the words and phrases used by these adults were not always understood by them. For example, two individuals used specific words apparently appropriately within their conversation, asking shortly afterwards what the words meant.

The conclusion from this study was that imitation, repetition and formulaicity are utilised by these relatively voluble adults to maintain discourse to the best of their ability, but often in the absence of comprehension even of the language they themselves are using. Perkins et al. (2006) suggest that the language used by individuals with ASD-LI does not accurately represent the individual’s conceptual knowledge. This conclusion is reminiscent of Fay and Schuler’s (1980) comments regarding the narrowed meaning of ‘language set in concrete’. It is also consistent with a comment by Lord and Paul (1997, p. 212) that individuals with ASD-LI have ‘limited ability to integrate linguistic input with real-world knowledge’. In a detailed account of the speech, syntax and discourse of the adults studied by Perkins et al. (2006), Dobbinson (2000) reported that articulatory errors occurred only in the less able participants (thus associated with mental age rather than with ASD). However, grammatical errors occurred in all the participants studied. These did not affect word order, but consisted generally of truncations, omissions, or substitutions especially of ‘closed class’ words such as conjunctions, articles or pronouns.
Summarising findings on language in individuals with ASD-LI is not easy, not least because of the paucity of research, especially recent research investigating language in low-functioning people with ASD-LI. Compared with the number of recent studies on perceptual abilities, executive functions and social skills including communication, recent studies of language in ASD-LI are rare. Moreover, such studies as exist tend to focus on individuals with normal non-verbal IQ. Early studies, which were relatively more common and which did include low-functioning participants, seldom used large groups, and the methods used may have lacked rigour by contemporary standards (Lord and Paul, 1997; Tager-Flusberg et al. 2005). Attempts to draw some meaningful picture from the available research are also difficult because there are many different facets of language to be assessed including comprehension and expression, articulation, multiple grammatical forms and rules, meaning and conceptual knowledge. In addition, the methods that have been used to collect and analyse linguistic data are very varied, including parental report, standardised clinical tests, experimental investigation, and the collection and analysis of corpora of spontaneous language, each method having some unique influence on the findings reported. This makes comparisons across studies difficult. It is in any case unlikely that a single ASD-LI phenotype exists, even when the effects of deprivation, hearing impairment or other co-morbid conditions have been excluded as influences on language outcomes (as has generally been the case in studies referred to above).

Given all the above limitations, it might be wiser not to try to summarise the findings at all. However, a few generalisations—ignoring the considerable individual variation that exists—can be made with reasonable confidence, as follows:

1. Language impairment in ASD-LI is non-modality-specific, acquisition of written or signed language being generally as much affected as the acquisition of spoken language.
2. Semantics is universally and persistently affected, being strikingly deviant in the most severely language-impaired individuals. Deviancy is most obvious in the oddities of language production which, though varying with age and ability, is characterised by narrowed and idiosyncratic (non-shared) meaning and repetitiveness. However, impaired semantics has more severe effects on comprehension (where the language to be understood is not under the individual’s control) than on production. Impaired lexical semantics and also impairments in the use of semantic knowledge in some cognitive tasks might suggest that the semantic meaning-base (networks of conceptual knowledge) is abnormal in content and/or organisation. However, this is unproven.
3. Grammar is also impaired in individuals with ASD-LI, especially in young children. Syntax (in the sense of word order) may be less affected than morphology (grammatical forms and rules for their use). It is unclear whether morphological impairments reflect delayed and incomplete development, or deviant development. The tendency for grammatical impairments to decline with age might argue for the former. On the other hand, evidence for unevenness in grammatical development and for the persistence of certain kinds of morphological errors is more indicative of deviant development.

4. Phonology (‘articulation’) is least likely to be impaired, especially in older children and adults with ASD-LI; and if impaired is probably mental age appropriate, rather than deviant in ways that are autism-specific.

5. Non-verbal ability within the normal range does not protect an individual from language impairment. However, verbal IQ and language level generally covary and (a point not made above) the more severe the language impairment the greater the discrepancy between verbal and non-verbal IQ, generally speaking, with non-verbal IQ the better preserved (see for example Lord and Paul, 1997).

6. The preceding generalisations relating to language in individuals with ASD-LI mirror the distribution of subclinical language anomalies in individuals with Asperger syndrome or high functioning ASD with currently normal language. Specifically, anomalies of semantic processing are common if not universal in these groups; mild, subclinical grammatical impairments have occasionally been noted in individuals whose language has normalised following initial delay; but clinically significant phonological impairments are never noted in group studies of people with Asperger syndrome or of people whose language has normalised following initial delay.

9.3 Causes of language impairment across the spectrum

There are undoubtedly numerous contributory causes of linguistic anomalies and impairments, whether subclinical or clinically significant, in individuals with ASD. There are, for example, numerous medical conditions that co-occur with ASD more often than can be explained by chance, and which have varied and specific effects on language acquisition. Such conditions include hearing loss, visual impairment, Down syndrome, Fragile-X syndrome, Turner’s syndrome and epilepsy, to name a few. Children with ASD are also as vulnerable as other children to psychosocial deprivation or diseases occurring sporadically, with effects on language acquisition. The fact that co-morbidities are very common in association
with ASD undoubtedly helps to explain why language is so often impaired, and why language profiles are so heterogeneous, especially in unselected groups (i.e. those where no exclusion criteria have been applied).

The aim of this section of the chapter is to present and discuss theories that try to account for such homogeneity as may be observed in individuals without significant sensory impairment or other co-morbid medical condition with known effects on language, as represented by the generalisations listed at the end of the previous section. Theories to be discussed fall into two groups: those that implicate social impairments and those that implicate cognitive impairments.

9.3.1 Explanations invoking social deficits

Impaired ‘mindreading’ (Baron-Cohen, 1995) undoubtedly affects the way in which language is acquired by people with ASD (Bloom, 2000; Hobson, 1993). Typically developing infants routinely infer the speaker’s intention when forming an association between a novel object or action and a novel word – something that children with autism do not generally do (Baron-Cohen et al. 1997; Parish-Morris et al. 2007; Preissler, 2008). Moreover, impaired social attention (Bopp et al. 2009) and especially joint attention (Siller and Sigman, 2008) are predictive of delayed language development. It can be assumed, therefore, that impaired mindreading contributes to the abnormalities of lexical-semantic meaning that occur across the spectrum, and especially to the tendency to use words and phrases with idiosyncratic (i.e. unshared) meaning. Impaired mindreading can also explain the problems that younger and less able individuals have in understanding and using deictic terms, the meaning of which depends on the identity of the speaker (‘you’/’me’), or the speaker’s location in space (‘here’/’there’) or in time (‘now’, ‘then’). Impaired mindreading also helps to explain why comprehension of others’ current speech is invariably impaired, since not only does the person with ASD have a narrow, idiosyncratic meaning-base, but they also fail to take account of other people’s knowledge, thoughts and feelings in interpreting heard speech. Thus comprehension impairments derive in part from pragmatic or use-of-language impairments that are closely allied to semantic impairments in structural language.

However, as pointed out by Bloom (2000), impaired mindreading cannot offer a sufficient explanation of clinically significant language impairments co-occurring with ASD. This is because individuals with AS or other form of high-functioning ASD without language impairment have impaired mindreading abilities but nevertheless develop clinically normal language without early delay. As Bloom argues, there must be other prerequisites for language acquisition that are available to these able individuals (but not to individuals with ASD who do not acquire normal language), and that are sufficient for the acquisition of ostensibly normal language.
In sum, impaired mindreading may explain some of the semantic anomalies observed in the language of high-functioning individuals with intact language, but cannot by itself explain the clinically significant structural language impairments in people with ASD-LI. By contrast, mindblindness and the plethora of social difficulties associated with it is the major cause of impaired communication, including use of language, in people with ASD.

9.3.2 Explanations invoking cognitive deficits

When ‘early childhood autism’ was conceptualised as invariably involving impaired language, it was suggested by various researchers that the condition was, at root, a particularly severe type of developmental language disorder with secondary effects on social behaviour and behavioural flexibility (Churchill, 1972; Rutter, 1968; Rutter et al. 1971; but see Boucher, 1976b). Attempts to identify the cause or causes of the language impairment were therefore given high priority. Explanations that were proposed at the time included impaired ability to form semantic categories that are integrated into an underlying conceptual system (Fay and Schuler, 1980; Menyuk, 1978; Tager-Flusberg, 1981); impaired ability to form symbols (Ricks and Wing, 1975); difficulties in processing transient sequential inputs (Rutter, 1983; Tanguay, 1984); and (related to this) impaired ability to segment heard speech into its constituent components (Prizant, 1983). None of these hypotheses was reliably confirmed or disconfirmed at the time. They are not necessarily mutually exclusive, and all remain of potential interest especially in terms of how they may or may not fit in with current theories, as considered next.

An implication of the early suggestion that autism results from a severe developmental language disorder was that language impairment in ASD-LI constitutes a type of specific language impairment (SLI). Rutter and his colleagues investigated this hypothesis in the set of longitudinal studies that has been described above (Bartak et al. 1975; 1977; Cantwell et al. 1978; Howlin et al. 2000; Mawhood et al. 2000). The aim of this set of studies was to compare not only language profiles but also cognitive, social and behavioural characteristics of individuals with ASD-LI and individuals with receptive-expressive developmental language disorder, a subtype of SLI. Had substantial overlap been found, especially in terms of linguistic profiles, then it might have been inferred that the causes of language impairment in ASD-LI and in SLI were at least partly the same. In the event, discriminant analyses using either linguistic or cognitive measures differentiated the two groups reliably when the children were first seen, again two years later, and again (though less reliably) in early adulthood. In addition, successive assessments revealed different developmental trajectories in the two groups.
Several recent studies have, however, revived interest in the theory that an important cause of language impairment in ASD-LI is co-morbid SLI. Evidence from these studies concerns common features within linguistic profiles and shared cognitive ‘markers’ in the two conditions; some possibly shared abnormalities of brain structure and function; and some possibly shared genetic factors. This evidence is reviewed by Williams et al. (2008) who conclude the following. First, although there is some overlap in linguistic profiles in the two conditions, especially in younger children, there are also significant differences. Most obviously, phonological impairments are common and relatively persistent in prototypical forms of SLI, whereas persistent phonological impairments are rare in ASD-LI. Second, although certain impairments that are reliable diagnostic markers of SLI – namely impaired non-word repetition and sentence repetition, and certain errors of verb tense marking – also occur in individuals with ASD-LI, there is evidence to suggest that the overlap is superficial and differently caused in the two conditions. Third, neither the evidence from brain studies nor from genetic studies is robust. Williams et al.’s (2008) overall conclusion is that the ‘ASD-LI = ASD + SLI’ theory remains unproven, at least in terms of its capacity to explain most or all cases of ASD-LI (when non-specific factors such as co-morbid sensory impairment have been excluded).

Tager-Flusberg and her colleagues, whose research has done much to revive interest in the suggestion that co-morbid SLI is the major cause of ASD-LI (Kjelgaard and Tager-Flusberg, 2001; Tager-Flusberg, 2004; 2006) have, however, assumed that the evidence of behavioural overlap is sufficiently strong to warrant a hypothesis concerning shared causes. Accordingly, Walenski et al. (2005) propose that both SLI and ASD-LI result at least in part from deficits of procedural memory. This hypothesis builds on Ullman’s (2001) model of the cognitive prerequisites for language acquisition in which it is argued that phonological and grammatical development are largely dependent on procedural memory, whereas lexical development is dependent on declarative memory. Walenski et al.’s (2005) hypothesis also builds on a paper by Ullman and Pierpoint (2005) in which it is argued that procedural memory deficits cause the phonological and grammatical impairments in prototypical SLI. Walenski et al. (2005) argue that procedural memory deficits cause the grammatical impairments in ASD-LI and some problems of word retrieval. However, they argue in addition that mindblindness is the major cause of lexical-semantic impairments in ASD-LI, and that problems of linguistic meaning are more marked in ASD-LI than in SLI because children with SLI do not have major mindreading difficulties.

Whereas the latter part of Walenski et al.’s explanatory theory is empirically supported (see above), empirical evidence of procedural memory impairments in ASD is either negative or lacking (see Boucher and Mayes (in press), for a review
of studies of memory in ASD). Moreover, studies of language in ASD-LI (reviewed above) do not suggest that grammatical – let alone phonological – impairments are the most prominent or persistent kind of impairment characteristic of ASD-LI.

The procedural memory deficit explanation of SLI is only one of several competing explanations of that disorder. Assuming for the moment that language impairment in ASD-LI generally results from co-morbid SLI, is there any other theoretical explanation of SLI that might apply to language impairments in ASD?

Several longstanding theoretical explanations of SLI focus on impairments in the sensory-perceptual processing of heard speech (see Leonard and Deevy (2006) for a review of theories). Deficits in auditory (speech) perception are consistent with increasing evidence of anomalies and impairments in auditory processing and perception in individuals with ASD generally, and in low-functioning and language impaired individuals in particular (e.g. Cardy et al. 2008; Tecchio, 2003). These findings are additional to well-established findings that children with ASD lack the normal preferential responses to speech as opposed to non-speech sounds (Klin, 1991; Lepisto et al. 2005). However, sensory or perceptual problems confined to the auditory modality cannot explain why language impairment in ASD-LI is non-modality specific (see generalisation (1) above). If, on the other hand, findings of impaired auditory processing were shown to be representative of non-modality-specific sensory-perceptual impairments, then they might help to explain language impairments in ASD-LI. In this case, however, the causes of language impairments in ASD-LI and SLI would diverge, because language impairments in SLI have predominant effects on spoken language only.

Another strongly argued theory identifies problems of phonological short term and working memory as a critical cause of SLI (Gathercole, 2006; Gathercole and Baddeley, 1990). However, this theory seems unlikely to offer an explanation of language impairment in ASD-LI because immediate verbal recall of unrelated words or digits is relatively unimpaired (Boucher and Mayes, in press). Moreover, although non-word repetition is impaired in individuals with ASD-LI as well as those with SLI (Kjelgaard and Tager-Flusberg, 2001; Whitehouse et al. 2007b), there is evidence to suggest that the impairment stems from different causes in the two conditions (Whitehouse et al. 2008).

In sum, the theory that language impairment in ASD-LI generally results from co-morbid SLI is contraindicated by differences in presenting profiles in most individuals, and also by differences in the developmental trajectories in the two disorders (Howlin et al. 2000; Rapin and Dunn, 2003). This conclusion holds even when the additional effects of social impairments on language development in ASD but not in SLI are taken into account (Williams et al. 2008). However, there is sufficient evidence to suggest that ASD and SLI are loosely related in some way not yet identified.
In the first place, in their comparison of language in children with SLI and children with high-functioning ASD-LI, Bartak et al. (1975) identified ‘mixed’ cases of autism and SLI in approximately 15% of potential participants. Although studies carried out many years ago may be questioned on grounds of differences in diagnostic criteria or other methodological detail, differences in criteria mainly concern the presence of structural language impairment; moreover, this particular study was methodologically exemplary. The finding of mixed cases should not, therefore, be discounted. In the second place, and as already noted, findings from numerous studies over recent years have been interpreted as indicative of possible links between ASD and SLI at aetiological, neurobiological and behavioural levels of description. Although it has been argued that this evidence is not robust and that the case for a meaningful link between SLI and ASD-LI is unproven (Williams et al. 2008), it must also be concluded that the case against such a meaningful link is unproven.

A third and quite different source of evidence is sufficient grounds by itself for keeping an open mind concerning the relationship between ASD and SLI. This concerns the occurrence of forms of language and communication disorder that are intermediate between prototypical forms of SLI and ASD-LI. Initially, children with these kinds of intermediate difficulties were described as having ‘higher order language processing’ problems affecting semantics and pragmatics (Allen, 1989; Rapin and Allen, 1983). Because communication was affected in these children in addition to semantic aspects of structural language, there was considerable discussion as to whether ‘semantic-pragmatic disorder’ was a form of ASD or a subtype of SLI (Bishop, 1989; Boucher, 1998; Brook and Bowler, 1992). However, subsequent research has established that pragmatic language impairments can occur independently of both significant structural language impairments (including semantic impairment) such as define SLI, and of the social impairments characteristic of ASD. Pragmatic language impairment (PLI) is therefore now treated as a rare ‘stand-alone’ condition intermediate between SLI and ASD (Bishop and Norbury, 2002; Botting and Conti-Ramsden, 1999; 2003).

It could be the case that language-related impairments in SLI, PLI and ASD-LI are all subtly different in kind and differently caused. However, there is both an orderliness and a relatedness amongst patterns of language impairment that occur in subtypes of SLI through PLI to ASD-LI that suggests otherwise. The orderliness concerns the fact that combinations of impairments along different dimensions of language co-occur only along ‘adjacent’ dimensions of language, whether in SLI or in ASD-LI, as illustrated in Table 9.1. The relatedness concerns the fact that in SLI language is most commonly impaired within the dimensions of phonology and grammar, less commonly involving semantics, and least commonly involving pragmatics, whereas the exact opposite is the case in ASD-LI. This is also
Table 9.1 Schematic representation of the orderliness of patterns of spared and impaired abilities across linguistic dimensions in SLI through PLI to ASD, and of the symmetry of these patterns across the three disorders

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Key

- Linguistic dimension most likely to be significantly impaired.
- Linguistic dimension second most likely to be significantly impaired.
- Linguistic dimension third most likely to be significantly impaired.
- Linguistic dimension least likely to be significantly impaired.
- No significant impairment.

illustrated in Table 9.1. This orderliness and symmetry seems unlikely to be a chance occurrence, although not easy to explain (but see Boucher, 2000 for an attempted explanation)³.

³ This explanation focused on the different frequencies at which temporal analysis must be carried out during the acquisition of different facets of structural language including the rules and conventions contributing to pragmatics. Thus, acquisition of phonology requires very high frequency temporal analysis (putatively impaired in prototypical forms of SLI, spared in ASD); acquisition of syntactic and morphological rules requires somewhat less high frequency temporal analysis (putatively impaired in most individuals with SLI; somewhat affected in ASD); the acquisition of conceptual knowledge, word meaning, and the rules and convention of pragmatics such as require temporal analysis of ongoing events (as opposed to syllables, or phrases, clauses and sentences), require a slower rate of temporal analysis (less affected in prototypical forms of SLI but significantly impaired in PLI and ASD). Neurophysiological timing mechanisms are genetically determined, and it may be assumed that related genes contribute to the development of timing mechanisms at the rates hypothesised to be differentially affected across various forms of SLI and ASD-LI.
Boucher et al. (2008a) have proposed an explanation that accepts, or partly accepts, some of the theories discussed above, but that goes beyond them in one critical respect. Boucher et al. (2008a) agree with numerous others that impaired mindreading contributes to the semantic anomalies characteristic across the spectrum. They also accept a role for co-morbid SLI, as proposed by Tager-Flusberg and various colleagues. However, Boucher et al. argue that co-morbid SLI probably affects a minority of individuals with ASD-LI – (perhaps the 15% identified as ‘mixed’ cases in the Bartak et al. 1975 study) – including those high-functioning individuals in whom grammatical impairments are most prominent. Boucher et al.’s main argument, however, is that language impairment in lower-functioning individuals with ASD-LI can best be explained by a combination of impaired declarative memory, with intact procedural memory and also immediate and working memory.

Declarative memory can be subdivided into episodic and semantic memory. The latter form of declarative memory is known to be impaired across the spectrum (see Chapter 10) and can have subtle effects on the acquisition of word meanings (Holdstock et al. 2002), contributing to the subclinical semantic anomalies observed even in individuals with AS. Boucher et al. (2008a) hypothesise that semantic memory as well as episodic memory is impaired in lower-functioning individuals with ASD, constituting a more pervasive impairment of declarative memory than that which occurs in high-functioning individuals. According to Ullman’s (2001) model, declarative memory is essential for the acquisition of lexical items. These include not only open class words such as nouns, adjectives and verb stems, but also closed class words with grammatical functions, such as articles, prepositions and conjunctions; also irregular grammatical forms such as irregular past tense forms or plurals. Thus, a pervasive declarative memory impairment would have predominant effects on semantics, but would also affect certain facets of grammar. At the same time, intact immediate memory would be used compensatorily in ways that can help to explain the repetitiveness and formulaicity of autistic language. Equally, intact procedural memory (in those individuals without co-morbid SLI) would help to ensure relatively normal acquisition of phonology, and also of regular, rule-based aspects of grammar. Finally, a pervasive impairment of declarative memory would limit the ability to acquire factual knowledge both directly (via semantic memory) and indirectly (via language based learning). Thus, this component of Boucher et al.’s (2008a) overall explanation of language impairments across the spectrum can explain why language and learning impairments are so closely linked in lower-functioning individuals with ASD-LI.

The declarative memory hypothesis is in the early stages of empirical testing (see Boucher et al. (2008b) for a preliminary report). This hypothesis therefore takes its place alongside other untested explanations of language impairment in ASD-LI, as outlined earlier in this section.
9.4 Summary

Structural language acquisition varies from clinically normal to absent across the autistic spectrum. However, even individuals with clinically normal language have oddities of semantic usage and atypical brain activity during semantic processing tasks. Brain regions involved in language processing more generally are also structurally and functionally atypical in this group. It is uncertain whether or not initial language delay in high-functioning individuals with ASD and clinically normal language predicts language outcomes. Most available evidence suggests not, but there is some slight contrary evidence.

Individuals with ASD and some useful, though clinically impaired, language (ASD-LI) may have significant phonological and grammatical output problems in early childhood, additional to poor comprehension and limited semantic knowledge. Over time, phonological impairments tend to resolve to mental-age appropriate levels (but short of normalising in low-functioning individuals), and expressive grammatical impairments become less prominent (but still present), leaving receptive language and higher order semantic processing as the predominant language impairment. Various explanations of ASD-LI have been proposed. Leaving aside the many non-specific factors that may impair language acquisition in individual cases (e.g. co-morbid hearing loss, Down syndrome, environmental deprivation), it is agreed that impaired mindreading and associated impairments of social interaction invariably contribute. The role of co-morbid SLI is controversial, some recent theorists claiming a major role for this factor. It is argued here that co-morbid SLI probably contributes to language impairment in a minority of individuals with ASD-LI, including those cases where clinically significant LI occurs in otherwise high-functioning individuals. It is proposed instead that the major factor underlying LI and also intellectual disability in lower-functioning individuals is a pervasive impairment of declarative memory involving semantic as well as episodic memory difficulties, but leaving other memory systems mainly intact.

9.5 References


Memory in autism: binding, self and brain

DERMOT BOWLER, SEBASTIAN GAIGG AND SOPHIE LIND

Memory can be thought of as the capacity of an organism to utilise past experience in order to direct current and future behaviour. Such a capacity entails the registering and recording – the encoding – of that experience in such a way as to enable its subsequent retrieval. Retrieval can be either voluntary or involuntary and the resultant information may or may not form part of conscious awareness. The processes of encoding and retrieval are the result of a range of psychological processes and are in turn influenced by other factors both psychological and physiological. In this respect, study of the patterning of memory processes and the factors that influence their operation can give clues to the wider psychological functioning of the individual. It is in this last respect that the study of memory can enhance our understanding of people with Autism Spectrum Disorder (ASD). ASD is not ‘caused by’ difficulties in memory, but the patterning of memory seen in individuals with ASD can provide clues to underlying cognitive and neuropsychological atypicalities as well as giving us a window onto their inner experiences of the world.

10.1 Preliminary remarks

Any discussion of memory in ASD must first emphasise the heterogeneous nature of the conditions that comprise the autism spectrum. An important aspect of this diversity is the distinction between ASD with accompanying intellectual disability (often referred to as ‘low-functioning ASD’ or LFA) and ASD without it (often termed ‘high-functioning ASD’ or HFA), a group that, as here defined, also
includes individuals with Asperger’s disorder. Intellectual disability in itself has consequences for memory (see Bray et al. 1997 and Wyatt and Conners, 1998 for reviews), but we should be careful about assuming that these consequences operate similarly in individuals with co-occurring ASD. Nor should we assume that atypical memory patterns identified in individuals with HFA necessarily hold for those from the lower functioning parts of the spectrum. Similar arguments hold for the distinction between individuals who have good language and communication skills and those whose language capabilities are diminished or absent. At present, systematic investigations into how these dimensions affect memory in the context of ASD are thin on the ground, so readers need to be aware of potential difficulties of interpretation when drawing conclusions from research that has been limited to particular subgroups of people within the ASD population.

The same caveat applies to the topic of memory. Although at first it appears to be a straightforward process – the recollection of something that happened in the past – a moment’s reflection throws up quite considerable complexity. ‘Memory’ is always of something and is assessed using particular procedures, often with a particular aim or purpose in mind. The writing of this chapter entails the recollection of words (verbal memory) and concepts (semantic memory) that have to be organised in a way that takes into account (however, imperfectly) the minds of potential readers. Some of the information comes into the author’s mind through a deliberate act of recollection (albeit prompted by the various cues that nudge authors to complete manuscripts on time) while other ideas are engendered by the reading of source texts. And all of these ideas are sorted and edited, accepted or rejected, in the light of the overall aim of the exercise. Even this anecdotal scenario highlights the complexities that begin to emerge when considering where to draw boundaries for the concept of ‘memory’. We need to be clear about the kinds of material that are being remembered, whether the memory involves unsupported recollection, prompted recollection or simply recognition that we had encountered something previously. We also need to decide whether the remembered material was learned very recently or some time (maybe even years) ago. The topics of recollection, prompting or recognition have engendered some of the principal test measures used in laboratory and clinical studies of memory. Recollection is usually tested by free recall, in which participants study lists of words and then recall as many as they can in any order. The prompt here is minimal, usually involving a request from the experimenter to recall the words just studied. Cued recall provides more concrete and specific hints to aid recall. These hints may be phonological (e.g. words that rhyme with . . . ; words that begin with . . . ) or semantic (e.g. there were flowers, items of furniture, etc.) in nature. Recognition involves studying long lists of items and then presenting these again, interspersed with non-studied items, asking the participant to indicate whether or
not they had seen the item at study. Recognition may also be tested by presenting participants with a studied and a new word and asking them to indicate which they had seen before.

In parallel with material and procedural issues is the question of how we conceptualise what is going on in the brain and the mind during the operation of memory. New information must be encoded, which implies some kind of storage system, or a system that marks already-stored information in a way that links it to the study episode. For example, when we see the word CAT in a list of items presented in a memory experiment, we mark our existing representation of ‘cat’ in a way that informs us that it was one of the studied items. Subsequent retrieval implies its own system or set of processes (for a fuller exposition of these topics, see Gardiner, 2008). Some theorists argue that memory can be divided into two distinct sets of processes, those that operate over the very short term (e.g. working memory, Baddeley and Hitch (1974)), and which are distinct from the processes that subtend long-term memory. Others (e.g. Bjork and Whitten (1974) and Crowder (1976)) argue for an undivided memory system that may vary in its particular characteristics depending on when retrieval happens. Advocates of both positions generally argue that memory (or long-term memory, in the case of advocates of multi-store models) can be divided into procedural and declarative memory systems. Procedural memory involves skills such as riding a bicycle or playing a musical instrument; declarative memory involves the conscious retrieval of facts or events and can be further subdivided into sub-systems and processes. For reasons of space, our discussion here will be limited to declarative memory in ASD. More detail on short-term and working memory in ASD can be found in Poirier and Martin (2008), on procedural memory in Mostofsky et al. (2000) and on implicit memory in Bowler et al. (1997), Gardiner et al. (2003), Roediger and McDermott (1993) and Schacter and Tulving (1994).

Declarative memory is memory that is generally accessible to conscious awareness (Eichenbaum, 1999), different kinds of which are used by many theorists to delineate separate memory sub-systems and processes. Tulving (2001) posits several systems, each associated with a characteristic type of conscious awareness. The first of these systems is the semantic memory system, which is one’s store of general knowledge or what Tulving calls ‘timeless facts’, the recall of which is accompanied by noetic conscious awareness, which is the experience one has when recalling items of general knowledge that are unaccompanied by any contextual detail or re-experiencing of the time at which they were learned. The second is the episodic memory system, which comprises recollection of personally experienced events and involves the self engaging in mental time travel to re-experience the spatio-temporal context of the recollected episode. It is this experience of the self
re-experiencing the past that he terms *autonoetic conscious awareness* and regards as being the hallmark of episodic memory. To a similar end, Jacoby (1991) contrasts *familiarity*, a non-effortful process, and *recollection*, which involves active, conscious control by the participant. On this view, the quality of the conscious recollective experience depends on the relative contributions of familiarity and recollection to a particular memory. Across all these different systems and processes memory is affected by the depth of processing (Craik and Lockhart, 1972) called for by different kinds of material and by different memory tasks. For example, focusing on phonological aspects of words is thought of as entailing shallower levels of processing than does working out meaningful relations among them. All these different theoretical positions are tested experimentally using manipulations of the procedures outlined earlier. It is important to bear in mind that the results of a given experiment can often be interpreted in the light of different theoretical perspectives.

### 10.2 Empirical findings

#### 10.2.1 Standard experimental procedures

Amongst the earliest studies of memory in ASD were ones concerned with memory span, a classic measure of short-term memory, which is determined by the number of items that a participant can correctly recall in the order in which they were presented. Initial reports showed that individuals with ASD exhibited relatively undiminished performance on such tasks by comparison with mental-age matched participants without ASD (Boucher, 1978; Hermelin and O’Connor, 1967). However, as Poirier and Martin (2008) observe, these early studies are compromised by the fact that groups were often matched on psychometric measures of digit span, which equates groups on their ability to recall the order of a series of numbers. When matching was based on non-span measures and when more demanding measures of span were utilised, Martin *et al.* (2006) found marginally diminished span in adults with HFA. More specifically, even though the absolute numbers of items recalled was undiminished, there was a significantly higher number of order errors in the recall of the HFA participants. These findings show that although the maximum number of items that individuals with ASD can recall is not different from that recalled by typical individuals, they have difficulties in recalling the precise order of the items, at least after a single exposure.

Free recall of longer lists of words – supra-span lists – without the requirement to preserve the order of the studied words has a number of characteristic features in typical individuals. The first few and the last few items in a list are more likely
to be recalled than the middle items, yielding the classic serial position curve in free recall (Murdock, 1962). Recall of the last few items – the recency effect – is thought, by advocates of multi-store theories, to reflect the contents of a short-term store, whereas recall of the first few items – the primacy effect – is thought to result from processing of information into long-term memory. Another characteristic of supra-span list recall is that typical individuals tend to cluster (i.e. recall in sequence) items that are drawn from the same semantic category (Bousfield, 1953), and this clustering usually yields higher overall recall than for uncategorised lists. If the same list is presented repeatedly over several trials, then recall on each trial increases (free recall learning), and if the list is uncategorised, then participants will typically impose their own subjective organisation on the material, irrespective of the organisation of the studied list (Tulving, 1962). Assessments of phenomena such as these in ASD have yielded a characteristically distinct pattern of observations.

Free recall of uncategorised material in individuals with ASD is usually undiminished (Bowler et al. 1997; Minshew and Goldstein, 1993; 2001; Tager-Flusberg, 1991) unless there is concomitant intellectual disability (see Boucher and Lewis, 1989; Boucher and Warrington, 1976). In terms of the classic serial position effect, individuals with LFA tend to show diminished primacy and enhanced recency effects compared with typical controls (Boucher, 1978; 1981; O’Connor and Hermelin, 1967; Renner et al. 2000) whereas HFA individuals generally show typical serial position effects (Bowler et al. 2000b; Toichi and Kamio, 2002). The latter finding, however, needs to be interpreted with some caution since a recent study by Bowler et al. (2009) showed that the primacy effect of HFA participants shows a slower improvement over successive trials than that of typical individuals. This raises the possibility that the primacy effect observed on a single trial, although superficially similar between typical and HFA participants, may be mediated by qualitatively different processes.

The idea that memory operates in a qualitatively different manner in ASD and typical individuals is also evident in other memory phenomena. For instance, on later trials of multi-trial list learning, adults with HFA show slower rates of learning (Bennetto et al. 1996; Bowler et al. 2008a). Diminished learning is often a sign that participants fail to subjectively organise material for effective recall but surprisingly, individuals with ASD engage in such organisation to a similar extent as do typical participants (Bowler et al. 2008a). Individuals with ASD do, however, seem to engage in qualitatively different forms of subjective organisation. More specifically, while typical participants tend to converge in the way in which they organise a repeatedly presented list of words during their recall attempts (for example, by grouping items semantically or associatively), participants with ASD do not, indicating that their subjective organisation follows
a rather idiosyncratic pattern. Differences in how memory operates in typical and ASD individuals are even more obvious when the to-be-remembered material is semantically interrelated. Typical individuals consistently exhibit a memory advantage for more meaningful information but in ASD this phenomenon seems to depend on the nature of the task. Failure to use semantic aspects of study lists to aid free recall has long been known to be a feature of memory in LFA and HFA (Bowler et al. 1997; 2000b; Hermelin and O’Connor, 1970; Tager-Flusberg, 1991; but see Leekam and Lopez, 2003). Moreover, individuals from all parts of the autism spectrum are less likely to cluster semantically related items together in recall (Bowler et al. 2010; Hermelin and O’Connor, 1967). When category-cued recall or recognition procedures are employed, however, individuals with ASD often exhibit a relatively typical memory advantage for semantically interrelated materials (Boucher and Warrington, 1976; Bowler et al. 2008b; Mottron et al. 2001; Tager-Flusberg, 1991; Toichi and Kamio, 2002). These more supported test procedures generally seem to prove less difficult for individuals with ASD (e.g. Bennetto et al. 1996; Bowler et al. 1997; Gardiner et al. 2003; Tager-Flusberg, 1991), suggesting that whatever processes are involved in free recall situations pose a particular difficulty for them. Individuals with ASD are, nonetheless, susceptible to associatively induced illusions using the Deese, Roediger, McDermott DRM paradigm (Deese, 1959; Roediger and McDermott, 1995) regardless of whether recognition or free recall procedures are employed. During the DRM paradigm, participants study a series of strong semantic associates of a non-studied word (e.g. bed, snooze, blanket, pillow, night... all of which are strong associates of sleep), which often leads them to falsely recall or recognise the non-studied associate during a test phase. Two out of three studies (Bowler et al. 2000b; Hillier et al. 2007) found that adults with HFA were as likely as typical participants to falsely recognise the non-studied associate and in the Bowler et al. (2000b) study the authors also failed to find significant group differences in a free recall test. The third study (Beversdorf et al. 2000), using a slightly different method from the standard DRM paradigm, reported increased discrimination of non-studied items in adults with ASD as did Hillier et al. (2007) when pictorial stimuli were used.

The final source of evidence, which suggests that memory operates differently in ASD, stems from a series of recent studies that have investigated whether individuals with ASD, like typical participants, remember emotionally significant information better than emotionally neutral information (see Reisberg and Hertel, 2004 and Uttt et al. 2006 for reviews). The first study to investigate this phenomenon in ASD (Beversdorf et al. 1998) asked adults with and without ASD to try to remember a series of emotionally charged and neutral statements (e.g. ‘He talks about death’ vs. ‘He is talking with his roommate’) for a subsequent free recall test. The results showed that only the typical comparison group recalled the emotionally charged
statements significantly better than the neutral ones despite the fact that groups did not differ in terms of their recall of sentences and paragraphs that varied in terms of their syntactic and conceptual coherence. Recent studies have extended this finding. In one of these, Gaigg and Bowler (2008) presented participants with a list of words containing emotionally charged and neutral words and asked them to rate how emotionally intense they felt about them. During study, skin conductance responses, which index the extent to which participants are physiologically stimulated by the study material, were also measured. After participants had seen all the words, their free recall was tested at three points in time – immediately after they had seen the words, again after an hour and once more after at least one day. The findings showed that while groups did not differ in terms of their ratings of the words, their skin conductance responses to the words or their free recall performance on the immediate test, forgetting rates of emotional words over time were different in the ASD group. In a second experiment, Gaigg and Bowler (2009) employed a variant of the DRM illusion task developed by Pesta et al. (2001) in order to determine the extent to which it would be possible to induce false memories of emotionally charged words in individuals with ASD. Unlike typical participants who were far less likely to falsely recognise emotionally charged as compared to neutral words, those with ASD falsely recognised emotional and neutral words at roughly the same frequency. Finally, Deruelle et al. (2008) have recently shown that memory for pictorial stimuli is also atypically modulated by emotional factors in ASD. In that study individuals were asked to remember a series of positive, negative and neutral images and on a subsequent yes/no recognition test only the typical comparison group exhibited enhanced memory for the emotionally charged pictures. Only one study to date has failed to demonstrate differences between ASD and typical participants in their memories for emotionally charged stimuli and interestingly this study also employed a recognition test procedure albeit for verbal rather than pictorial stimuli (South et al. 2008). Recognition procedures generally pose few difficulties for individuals with ASD (Barth et al. 1995; Bennetto et al. 1996; Bowler et al. 2000a; 2000b; 2007; Minshew et al. 2001; but see Bowler et al. 2004)\(^1\) and, in the context of verbal material, use of recognition procedures has been found to attenuate group differences in the use of semantic relations among study words to facilitate memory (e.g. Bowler et al. 2008b). Thus, the absence of group differences in the South et al. (2008) study may not

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\(^1\) Individuals with LFA sometimes do exhibit difficulties on tests of recognition (Ameli et al. 1988; Barth et al. 1995; Summers and Craik, 1994) although this seems to depend on the precise nature of the recognition procedure used. What is needed to settle this question is a systematic evaluation of the effects of procedural and participant characteristics on recognition memory.
necessarily indicate preserved influences of emotional factors on memory in ASD. In fact, Gaigg and Bowler's (2008) observation of preserved memory enhancement for emotional words in ASD on immediate but not delayed free recall procedures suggests that quantitative similarities between ASD and typical individuals may be mediated by qualitatively different processes in the two groups.

The findings outlined above show that the memory difficulties experienced by individuals with ASD are relatively subtle, and are present on tasks where minimal clues are given for recall and where information has to be manipulated or processed in some way. Before the broader implications of these observations are discussed, we need to present a further, and rather paradoxical set of findings centred on the fact that relatively spared recognition memory in ASD hides a subtle but persistent difficulty in episodic memory.

10.2.2 Episodic memory

Despite recognition being an aspect of memory that poses few difficulties, at least for individuals with HFA, recent research has shown that this spared capacity conceals an important difficulty with episodic memory. One of the hallmarks of human memory is the ability to re-experience oneself at the heart of the spatio-temporal context of a previously experienced episode. The ability to do this involves an awareness of self that is continuous through past, present and future, as well as an ability to recollect not only that a particular event took place but also the context in which it happened. Some of the research on memory in ASD discussed above is consistent with a prediction that individuals on the autism spectrum might have atypicalities of episodic memory. Their relatively greater difficulties on recall-based compared to recognition-based tasks points to episodic difficulties. In addition, their diminished recall of incidentally encoded context (Bennetto et al. 1996; Bowler et al. 2004; 2008b) – sometimes referred to as source memory – constitutes another strand of evidence, and the presence of frontal lobe-related executive function difficulties in ASD (see Hill, 2004a; 2004b), together with the finding of episodic memory difficulties in frontal lobe patients (Wheeler and Stuss, 2003), is a third. More indirect support comes from a theoretical perspective of Perner and colleagues (see Perner, 2001), who argue that the cardinal characteristic of episodic memory – the re-experiencing of the self at the heart of a personally experienced episode – depends on the ability to represent oneself as an experiencer of events, and to evoke that representation in memory. This metarepresentational ability\(^2\) develops during the child’s fourth and fifth years and according

\(^2\) What is described here is Perner’s conception of the term ‘metarepresentation’ (see Perner, 1991), which differs radically from that used by Leslie (e.g. Leslie, 1987), and which is also used in the context of ‘theory of mind’ in ASD.
Researching the Autism Spectrum

to Perner, also underlies the ability to understand the behavioural consequences of false belief in others. Difficulties with false belief understanding are seen in at least some manifestations of ASD (Baron-Cohen et al. 1985; but see Bowler, 2007), and on Perner’s arguments they should, as a consequence, experience diminished episodic remembering.

A widely used test of episodic memory is the ‘Remember/Know’ (R/K) procedure developed by Tulving (1985). Participants are asked to study a supra-span list of words for a later memory test. At test, they are presented with single words, half of which comprise the earlier-studied items, and are asked whether or not they had seen the word at study. If they answer ‘yes’, they are then asked to make either a ‘remember’ (R) judgement, where they can clearly recollect the episode of having studied the word, or a ‘know’ (K) judgement, where they simply know that they studied the item without any recollection of details of the study episode. Bowler et al. (2000a) utilised this procedure with adults with ASD and normal intelligence and found that the ASD group showed diminished R but not K responses by comparison with typical individuals matched on age and verbal IQ. In order to assess whether the R responses that the ASD participants did produce were the result of similar underlying processing to that of the comparison group, Bowler et al. (2000a) included in the study list words that are encountered in English either frequently or infrequently. Low frequency words typically yield more R responses in the R/K paradigm, and a similar pattern in the ASD group would suggest that although diminished in quantity, their R responses would be similar in quality to those of typical individuals. This is what Bowler et al. (2000a) found, and in a further series of studies that manipulated other factors known to affect levels of R and K responses in typical individuals, Bowler et al. (2007) found that adults with ASD and normal IQ responded to these manipulations in a similar manner to matched typical comparison participants. Dividing attention at study diminished R but left K responding unaffected, emphasising a perceptual set at study by asking participants to look out for blurred letters increased K responses but left R responses unaffected, and increasing number of study episodes increased R but not K responses.

The picture that emerges from the studies of Bowler et al. (2000a, 2007) is that individuals with ASD show quantitatively diminished but qualitatively similar experiences of episodic recollection. What remains to be established is whether this is the result of problems in re-constructing the spatio-temporal aspects of the recollected episode or in imagining the self at the heart of such recollection or of difficulties in both these factors. We will now discuss the research relating to both these possibilities as well as on the related issue of the ordering of elements of experience in time.
10.2.3 Re-creating the spatio-temporal context of an episode

Individual episodes are characterised by the co-occurrence of elements of experience (e.g. meeting a particular friend at a particular time of day in a particular place, etc.) that may form part of other, distinct episodes. What defines an individual episode is the combination of attributes that are unique to it. For an episode to be successfully retrieved, its elements need to be marked in such a way as to enable their subsequent retrieval as a bound unit. Bowler et al. (unpublished data) showed that this relational binding capacity is diminished in individuals with ASD. They replicated a study of Chalfonte and Johnson (1996) who asked older and younger typical adults to study sets of objects located in the cells of a grid. The objects were presented in non-canonical colours (e.g. a blue banana or a pink leaf). Participants’ recognition of individual features (location, item, colour) and combinations of these features (item + location, item + colour) were then tested. Whereas older participants showed undiminished recognition of features, they were significantly poorer on recognition of combinations. Bowler et al. (unpublished data) found similar intact feature and diminished combination recognition in a group of HFA adults, demonstrating that they too had difficulties in recognising episodically defined bindings of elements of experience. They also found that this difficulty survived co-varying out performance on the Colour Trails Test, which is a measure of executive functioning. These findings were particularly surprising in that they demonstrate binding difficulties on a memory task – recognition – that does not usually pose problems for individuals with ASD.

It can be argued that an intact ability to re-construct the combinations of features unique to an episode and the development of an accurate sense of the temporal order of events are intimately and necessarily related. It follows from this that difficulties with the relational binding needed to recollect an episode should be accompanied by difficulties in temporal aspects of memory. There are several strands of evidence from the ASD literature that support the conjecture that this is the case in ASD. Bennetto et al. (1996) demonstrated diminished performance on an adaptation of the Corsi task in adolescents with ASD. This task presents participants with sequences of concrete words or line drawings. From time to time, a yellow card accompanied by a pair of previously presented items is presented and participants have to decide which of the two items had been presented more recently. Diminished performance was also reported in a serial order recall task in which Martin et al. (2006) asked adults with ASD to recall lists of digits that are close to their memory span. Although the number of items correctly recalled was similar to that of comparison participants, the ASD group made more order errors in recall, suggesting that they have difficulty recalling which items preceded and
succeeded each recalled item. Theorists such as Brown et al. (2007) argue that sensitivity to such micro-contextual detail underlies successful serial recall, and its diminution in ASD further reinforces the idea that this population experiences particular difficulty in the accurate recall of the context of remembered material. The occurrence of the phenomenon in serial recall further supports the idea that accurate recall of context is needed for accurate temporal memory.

Individuals with ASD have also been shown to have difficulties in reconstructing the order of occurrence of a set of items. Gaigg et al. (unpublished data) asked adults with ASD and matched typical comparison participants to re-order alphabetically presented lists of seven historical figures either into their actual chronological order or into a pseudo-random order that had been studied just beforehand. Whereas performance on the first task was comparable between the two groups, the ASD participants were significantly worse on the second task, indicating that they had particular difficulty in encoding an episodically determined ordering of the studied material. Difficulty in temporally ordering recall of material is also reflected in poor performance on narrative tasks. Reported difficulties include poor narrative organisation (Losh and Capps, 2003), diminished story recall (Williams et al. 2006) and reduced use of temporal referential devices in narrative (Colle et al. 2008). In a series of tests of diachronic thinking (the ability to reason about the unfolding of events over time), Boucher et al. (2007) found poorer performance in children with ASD compared to matched typical children.

All these findings reinforce the long-held view (see Boucher, 2001; O’Connor and Hermelin, 1978) that individuals with ASD experience difficulties with remembering the temporal ordering of experience. The argument is made here that this problem is a consequence of difficulties with the binding together of elements of experience in episodic memory and which may have repercussions for the development of self-awareness. In a later section, we outline how such binding difficulties might have wider application to difficulties with semantic organisation as well as to episodic memory. First, we need to consider the other key aspect of episodic memory: the role of self awareness.

10.2.4 The self and memory in ASD

Memory and the self are thought to be intimately related. For example, it has been argued that the encoding of autobiographical (i.e. self-relevant) episodic memories presupposes a sufficiently elaborate self-concept (Howe and Courage, 1993). Likewise, autobiographical episodic memory allows one to re-experience past states of self, further enriching the self-concept (e.g. Conway and Pleydell-Pearce, 2000).

It is established that individuals with ASD have diminished autobiographical episodic memory (e.g. Crane and Goddard, 2008). Although such a diminution may
potentially be accounted for in terms of difficulties with relational binding, it is also possible that such difficulties stem from an under-elaborated self-concept (see Lind, 2010, for a review). Although studies of mirror self-recognition (e.g. Ferrari and Matthews, 1983) and delayed video self-recognition (Lind and Bowler, 2009) indicate that individuals with ASD do possess explicit self-concepts, there is also evidence to suggest that their self-concepts may be under-elaborated in certain respects.

For example, individuals with ASD appear to have diminished awareness of their own mental states (e.g. Williams and Happé, 2009), emotional states (Ben Shalom et al. 2006; Gaigg and Bowler, 2008; Hill et al. 2004) and autistic traits (Johnson et al. 2009). Each of these sources of evidence suggests that individuals with ASD have reduced self-knowledge and hence under-elaborated self-concepts. More directly, using a self-understanding interview, Lee and Hobson (1998) found that individuals with ASD showed diminished self-knowledge in the social and psychological domains.

Studies of self-referential memory also shed light on these issues. Such studies typically involve asking participants to encode personality trait adjectives under self-referential (e.g. asking whether the words describe them) and non-self-referential (e.g. asking whether the words contain seven or more letters) conditions. Typical participants generally show a self-reference effect – i.e. an advantage for words encoded in the self-referential condition – and this is attributed to the fact that the self-concept is thought to act as an effective elaborative and organisational structure for memory encoding. Lombardo et al. (2007) and Henderson et al. (2009) found that individuals with ASD showed a reduced self-reference effect and this suggests that individuals with ASD have self-concepts that are under-elaborated and less effective as elaborative and organisational structures for memory encoding.

Thus, although there is no direct evidence for a causal connection between under-elaborated self-concepts and impaired autobiographical episodic memory in ASD, it is at least a plausible hypothesis. Irrespective of the underlying cause of autobiographical episodic memory impairments in ASD, the fact that such impairments exist suggests that individuals with ASD have difficulties with re-experiencing past states of self. Such a reduced awareness of past states of self implies that individuals with ASD have a diminished sense of personal history and a diminished temporally extended self (see Lind, 2010).

10.3 Wider conceptual themes

The findings reviewed so far show relatively subtle memory difficulties that tend to centre on manipulation of information in memory rather than the
memory for the information itself. These difficulties tend to have greater repercussions on measures that provide less support at test (e.g. free recall) than those that do not (e.g. recognition). From the perspective of dual-store or working memory models, the findings both of span studies and on serial position effects show that difficulties seem to lie less with any of the memory storage systems and more with the central executive of the working memory system (Baddeley, 1986). Research also shows that there is particular difficulty in manipulating material in ways that enable the detail of past episodes to be re-constructed and that this interacts in some way with the ‘mental time travel’ that is needed for the operation of episodic recollection. And finally, the way in which memory is modulated by emotional factors operates atypically in ASD. In the following two sections, we will tease out some implications of these patterns of memory performance in an attempt to elucidate underlying processes that give rise to them. In a final section, we attempt to reconcile the empirical findings and theoretical speculations with a brain-based account.

10.3.1 Task support

The research reviewed so far paints a picture of difficulties in recalling material, especially when recall entails some effort, such as elucidating and manipulating semantic aspects of the material or when recall has to be enhanced over repeated trials. By contrast, fewer difficulties are seen on tasks that provide more explicit support for retrieval, such as cued recall or recognition. This particular pattern was first noted by Boucher (Boucher, 1981; Boucher and Warrington, 1976) and again by Bowler et al. (1997) and led to the coining of the term Task Support Hypothesis (TSH) by Bowler et al. (2004). As well as describing the patterning of memory performance across tasks in ASD, the TSH has proved to have considerable heuristic value. It has highlighted a parallel between the patterning of memory performance seen in typical ageing (Craik and Anderson, 1999) and in frontal lobe damage (Schacter, 1987) and has helped to account for some apparently contradictory findings in the literature. For example, Bennetto et al. (1996) reported diminished source memory in adolescents with ASD, whereas Farrant et al. (1998) reported no difficulties in a younger, lower-functioning group. The first study defined source memory as the number of intrusions from an earlier-learned list into the recall of a later list, whereas the second defined it in terms of children’s capacity to indicate whether they themselves or the experimenter had spoken a given word at study. Bowler et al. (2004) noticed that the first study involved an unsupported measure of source, whereas the second involved a supported test. On this basis, they devised two experiments in which HFA participants studied lists of words, which were either presented in one of four ways, or which the participant had to manipulate in one of four ways. At test, participants were given a yes/no
recognition test and if they said ‘yes’ to a test word, were asked either to select the means of presentation or the kind of action from a list on the screen (supported test), or else simply to recall what it was (unsupported test). The results showed no HFA-comparison group difference on the supported test, but diminished performance in the ASD group on the unsupported test, thus extending to source memory the view that memory is particularly difficult for people with ASD when unsupported test procedures are used. A similar role for task support on memory for incidentally encoded context was demonstrated by Bowler et al. (2008b). Participants with and without HFA studied a series of words on a screen. Each word was surrounded by a red rectangle, outside of which was another word that was either strongly or not at all associated with the word inside the frame. Participants were told to ignore the words outside the frame. Later testing used either a free recall or a four-option forced-choice procedure. In each case, participants were told to try to remember all words they had seen, whether inside or outside the frame. The results showed that associative relatedness between studied and incidentally encoded words (those inside and outside the frame respectively) benefitted both groups’ recognition but enhanced recall only in the typical group. Both these studies show that supported test procedures yield better memory than unsupported procedures for incidentally encoded context as well as for incidentally encoded item–context relations.

The TSH paints a picture of memory in ASD as being heavily influenced by the here-and-now. This would suggest less ‘top-down’ processing in which stored representations influence how incoming information is interpreted. The diminished use of semantic structure to aid recall described earlier, together with demonstrations of diminished top-down processing in visual perception (see Mitchell and Ropar, 2004 for review) provide converging evidence that individuals with ASD store information in ways that are less likely to influence the processing of later, new information. The question now arises of why stored information is less effective in modulating the processing of incoming information in ASD, thus yielding a behavioural reliance on task support.

10.3.2 Relational processing difficulties

Research on episodic memory in people with ASD strongly supports the idea that they experience difficulty in processing relations among elements of experience. Understanding this difficulty can be enhanced by a more detailed consideration of the parallel problem that they sometimes experience in utilising semantic relations among studied items in order to enhance their recall. As we have already seen, failure to use meaning to aid recall has long been known to be a characteristic of ASD (Bowler et al. 1997; 2000a; Hermelin and O’Connor, 1970; Smith et al. 2007; Tager-Flusberg, 1991; but see Leekam and Lopez, 2003),
yet performance on other tasks that rely on semantic processing seems relatively unimpaired. We have already mentioned that people with ASD perform as well as typical individuals on category-cued recall (Boucher and Warrington, 1976; Mottron et al. 2001; Tager-Flusberg, 1991; Toichi and Kamio, 2002), suggesting some ability to use meaningfulness to aid memory. One way to account for these apparently contradictory findings is to invoke the TSH, since semantic relatedness appears to be a problem only when less supported test procedures are used. This argument is further supported by Bowler et al.’s (2008b) observation that whereas relatedness between studied words and context enhanced recognition and recall of studied items for typical individuals, it enhanced only recognition for ASD adults of normal IQ. Thus, we can see that the requirement to engage in semantic processing is more likely to adversely affect memory in individuals with ASD when unsupported task procedures are utilised.

This account is problematic in that it merely describes and does not explain why support is needed for semantic processing. It may simply be that the two phenomena are opposite sides of the same coin. One way to go beyond description is to invoke the distinction between item-specific processing and relational processing. Item-specific processing refers to a tendency to focus on individual items of information without reference to relations among them. Item-specific processing has been shown to contribute heavily to performance on tests of recognition (Anderson and Bower, 1972), on which individuals with ASD perform well. Their pattern of performance on depth-of-processing tasks (for example, where memory is enhanced if studied words have to be rated on deeper, often semantic aspects such as asking if it is a fruit, rather than on shallower features such as number of vowels) also suggests that they perform as well as comparison participants on deeper processing tasks and better on shallower processing tasks (Toichi and Kamio, 2002; Toichi, 2008). The pattern of performance on the two processing levels suggests that individuals with ASD, unlike typical individuals, process words in the two conditions in a similar manner, one, moreover, at which they are highly proficient. It can be argued that this is likely to be an item-specific strategy, since it is difficult to see how shallow tasks could be accomplished by recourse to a relational strategy. More direct evidence on this question comes from a study by Gaigg et al. (2008), who adopted a procedure developed by Hunt and Seta (1984) in which participants studied lists of words drawn from a number of different categories. Some categories were represented by only 2 exemplars, whereas others had 4, 8, 12 or 16. Whereas typical comparison participants recalled similar proportions of items from small as from large categories, adults with ASD recalled far fewer items from the smaller categories. Following Hunt and Seta (1984), Gaigg et al. (2008) argue that this is because identification of exemplars from smaller categories requires alertness to semantic relations among items. By contrast, ability to recall individual
exemplars from large (i.e. frequently represented) categories requires alertness to the unique features of each item. Moreover, Gaigg et al. (2008) found that whereas provision of a relational orienting task (sorting words into categories) enhanced the recall of the typical individuals, it did so for the ASD group to a lesser extent. Provision of an item-specific orienting task (rating word pleasantness) had similar effects on recall for both groups. Gaigg et al.’s findings are consistent with the view that whereas typical individuals have both relational and item-specific processing strategies at their disposal when performing memory tasks, individuals with ASD are dependent to a greater extent on item-specific processing alone. This would explain not only the patterning of performance across tasks described at the start of this chapter but also the greater reliance on task support seen in ASD. A focus on individual items of information diminishes relational semantic information available to aid recall, and diminishes the amount of related contextual information that can be drawn on to re-create episodic recollections and their associated self-involved states of conscious awareness.

Two caveats are in order concerning the foregoing account. The first is that we should be wary in attributing an absence of relational processing in ASD. It may simply be the case that the balance between the two types of processing is different in this population. The second, more serious concern, is that there exist tasks that appear to involve relational processing (deeper levels-of-processing manipulations, susceptibility to associatively generated memory illusions) that are, nevertheless, relatively unproblematic for individuals with ASD. To avoid inconvenient, post hoc attempts to accommodate these findings, we need a more principled theoretical account of the relational processing difficulties seen in ASD.

A speculative, yet empirically testable way to explain why relational processing difficulties are more likely to be seen on some tasks but not on others is through a detailed analysis of the demands that different memory tasks place on participants. When participants engage in free recall of a categorised list, in order for them to become aware of the categorical nature of the studied items, they have to consider each in relation to other words on the list (e.g. cat with dog or apple) and then to relate this comparison to higher order category labels (animal, fruit). Contrast this with the situation in a classic memory illusions experiment (e.g. Bowler et al. 2000b) described in an earlier section. Here, when participants study associates of a non-studied word, they are highly likely to remember the non-studied associate because it is activated by each of the studied items (e.g. bed-sleep, night-sleep, pillow-sleep, . . . ). The operations required of the participant in the case of recall of the categorised list involve three-way processing between pairs of words and their hierarchical categories, whereas the illusory memories require only two-way processing between a studied item and its associate. On this analysis, what seems to pose particular difficulty for individuals with ASD is the complexity of the
memory task. Task complexity in relation to typical children’s development has been explored in detail by Halford (1992) who argues that cognitive development proceeds from a stage where individual items are processed in isolation (unary relations) followed by the processing of items in a pair-wise fashion (binary relations) and finally by the ability to process three-way or ternary relations among triplets of items.

Although the above analysis of memory in ASD is consistent with Halford’s (1992) relational complexity account, it needs further confirmation by more systematic, hypothesis led investigations. Nevertheless, it is corroborated by evidence from other areas of psychological functioning in ASD. Andrews et al. (2003) report that the standard ‘Sally-Anne’ false belief task on which children with ASD are characteristically delayed (Baron-Cohen et al. 1985) correlates highly with performance on tasks of ternary relational processing, and Bowler et al. (2005) report similar levels of delay in children with ASD on a non-social task of complex reasoning and the Sally-Anne task. Both tasks are consistent with a ternary processing analysis, suggesting that it is the processing complexity and not the mental state nature of the Sally-Anne task that poses particular difficulty for the children with ASD.

Difficulty in processing three-way relations is also a theme that recurs in two of the major theoretical accounts of the development of ASD. Early in development, infants who fail to engage in joint attention behaviours are almost certainly on an autistic developmental trajectory. Joint attention, which involves children’s coordinating attention between themselves, an object and another person involves what Bakeman and Adamson (1984) refer to as triadic deployment of attention. A similar conceptualisation of the child’s relation between self, other and objects of shared attention is put forward by Hobson (1993), who argues that the core of autism is a difficulty with the patterning of affectively charged interactions with other people. Earlier on we saw how difficulties with emotion spill over into the memory performance of individuals with ASD. But Hobson’s characterisation of the structure of interpersonal relatedness and its role in the development of symbolic understanding also invokes the child’s developing awareness of themselves in relation to another person and to objects to which both themselves and that person also stand in relation (see Hobson, 1993, pp. 140–153 and Chapter 8 of this volume). In a similar vein, albeit from a radically different theoretical perspective, Leslie’s (1987) analysis of children’s understanding of pretence and mental state representation emphasises the importance of the child’s developing awareness of action-centred representations, metarepresentations or M-representations (Leslie and Roth, 1993). This development marks an enlargement of the child’s conception of objects from one which considers their true identity (e.g. a banana as a piece of fruit) to one where they can also be defined in terms of the pretend actions of
an agent (e.g. Mummy pretends that the banana is a telephone). This last development involves the child’s being able to coordinate its own relation to the object with that of another person’s relation to it in the context of a playful interpersonal exchange. Both Leslie and Hobson see autism as resulting from a breakdown in their respective systems, and the position advocated here is that the two systems may be different manifestations of a wider difficulty with processing ternary relations, which also has repercussions in the domain of memory.

A further advantage of adopting Halford’s relational complexity account is that it elaborates on a position first advocated by Minshew and her colleagues (Minshew et al. 2001) who argue that autism is a disorder of complex information processing. This position makes intuitive sense when the pattern of performance across memory tasks identified by Minshew and colleagues is considered, but runs the risk of circularity by defining any task that poses difficulty for people with ASD as being ‘complex’, without establishing any a priori criteria for what constitutes complexity. Relational complexity allows predictions to be made in advance about which tasks should be easy and which difficult for individuals with ASD. In addition, its resonance with other behavioural characteristics of ASD suggests that difficulties with ternary relations may be a pervasive cause of a range of psychological atypicalities in this population.

Finally, readers of this section may be tempted to draw parallels between our account of relational processing difficulties and the Weak Central Coherence (WCC) theory put forward by Frith and Happé (Happé and Frith, 2006 – see Chapter 7 in this volume). However, the two approaches differ in a number of respects. For example, the way they envision how elements are processed both singly and in combination has knock-on effects for the kinds of predictions the two accounts make. Our account emphasises the processes that enable an individual to constitute complex representations, often on the basis of limited exposure. This process-oriented view has the potential to provide a developmental description of how people with ASD build representations of their experience in the world and formulates testable hypotheses about the kinds of complexity that people with ASD might find difficult. WCC theory by contrast locates complexity or ‘wholeness’ in the stimulus and characterises individuals with ASD as being intrinsically more detail-focused and consequently less aware of wholes. This leads WCC theory, for example, to predict that individuals with ASD would be less susceptible to memory illusions because of their tendency to focus on the detail of individual words to the detriment of global relations among them. Our theory of diminished relational processing, by contrast, predicts that it is only when the relational complexity of the inter-item relations crosses the threshold from binary to ternary relations that individuals with ASD experience memory difficulties. Relations below that threshold (as is the case with memory illusions) tend not to pose problems.
10.4 Memory and the brain

An important development in the typical memory literature in recent years has been an increasing refinement of our understanding of how the brain mediates our capacity to remember the past. In combination with our growing knowledge of memory in ASD, this development can help to enhance our understanding of functional and structural brain atypicalities in that population. The literature on structural brain atypicalities in ASD is converging on four broad themes. First, studies of brain size indicate that the brains of infants with ASD are often larger than normal and that the developmental trajectory of brain size is atypical (Akshoomoff et al. 2002; Aylward et al. 2002; Courchesne et al. 2001). Second, neurological abnormalities at the cellular level have been reported for the cerebellum, the frontal cortex and certain medial temporal lobe (MTL) structures such as the hippocampus and the amygdala (see Bachevalier, 2000; Bauman and Kemper, 2005; Casanova et al. 2002; DiCicco-Bloom et al. 2006; Palmen et al. 2004 for relevant reviews). Third, functional imaging studies indicate abnormalities in these same regions, particularly MTL structures and the frontal lobes (e.g. Bachevalier and Loveland, 2006). Finally, behavioural and neuroscientific evidence is starting to converge on the idea that MTL structures and the frontal lobes are characterised by abnormalities in their functional connectivity with one another and with other areas of the brain (e.g. Bachevalier and Loveland, 2006; Gaigg and Bowler, 2007; Just et al. 2007; Rippon et al. 2007). It is perhaps no coincidence that two of the three brain regions that manifest greatest structural abnormalities in ASD are also those that are implicated in memory, especially those aspects of memory that appear to operate atypically in this population. Although we should be careful about seeing ‘memory’ as residing in one or more specific areas of the brain (see Graham et al. (2008) for discussion), there is now a broad consensus that declarative memory is mediated by frontal and MTL structures (see Brown and Aggleton, 2001 for review).

Support for some frontal involvement in memory in ASD is evidenced by the greater need of these individuals for task support in memory. The need for task support is also a characteristic of memory in typically ageing individuals, especially those in whom there is a suspicion of frontal lobe dysfunction evidenced by diminished performance on executive function tasks (Craik and Anderson, 1999; Craik et al. 1990). Similarly, patients with acquired frontal lobe damage also show a pattern of performance across memory tasks that is not dissimilar to that seen in people with ASD (Schacter, 1987). More specifically, such frontal lobe patients exhibit difficulties with minimally cued recall and episodic memory tasks while their performance on tests of recognition memory is undiminished. Together with the literature on executive dysfunction in ASD (see Hill (2004a; 2004b) for reviews),
this parallel between ASD, typically aging and frontal lobe patients provides converging evidence for frontal dysfunction as a component of memory difficulty in ASD.

Although the arguments for frontal contributions to memory in ASD are strong, there is increasing evidence pointing to the involvement of other brain areas. In typically developed individuals, the most severe memory disorders result from damage to the medial temporal lobes, especially the hippocampus and associated structures of the ento- and perirhinal cortices and the amygdala (see Mayes and Boucher, 2008 for review). It was this observation that led Boucher and colleagues (Boucher, 1981; Boucher and Warrington, 1976) to suggest that autism might be a variant of the amnesic syndrome and as such would involve medial temporal structures. In the period since this earlier work, which was carried out mostly in children with severe and low-functioning ASD, this view has been less and less advocated (see, for example, Bowler et al. 1997). The reason for this change is partly because it is evident that individuals with ASD are not amnesic in the same way as individuals with severe temporal lobe damage are, but also because our conception of ‘autism’ has enlarged to a spectrum view that encompasses subtler forms of the condition and includes individuals of normal cognitive and language ability and who therefore present subtler forms of memory difficulty. Nevertheless, the most recent empirical findings are prompting a return to a consideration of medial temporal lobe structures as contributing to atypical memory in ASD.

The capacity to recollect context implies that the disparate elements that constitute an episode have to be bound together in memory in a way that enables subsequent retrieval. There is now considerable evidence that this relational binding is mediated by the hippocampus (Brown and Aggleton, 2001), while related medial temporal lobe structures such as the perirhinal and entorhinal cortices mediate the processing of individual elements. As noted in the previous section, the patterning of memory in ASD suggests that such individuals experience difficulties in processing relations among elements of experiences in memory while their processing of the individual elements seems preserved. Recall, for instance, the observation of diminished recognition of episodically defined combinations of elements in the presence of undiminished recognition of the individual elements themselves (Bowler et al., unpublished data) or of diminished influence of item-context relatedness on recall but not on recognition of context (Bower et al. 2008b), or the finding that individuals with ASD experience relatively specific difficulties in drawing on relations amongst words to facilitate recall while their use of information specific to individual words is undiminished (Gaigg et al. 2008). All of these findings, together with the general difficulties in episodic memory characterising ASD, strongly suggest compromised hippocampal and spared perirhinal and entorhinal functioning in this population. In addition, this framework is
compatible with the analysis of complexity by Halford (1992) and thus provides a useful starting point for investigating the importance of relational information in other cognitive domains such as ‘Theory of Mind’ and logical reasoning. Many theorists argue that an important function of the hippocampus is the ability to encode objects, events and relations among them rapidly and in a way that allows the adaptive use of encoded information in different settings (Eichenbaum, 2000). This ability is evidenced by tasks such as Transitive Inference (TI) in which an individual can infer that $A > C$ having been told that $A > B$ and $B > C$. TI performance is reflected in hippocampal activation (Greene et al. 2006), is sensitive to hippocampal damage and is impaired in people with amnesia (Smith and Squire, 2005). On the basis of the arguments presented here on diminished relational processing in ASD, we would predict diminished TI performance in this population and, moreover, would predict that TI performance would correlate both with those aspects of semantic organisation of material – clustering and the use of categories to aid recall – that pose difficulty for people with ASD, and with measures of binding and memory as well as measures of episodic remembering.

In an earlier section, we noted that an important characteristic of episodic memory is an awareness of self in time. Although the evidence from the domain of memory does not suggest that abnormalities in the experience of such temporally extended self-awareness are solely responsible for the episodic memory difficulties evident in ASD, abnormalities in this domain may nevertheless contribute to it. Given the close relation between self-awareness and episodic remembering, it is therefore possible, and perhaps even likely, that neural correlates of self-awareness are compromised in ASD. There is currently considerable debate about the neural correlates of self-awareness (see Feinberg and Keenan, 2005; Keenan et al. 2005; LeDoux, 2002; Morin, 2005) and although some recent studies suggest abnormalities in this domain in ASD (Chiu et al. 2008) more work is clearly needed before one can draw any conclusions.

Although the patterning of memory functioning in ASD is consistent with the idea that it stems from hippocampal dysfunction, albeit with some frontal involvement, it does not follow that such atypical function results from hippocampal damage per se. The hippocampus receives rich sensory information from a range of cortical and sub-cortical areas of the brain via the entorhinal cortex, which in turn relays information from the hippocampus back to a host of cortical areas (e.g. Squire, 1992). This arrangement is ideal for its function in relation to episodic memory and relational processing as it is in a position (literally) to integrate information processed in various different parts of the cortex and also modulate the processing of information in those cortical areas accordingly. It also means, however, that the patterning of memory functioning in ASD is not necessarily a reflection of hippocampal dysfunction per se but could also be the result of atypical
connectivity between the hippocampus and functionally associated areas. Or the information flowing along those pathways could be abnormal. Both the empirical and theoretical literature offer some support for these possibilities. As mentioned above, a considerable amount of evidence suggests that disparate brain areas are abnormally connected in ASD (e.g. Rippon et al. 2007) suggesting that the hippocampus may receive inadequate input, or may have difficulty in adequately transmitting outputs. The finding that emotional arousal atypically modulates forgetting in ASD (Gaigg and Bowler, 2008) is particularly relevant in this context, since such modulation is widely thought to be mediated by interactions between the amygdala and the hippocampus (e.g. Hamann, 2001). It is also possible that the information from primary sensory areas that is marked for bound representation by the hippocampus is atypical because of compromised functioning in those areas. This account has resonances with the Enhanced Perceptual Functioning model of ASD advocated by Mottron and colleagues (Mottron et al. 2006). Their argument is that the processing of information by people with ASD is characterised by the retention of lower-level perceptual features that remain available even when higher-level, conceptual processing has taken place. This has consequences in situations where typical individuals process in a predominantly global or conceptual manner. In such situations, individuals with ASD may tend to process perceptually rather than conceptually, even when both options are available, often producing atypical performance patterns. There is some evidence that this happens in memory. Bowler et al. (2008a) found that adults with ASD showed less inter-individual convergence of subjective organisation of unrelated words than did typical individuals, suggesting that whereas the latter group organised words along semantic/associative lines, the ASD group may, in addition to this strategy, have organised the words along more perceptual features such as phonology or number of syllables. What is needed to confirm this account is a series of demonstrations of enhanced perceptual influence on psychological processes other than memory.

The argument just outlined leaves open the possibility that atypical hippocampal function may be the result of structural or functional problems elsewhere in the brain, which modify information fed to the hippocampus. But it ignores one fundamental aspect of ASD, namely that it is fundamentally a developmental problem, that is to say it affects the trajectory of development of the individual in a way that yields an atypical endpoint. We can reasonably expect this atypical developmental trajectory to be as evident in brain structures as in adaptive behaviour. So, for example, it may be the case that enhanced perceptual functioning may feed information to the hippocampus in a manner that influences the bindings it makes, and that these different bindings in turn affect the way in which the hippocampus develops and influences processing in other brain areas. There is some
evidence from the neuroimaging literature that is consistent with this position. Schumann et al. (2004) report atypical development of the hippocampus in children and adolescents across the autism spectrum. They also report atypicalities in the development of the amygdala in these groups. As we have seen, the amygdala plays an important role in emotional memory. In view of the connectivity between the hippocampus and the amygdala (Smith et al. 2006), it can be argued that diminished emotional modulation of memory in ASD is a specific aspect of more general difficulties with binding in memory.

10.5 Conclusions

It is now well established that ASD is characterised by a particular pattern of spared and impaired performance across different memory tasks. This pattern points to difficulties in the processing of information in ways that require binding of those elements of experience that uniquely define episodes, in the flexible relations among features that can be organised hierarchically, and in the emotional modulation of memory. Processing of individual items by contrast is relatively spared. All these types of processing implicate different structures of the medial temporal lobe of the brain, most particularly the hippocampus, the amygdala and the entorhinal and perirhinal cortices, as well as modulation of the functioning of these areas by the frontal lobes. Although these implications have yet to be systematically tested, they are consistent with the current state of knowledge of the development of these structures in the autistic brain. What also needs to be established is the extent to which atypical developmental trajectories in these structures are the outcome of abnormal input resulting from atypical processing in other brain areas or from some initial damage to the structures themselves. As well as providing a framework within which to test neural underpinnings of psychological underpinnings in ASD, the behavioural findings in memory also provide a window into the inner experience of these individuals by showing that they have diminished self-involvement in their memories for past experience and that the quality of these experiences, the connections that the individual makes between experiences and the here-and-now consequences of a particular memory can at times be radically different from those of a typical individual.

10.6 Acknowledgements

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10.7 References


Clinical experience and anecdotal written accounts suggest that school-age children with high-functioning autism spectrum disorders (ASD) have difficulties which can be described as ‘executive dysfunction’. Problems with organisation, planning and task completion impede academic achievement and cause disruption in daily routine. The authors review research of executive function in this population and conclude that clinicians will find little in the scientific literature to guide them in neuropsychological assessment and remediation. They describe their study of 23 clinic-referred children (18 boys, 5 girls; mean age of 9) illustrating the challenges facing clinicians who would measure executive function. Tests of executive function (including the NEPSY and the BADS-C) were administered. Parent and Teacher questionnaires (DEX-C, BRIEF and VABS) were completed. Scores on tests of executive function and other areas of cognition were found to be in the average or above average range. In contrast, responses on both teacher and parent questionnaires indicated significant executive dysfunction. Parents’ responses on the BRIEF and on the DEX-C were not correlated with teacher responses on the BRIEF. The authors consider the importance of a “halo effect” on questionnaire responses and challenge the notion that questionnaire measures have more ecological validity than laboratory measures. Suggestions for future research include observation, interviews and graded modification of the testing environment.
11.1 Introduction

Not enough attention is given to identifying individual neuropsychological deficits of children with ASD in the clinical setting with the aim of remediation despite being recommended by the National Autism Plan for Children (2003). This is partly because child mental health services and educational psychology services do not usually undertake detailed neuropsychological assessments and often cannot agree on who should take responsibility for this work (Humphrey, 2006). Even if existing services were to routinely offer such assessment, the question of which measures to use is open.

The study we are describing in this chapter was undertaken with the wish to identify measures which would enable the identification of executive dysfunction in the clinical setting for children with high-functioning ASD (HFA). Our results have, surprisingly, suggested to us that there is no ‘best’ measure, and that the evaluation of executive dysfunction and possibly all neuropsychological function in this group of children should be approached as a synthesis of information from several different sources. Our work has also shown the importance of considering and studying how the expectations of parents and teachers of children with ASD influence their view and reporting of a child’s abilities and disabilities.

School age children with HFA are routinely observed to have difficulty organising, planning and completing tasks such as school activities, homework and dressing. These difficulties can lead to time spent out of class, detentions and exclusions. They often require additional educational support. There are numerous anecdotal accounts of such difficulties:

Transitional periods may be the hardest part of the day . . . just give Justin a few minutes to organise his materials before and after instruction. (Betts et al., 2007)

[They] have difficulty with organization, with knowing, remembering, and attending to what is important. (Jacobsen, 2005)

. . . [We] are often unable to shift our attention away from the point at which we have become stuck, or generate new strategies . . . Organization abilities . . . were also affected. At secondary school, I adopted the strategy of carrying everything I might conceivably need at any point in the week . . . out of fear I might be caught without something I needed. (Sainsbury, 2000)

The difficulties described above can be classified as executive dysfunction. Executive function has been characterised as including: (1) inhibition: the ability to inhibit a pre-potent response; (2) intention: the ability to formulate appropriate
goal-directed plans and follow complex behavioural sequences to a satisfactory conclusion; and (3) executive/working memory: the mental representation of tasks and goals. These abilities are scaffolded by a host of skills such as flexibility and set-shifting, self-monitoring, sustaining attention and utilising feedback (Burgess et al. 1998; Emslie et al. 2003) as well as fluency and estimation (Baron, 2004). Eslinger (1996) offers a discussion of the various definitions of ‘executive function’. Executive function is considered a higher order cognitive function integrating more basic functions. Baron (2004) helpfully describes executive function as: ‘Metacognitive capacities that allow an individual to perceive stimuli . . . respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated or common-sense way, utilizing all these capacities to serve a common purposive goal’.

While the anecdotal accounts clearly point to executive dysfunction, laboratory studies of executive function in children with HFA have been equivocal in their findings. In general, meta-analyses suggest that there are inconclusive results with a lack of replication, that the deficits that are measured are mild and circumscribed, and that the evidence that executive dysfunction is characteristic of HFA is mixed (Hill and Bird, 2006; Kleinhans et al. 2005; Pennington and Ozonoff, 1996; Sergeant et al. 2002).

There are several possible explanations for the lack of consistent findings described above. Sampling differences in studies of children with ASD is, of course, one hindrance to replication. Historically, it has been difficult to recruit large samples of children with a single reliable diagnosis and samples will include children who fall into the diagnostic hinterlands between Asperger Disorder, High-Functioning Autism and Pervasive Developmental Disorder Not Otherwise Specified. A perusal of the literature on adults and children with ASD does suggest that deficits are less apparent in individuals without global learning disability (Baron-Cohen et al. 1999; Bogte et al. 2009; Hill, 2004).

Another threat to the validity of laboratory studies of executive function is the unavoidable fact that strict examination conditions differ from most conditions in the real world (Burgess et al. 1998). Several authors have identified an over-reliance on laboratory measures and the structured nature of the test setting (Gilotty et al. 2002; Liss et al. 2001). The need to use ecologically valid tests of executive function has been widely documented (Kenworthy et al. 2005; Lezak, 1995; Shallice and Burgess, 1991) as executive dysfunction is better captured when the cognitive demands required to do a particular task/s resemble real life.

Hill (2004) and Baron (2004) address the difficulty partitioning components of executive tasks. For example, the Wisconsin Card Sorting Test requires flexibility, working memory, inhibition and monitoring as well as set-shifting. The complexity of our measures challenges their discriminant validity; what are we really measuring? Anderson carried out a review of the most commonly used tests of
executive function for children and indicated several methodological limitations such as no standardised administration or valid developmental norms as well as lack of specificity of what the tests are supposed to measure (Anderson, 1998).

Clinicians working with children diagnosed with an ASD who have an IQ above 70 and are attending mainstream schools will, therefore, find little in the scientific literature to guide them in targeting and remediating areas of cognitive deficit that may be contributing to a child’s maladaptive behaviours or academic difficulties. However, while there may not be agreement on a pathognomonic profile of executive dysfunction or function in individuals with ASD, there is no reason that clinicians cannot choose from a range of well normed tests measuring executive function when working with individual children. Despite a lack of concordance in our scientific findings, clinically, it is of paramount importance to determine the strengths and weaknesses of students with ASD in order to facilitate learning, especially within a mainstream school environment where tailored educational approaches may depend on a comprehensive test report.

We wanted to measure and further characterise the difficulties with planning and organisation in daily life that the children we assessed and treated in our Tier 3 Child and Adolescent Mental Health Asperger Service were experiencing. We undertook a small study in a clinic-referred sample of children with ASD who had an IQ above 70 and were attending mainstream school. Rather than attempting to identify core and causal deficits in ASD, we wanted to identify an evidence-based assessment protocol that could guide intervention. We hypothesised that children in this sample would have executive function impairments as measured by neuropsychological and behavioural measures and that scores on laboratory and ecologically valid measures of executive function would be positively correlated.

11.2 Participants

Twenty-three children (18 boys and 5 girls) attending mainstream schools, with a diagnosis of ASD (Asperger Disorder, 65%; High Functioning Autism, 13%; or Pervasive Developmental Disorder Not Otherwise Specified, 22%) between the ages of 7 and 12 years (mean = 9.4, SD = 1.6) and with an IQ above 70 (mean = 104.5, SD = 10.8), participated in this study. This age group was chosen because our clinical observation suggested that children with ASD had increasing difficulty with executive function in the latter part of primary school and during the transition into secondary school. The sample was recruited by contacting all cases open to the Asperger Outreach Service (Cambridge and Peterborough Mental Health Partnership NHS Trust). A total of 65 families were contacted to participate
Measuring executive function in children with HFA

in the study. All children whose parents consented to the study were included. Two children who took part in the study had a co-morbid diagnosis, one of ADHD, the other of partial epilepsy, for which they were medicated. Since many of their task scores differed from the group's average by more than one standard deviation, they were excluded from the sample. Families who declined to participate in the study cited several reasons such as their children already had psychological testing, they didn’t want their child to feel different, they were on holiday or they felt it was going to take too long.

11.3 Materials

We chose tests normed for our age group with acceptable psychometric properties. Most executive function measures are designed to assess individual executive function components. We wanted to use test batteries and questionnaires which were inclusive and tapped into a range of executive function properties rather than choosing many separate tests. In addition, we wanted to use a battery which would also assess other cognitive functions including verbal and non-verbal ability. This narrowed our choice of measures significantly.

11.3.1 Neuropsychological assessment

**NEPSY (A Developmental Neuropsychological Assessment)** (Korkman et al. 1998). The NEPSY is normed for children from age 3 to 12 years and contains five domains: language, attention and executive function, memory, visuospatial ability and sensorimotor ability. The core sub-tests for children from 5 to 12 years of age were administered. The sub-tests included in the Attention/Executive Function domain, together with the areas of function tested, are shown below:

1. **Tower**: planning, monitoring, self-regulation and problem solving. Move three balls to target positions on three pegs in a prescribed number of moves.
2. **Auditory Attention and Response Set**: continuous performance task, vigilance, selective auditory attention, shift set, maintain complex mental set. Place a red square in a box when hearing the word ‘red’ in Part A. Place a blue square when hearing the word ‘red’ in Part B.
3. **Visual Attention**: speed and accuracy scanning an array and locating target. Scan an array of pictures and mark targets quickly and accurately.

The normative mean scores for all domains is 100 with a standard deviation of 15. Normative mean scores for individual sub-tests is 10 with a standard deviation of 3. The core domains exhibit moderately high reliability scores for internal
consistency (0.88 to 0.91 for 3–4-year-olds, and 0.79 to 0.87 for 5–12-year-olds). Inter-rater reliability has a coefficient of 0.99 (Nash, 1995).

**Behavioural Assessment of Dysexecutive Syndrome in Children (BADS-C)** (Emslie et al. 2003). The BADS-C is normed for children between the ages of 7 and 16 years and measures planning, flexibility, impulse inhibition and novel problem solving. The tasks included in the BADS-C are shown below:

1. **Playing Cards**: change established pattern of response. Part 1, say ‘yes’ to red card, ‘no’ to black. Part 2, say ‘yes’ to card that is same colour as card before and ‘no’ to card that is a different colour.
2. **Water Test**: develop a plan of action to solve a problem. Get a cork out of a tube using any of the objects placed out without touching beaker lid, stand, beaker and tube.
3. **Key Search**: plan an efficient, systematic, feasible plan of action, self-monitor, take into account unstated factors. Draw a line from a dot showing how they would search a field to find their keys.
4. **Zoo Map**: planning. Ability to plan a route in order to visit 6/12 possible locations in the zoo when there are restrictions on the number of times certain paths can be used. Zoo Map 1 is a demanding open-ended task with little structure provided. Zoo Map 2 is a low demand, rule governed task.
5. **Six Part Test**: planning, task scheduling and performance monitoring. Three different coloured coded tasks to do (arithmetic, naming, sorting). Each task includes two parts. Children need to schedule their time to attempt something from all 6 parts over 5 minutes with restrictions on the order in which the parts can be completed.

The mean score on the BADS is 100, SD is 15. The inter-rater reliability for the BADS-C is high, ranging between 0.53 and 1.00. Test–retest reliability correlation ranged from 0.289 to 0.814.

**11.3.2 Behavioural assessments**

**Dysexecutive Questionnaire for Children (DEX-C)** (Emslie et al. 2003). This is a 20 item Likert scale questionnaire that asks about executive difficulties in everyday life. Table 11.1 details the executive functions covered by the questionnaire. The DEX-C was completed by parents of children taking part in the study. The mean score is 15, SD is 13.

**Behaviour Rating Inventory of Executive Function (BRIEF)** (Gioia et al. 2002). This inventory of executive function provides a parent and a teacher rating form, each with 86 items yielding a Global Executive Composite score. The mean score
Table 11.1 Child characteristics measured by the Dysexecutive Syndrome Questionnaire for Children (DEX-C)

<table>
<thead>
<tr>
<th>Abstract thinking problems</th>
<th>Temporal sequencing problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impulsivity</td>
<td>Lack of insight and social awareness</td>
</tr>
<tr>
<td>Confabulation</td>
<td>Apathy</td>
</tr>
<tr>
<td>Planning problems</td>
<td>Loss of decision-making ability</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Planning problems</td>
<td>Disturbed impulse control</td>
</tr>
<tr>
<td>Temporal sequencing problems</td>
<td>Aggression</td>
</tr>
<tr>
<td>Planning problems</td>
<td>Perseveration</td>
</tr>
<tr>
<td>Planning problems</td>
<td>Lack of concern</td>
</tr>
</tbody>
</table>

Restlessness

- Inability to inhibit
- Distractibility
- Unconcern for social rules

Example questions and response choices

- ‘Gets events mixed up with each other, and gets confused about the correct order of events’
- ‘Acts without thinking, doing the first thing that comes to mind’

Never; Occasionally; Sometimes; Fairly Often; Very Often

is 50, SD is 10. In addition, the BRIEF includes two broad indexes (Behavioural Regulation and Metacognition) and eight scales. These are:

1. Behaviour Regulation Index:
   - Inhibit: resist
   - Shift: move freely, change focus
   - Emotional Control: moderate emotional responses

2. Metacognition Index:
   - Initiate
   - Working Memory
   - Plan/Organise
   - Organise Materials
   - Monitor: work checking habits

Internal consistency for both parent and teacher forms (Cronbach’s alpha) was high, ranging from 0.80 to 0.98. Mean test–retest correlations across clinical scales
were 0.81 (range = 0.76–0.85). Construct correlations with ADHD rating scale were good (DuPaul et al. 1998).

**Vineland Adaptive Behaviour Scales – Survey Form (VABS-S)** (Sparrow et al. 1984). The VABS is a measure of adaptive behaviour in the areas of communication (receptive, expressive and written), daily living (personal, domestic, community), socialisation (interpersonal relationships, play and leisure time, coping skills) and motor skills. The mean score for each domain is 100, with a standard deviation of 15. The Vineland provides age norms for the general population, as well as scores for various clinical groups. Internal consistency for both parent and teacher forms (Cronbach’s alpha) was high, ranging from 0.80 to 0.98. Mean test–retest correlations across clinical scales were 0.81 (range = 0.76–0.85). In the current study, the scales were completed by interviewing one parent of each child.

Normative data were obtained from all the instruments’ standard scores. A clinical comparison group would have been preferable. However, resource and time limitations prevented this. In addition, the central aims of the study related to how this sample of children would compare to their same age peers and whether neuropsychological and behavioural measures of executive function would be positively correlated. Both these questions can be answered by using the measures’ own population norms.

### 11.4 Procedure

Families were asked to attend our clinic for the administration of all measures which took approximately three hours (including measures given to the child and interview and questionnaires administered to the parent). All measures were administered by a research assistant. Parents were asked to give their child’s teacher the BRIEF and requested to send it back using a pre-paid envelope. All parents and all but one of the teachers completed and returned the questionnaires.

### 11.5 Results

First, normality of the different scores was tested, using one-sample Kolmogorov-Smirnov tests. Distribution of none of the scores significantly differed from a normal distribution. Next, in order to test for possible differences between diagnoses, Kruskal-Wallis non-parametric tests were conducted on the different task scores. No significant differences were found. In order to test whether scores of our sample differed significantly from the tasks’ normative averages one sample t-tests were conducted for the different scores, using Bonferroni correction for multiple comparisons. Contrary to our hypothesis, the sample’s average score on the attention/executive function domain of the NEPSY (mean (M) = 102.9,
SD = 12.2) did not significantly differ from the norm (t(22) = 1.13, NS) and 69.6% of the sample scored within ±1 SD of the scale's average score. All of the participants were within 2 SDs of the domain average. Furthermore, individual scores clustered around the population mean for the Tower and Auditory Attention sub-tests.

However, scores on the Visual Attention sub-tests were more diverse: three participants scored more than 1 SD above average (one of them scoring more than 2 SDs above average) and four participants scored more than 1 SD below average (two of them scoring more than 2 SDs below average). The group mean was, however, in the middle of the average range (M = 9.6, SD = 3.6). Figure 11.1 illustrates the distribution of participants’ scores around the sub-test means.

The sample’s average score on the language (M = 101.6, SD = 16.2) and memory (M = 102.7, SD = 13.4) scales did not differ from the normative average (t(22) = 0.48 for language, and 0.98 for memory, NS). However, the sample scored significantly higher than the norm on the visuospatial scale of the NEPSY (M = 113.0, SD = 13.0; t(22) = 4.77, P < 0.001), with 47.8% of the participants scoring more than one standard deviation above the normative average. In addition, the sample’s average on the sensorimotor scale of the NEPSY (M = 95.5, SD = 10.3) was lower than the normative average, although after correction for multiple comparisons, this difference did not reach significance (t(22) = 2.11, P = 0.047).

Contrary to our hypothesis, the sample’s average did not differ from the normative average on the BADS overall score (M = 97.8, SD = 24.9; t(22) = 0.42, NS). Sixty percent of the participants scored within ±1 SD of the BADS average score, and 73.9% scored within ±2 SD of the average. As with the NEPSY Attention/Executive Function sub-tests, the sample’s average scores on all sub-tests of the BADS were in the average range. However, the standard deviation for each sub-test was relatively large (SD for the sub-tests ranged between 3.7 and 4.7). Figure 11.2
Our hypothesis was, however, supported by parent and teacher ratings which were significantly higher for our sample, compared to the normative measures on the DEX-C ($M = 42.9$, $SD = 10.9$; $t(22) = 12.25$, $P < 0.001$), on the parent version of the BRIEF ($M = 73.3$, $SD = 6.1$, $t(22) = 18.38$, $P < 0.001$) and on the teacher version of the BRIEF ($M = 70.2$, $SD = 11.9$; $t(21) = 7.99$, $P < 0.001$). Higher scores indicate greater impairment on these measures. Ratings parents gave their children on the more general measure of adaptive behaviour, the VABS-S, were also lower than the average for their age ($VABS-S$ overall score: $M = 69.7$, $SD = 15.9$; $t(22) = 9.18$, $P < 0.001$) indicating greater impairment in the sample under study. Parent ratings on the DEX and the BRIEF were significantly correlated with each other ($r = 0.66$, $P < 0.01$). None of the parents’ measures correlated with the teachers’ ratings on the BRIEF.

In order to test whether NEPSY scores can predict the behavioural measures scores, three hierarchical regression analyses were conducted for the DEX, parent BRIEF and teacher BRIEF. In each of the analyses, the first block included the demographic variables: age, gender and IQ, followed by a second block which included all NEPSY sub-tests. A stepwise method was used to enter variables into the regression in each block.

The analysis conducted for the teacher BRIEF yielded four significant predictors: sex ($\beta = 0.59$, $P < 0.005$), NEPSY visual attention, from the Attention/Executive Function domain of the battery ($\beta = -0.43$, $P < 0.05$) and two sub-tests from the NEPSY sensorimotor domain: imitating hand positions ($\beta = -0.36$, $P < 0.05$) and finger tapping ($\beta = -0.34$, $P < 0.02$). Together these four variables explained 68.6% of the variance in the dependent variable (Adj. $R^2 = 0.686$). Table 11.2 shows the steps included in this regression.
In the regression analysis for the parent BRIEF only one significant predictor was included: NEPSY auditory attention ($\beta = -0.46$, $P < 0.03$), with only 17.7% explained variance. The regression analysis for the DEX revealed no significant predictors.

Three regression analyses, similar to those described above, were conducted with the BADS sub-test in the second block instead of the NEPSY sub-tests. Results revealed no significant predictors for the DEX or the parent BRIEF. The teacher BRIEF was predicted by two variables: sex ($\beta = 0.59$, $P < 0.005$) and the BADS cards sub-test ($\beta = -0.39$, $P < 0.05$), which together explained 43.6% of the variance of the teacher BRIEF.

In order to understand the sex effect on the teacher BRIEF scores, a t-test for independent groups was conducted, comparing teacher BRIEF scores of boys and girls (see Figure 11.3). The test was found to be significant ($t(20) = 3.3$, $P < 0.005$), suggesting girls ($M = 82.8$, $SD = 7.0$) were rated by teachers as having greater executive dysfunction than boys ($M = 66.5$, $SD = 10.4$). No such difference was found on parent BRIEF ($t(21) = 1.1$, NS) or the DEX ($t(21) = 1.2$, NS).

Lastly, in an attempt to predict more general adaptive scores on the VABS-S, a hierarchical regression with three blocks was conducted: the first block included the demographic variables and the second block included the NEPSY and BADS scores, as done in the regression analyses described above. The third block included the DEX-C and the parent and teacher BRIEF scores. The stepwise method was used for all three blocks. None of these variables had a significant contribution to the prediction of the VABS-S scores.

### Table 11.2 Steps included in the NEPSY hierarchical regression for the teacher BRIEF

<table>
<thead>
<tr>
<th>Step</th>
<th>Predicting variables</th>
<th>$\beta$</th>
<th>t</th>
<th>Adj $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sex ($1 = $male, $2 = $female)</td>
<td>0.59</td>
<td>3.25***</td>
<td>0.313***</td>
</tr>
<tr>
<td>2</td>
<td>Sex</td>
<td>0.60</td>
<td>3.77***</td>
<td>0.478*</td>
</tr>
<tr>
<td></td>
<td>NEPSY visual attention</td>
<td>-0.43</td>
<td>-2.71*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sex</td>
<td>0.59</td>
<td>4.18***</td>
<td>0.578*</td>
</tr>
<tr>
<td></td>
<td>NEPSY visual attention</td>
<td>-0.56</td>
<td>-3.67**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NEPSY imitating hand positions</td>
<td>-0.36</td>
<td>-2.35*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sex</td>
<td>0.57</td>
<td>4.62***</td>
<td>0.686*</td>
</tr>
<tr>
<td></td>
<td>NEPSY visual attention</td>
<td>-0.66</td>
<td>-4.81***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NEPSY imitating hand positions</td>
<td>-0.39</td>
<td>-2.96**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NEPSY finger tapping</td>
<td>-0.34</td>
<td>-2.68*</td>
<td></td>
</tr>
</tbody>
</table>

**$P < 0.005$  *$P < 0.01$  *$P < 0.05$.**
11.6 Limitations of study

We initially hoped to recruit only children with an Asperger Disorder diagnosis but expanded our inclusion criteria when faced with restricting our sample size to very small numbers. Future research with larger samples will need to undertake analysis of executive function in discrete diagnostic groups. It is worth noting that functionally, the children included in our sample were not idiosyncratic and shared common strengths and difficulties. It may, therefore, be more useful to analyse the association between symptom severity across defining domains of ASD such as repetitive behaviours with executive function. We excluded children who had co-morbid psychiatric disorders. However, a separate analysis in a larger sample of children with HFA and, for example, attention deficit disorder, would be valuable in understanding core deficits and in planning interventions.

11.7 Discussion

The findings of this study confirm the anecdotal and clinical view that children with HFA have difficulty with executive function. This is evidenced in teacher and parent responses on ecologically valid questionnaire measures of executive function. However, evidence of executive dysfunction was not found using laboratory administered standardised measures of executive function. Indeed, the children in our sample performed in the average range as compared to same age peers on most of the laboratory measures employed.

Our sample demonstrated weakness on the Sensory-Motor domain of the NEPSY only and while the group mean for the sample was significantly lower than the population test norms, this was by five points only. The sample mean was, therefore, still in the average range. The other laboratory measure of executive function, the BADS-C, also yielded a mean score in the average range for the group. There was, however, a large standard deviation on all of the BADS-C sub-tests. It is possible,
therefore, that in a larger sample the BADS-C score would have predicted scores on the questionnaire measures including on the DEX which was developed to complement the BADS-C and for which its authors have reported a high agreement with the BADS-C, especially for clinical groups.

Regression analysis found the only predictor of parent BRIEF to be the Auditory Attention sub-test of the NEPSY. It is important to remember that while some of the scores on the neuropsychological measures predicted variance on the ecological measures, these scores are not in themselves indicating impairment. We might expect children who have difficulty with auditory attention to have difficulty attending to parental instruction and subsequent difficulty organising their behaviour. In fact, the children in our sample were not having difficulty with auditory attention although parents’ perception of auditory attention may have, perhaps, been influencing parental scoring of the BRIEF. Similarly, teachers appeared to be influenced by pupils’ visual attention and sensorimotor ability as measured on the NEPSY and flexibility as measured by the BADS-C, although these scores were in the average range.

How can we explain what appears to be a heightened sensitivity by parents and teachers to particular aspects of the cognitive and motor ability of children with HFA? We would like to discuss several explanations and to suggest that some of these possible explanations deserve particular attention. One hypothesis is that there is something about the ‘real-life’ demands on executive function which we have not captured in our laboratory measures of executive function. One aspect of ‘real-life’ that we might consider are multiple task demands in contrast to the item-by-item approach in the laboratory setting. Studies of auditory processing in children with Asperger disorder have shown that they have significant difficulty attending to specific auditory stimuli in the context of ongoing background noise (Alcantara et al. 2004). Future research could create an approximation of a ‘real-life’ setting in which to administer standardised laboratory measures of executive function. If multiple demands contribute to the deterioration of executive function in this group of children, we would expect to see test scores indicating greater executive dysfunction and this would need to be significantly different when compared to a typically developing control group under the same conditions.

Another feature of ‘real-life’ executive function demands is the presence of social demands inherent in executive function tasks above and beyond one tester. In a study of novel problem-solving, Channon et al. (2001) showed videos of social ‘predicaments’ to adolescents with Asperger syndrome. An example of a scenario involved a story about a man who is not sleeping enough because of new neighbours who have a barking dog. The subjects were asked to offer a solution to this man’s predicament. They found that compared to the control group, adolescents with Asperger disorder did not differ on Problem Apperception or Effectiveness of
their solutions, but did differ significantly on the Social Appropriateness of their solutions. Because executive function demands in ‘real-life’ require not just application of the core attributes contained within the construct of executive function, but also require social judgement, parent and teacher ratings of executive function may, therefore, be indicating greater impairment than laboratory measures. While the children in our sample may have effectively implemented tasks requiring executive function, they may do so in a way which is not socially appropriate and, therefore, appears ineffective to parents and teachers, and may indeed prove to be ineffective in real-life settings.

The discrepancy we report here between laboratory and ecologically valid measures of executive function in children with HFA has been found by other researchers. Kenworthy and colleagues (2005) found in a sample of 72 children with high-functioning autism and Asperger disorder that parent ratings on the BRIEF, the Behaviour Assessment System for Children, and the VABS indicated significant impairment. However, the only laboratory test on which the same children scored significantly below the population mean was the reaction time on TOVA (Test of Variables of Attention) which was one standard deviation below population mean. Gilotty \textit{et al.} (2002) also reported high scores on the Parent BRIEF and low scores on the VABS indicating executive dysfunction and deficits in adaptive behaviour in a comparable group of children. These authors conclude that their study illustrates the ecological validity of such standardised questionnaire measures of executive function and cognition with this group of children.

We would like to suggest that there may be a reporting bias on questionnaire measures of executive function for this group of children. The strong predictive power of sex in relation to the teacher BRIEF also points to this possibility. Perhaps, teachers are rating girls with ASD as having greater executive dysfunction than boys because they have expectations that girls will demonstrate better executive function than boys. While we assumed that all teachers completing the teacher BRIEF knew that the children had a diagnosis of an autism spectrum disorder, we did not directly ask this question. We are not, therefore, able to comment on whether teachers might have different expectations of girls compared to boys, or girls with ASD compared with boys with ASD.

There is strong evidence of a ‘halo effect’ in teachers’ reporting of symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD) interacting with the sex of the child. Teachers scoring video-tapes of boys acting out ‘pure’ ADHD symptoms also rated ODD symptoms highly and rated ODD symptoms significantly higher than when the actor was a girl. However, when rating video-tapes of girls acting out ‘pure’ ODD symptoms they also rated ADHD symptoms highly and significantly more highly as compared to their rating of boy actors (Jackson and King, 2004). Other researchers have found that
parent as opposed to teacher ratings of ADHD behaviors in ‘real-life’ settings differ less as a function of the child’s sex (Achenbach et al. 1990; McGee et al. 1987). It has been suggested that these sex effects are a result of differing teacher expectations.

While parents’ reports on the BRIEF and DEX were not influenced by the child’s sex, the fact that ratings were partially predicted by auditory attention scores (despite the fact that these abilities were average) may also indicate that parental views about executive function are highly sensitive to neuropsychological function and that this sensitivity has a halo effect on assessment of executive function.

We suggest that the study of neuropsychological function in children with ASD would benefit from a less dichotomous view of the validity of laboratory versus ecological measures of executive function and, indeed, of other areas of cognitive function. Researchers and clinicians alike should consider employing qualitative and observational methods to understand the findings we describe here and to advance screening of cognitive function in ASD. For example, carefully constructed classroom observation may help us to understand teachers’ views and expectations of children with ASD, as would interviews with teachers and children themselves. Graded modification of our laboratory test environments, for example altering the number of social demands or distractions, may help us to understand how we could develop more valid measures for use in the clinic. The additional benefit of these methodologies is that they provide us with valuable information with which to construct interventions and remedial strategies. If we can understand just how and when intact executive function deteriorates, we may be able to alter the conditions under which the children with ASD are asked to employ these functions.

11.8 References


Measuring executive function in children with HFA


12

Autism spectrum disorders in current educational provision

RITA JORDAN

This chapter examines the research evidence for the learning style in autism spectrum disorders and ways in which this impacts on educational provision. It considers international evidence but has a focus on educational provision in England. The particular and dual role of education is considered and the effects of differences and difficulties in key areas of development (sensory, perceptual, conceptual, motivational, memory, language and social aspects). Key features of learning style and the implications for certain curriculum areas are analysed, including the need for homework support and the notion of a ‘24 hour curriculum’. The pervasive effects of anxiety and stress are discussed, and the factors that influence relationships with peers. The evidence of the value of different kinds of educational placement is also considered and the need for further research in this, and other, areas identified.

12.1 The role of education

Given that there is no medical ‘treatment’ for Autism Spectrum Disorders (ASD) and that even the idea of ASD as a medical disorder is problematic (Jordan, 2009), education has a special therapeutic role to play. Children and young people with ASD have the same entitlement as anyone else to acquisition of the culturally valued skills, knowledge and understanding that will enable full participation in their society, but, in addition, they need an education that will enable them to acquire the additional skills, knowledge and understanding that others acquire naturally and intuitively, without explicit instruction. In that sense, education has to take on the therapeutic role of compensating for the effects of ASD.

This dual role of education in ASD can be a source of conflict between parents and educational authorities. The latter will most commonly respond to what they see as their statutory obligation: to enable access to the same ‘broad and relevant curriculum’ as is provided for others. Parents may want this too, but, especially in the early years, may give a higher priority to the therapeutic aspects of education; they want an education that will help their children deal with or even overcome the difficulties that arise from their ASD. In an ideal world, the child should have access to both kinds of educational input, but first, both aspects have to be recognised.

This chapter will concentrate on the educational system. However, education continues throughout life and is not confined to the school years or to school hours. The relative failure to learn intuitively means that individuals with ASD need to be educated throughout their lives and in all aspects of their lives. It is also important that education prepares the individual to acquire life skills and social competence more naturally, to make education more self-sustaining, although this is unlikely to be entirely successful for everyone with ASD.

Above all, education needs to be individualised, to encompass the heterogeneity of the population, and to allow for different teaching goals at different times. Reviews of educational interventions that are adopting a therapeutic role, often in the early years, fail to support the use of any single intervention to meet all needs for all learners (e.g. Humphrey and Parkinson, 2006; Jones and Jordan, 2008; McConachie and Diggle, 2007; Perry and Condillac, 2003; Spreckley and Boyd, 2007). In all the comparative evaluations of educational interventions, it is always the case that some children do well in each intervention and others do not (e.g. Magiati et al. 2007; Remington et al. 2007). It is also true that children with ASD tend to learn what they are taught, and seldom go beyond it (e.g. Gulsrud et al. 2007; Howlin et al. 2007). Educators, therefore, need to take great care to select and monitor their teaching to ensure they are meeting the needs of each particular learner and that what is being taught is worthwhile and appropriate. Detailed case studies and single subject case designs often provide the most appropriate research for answering these questions. Randomised controlled trials (RCTs), even where these are possible and ethical, can only answer questions about the likely value of an intervention in general, and have little to say when it comes to individuals.

12.2 The particular challenges of the autism spectrum

As has been evidenced in the earlier chapters in this book, development in ASD is atypical. In ASD, without additional learning impairments, there will be some academic tasks that are easily mastered, at least if presented in an accessible way. Yet in other aspects of life, in common sense, social awareness, understanding
of the world and how to behave in it, the child with ASD may be barely functioning at all. When such everyday tasks are mastered they are achieved at such high cost in terms of effort that the child may be exhausted, and the continual confrontation of such difficult situations may lead to ongoing anxiety and stress. All this will naturally affect that child’s capacity to undertake academic tasks, in time, and so the ASD may come to have a general depressing effect on the child’s overall functioning in education. If there are additional learning difficulties of any kind (language impairment, cognitive impairment, sensory impairment, dyslexia, dyspraxia, etc.) then these too will interact with the ASD to cause greater difficulties.

However, it is not just the complexity of needs that causes problems. When development follows a typical path, even if severely slowed, educators can appreciate the problems faced by the child and, with some effort, good will and training, can adapt to meet the child’s needs. When development is atypical, this natural adjustment does not occur. It is as hard for the teacher to intuitively understand the mind of someone with an ASD as it is for children with ASD to understand their teacher. In other words they have a mutual failure in natural empathy. Just as the child with an ASD has to work cognitively to try to understand others so the educators of the child with an ASD (parents, teachers, therapists) have to adopt the same explicit cognitive ways of understanding the child, not being able to rely on typical natural intuition nor professional training. They will need education in understanding ASD, and time and resources to study each individual, to manage this successfully, and even then it will be exhausting. The extra cognitive load of teaching children with ASD needs to be researched, as do effective ways of managing this extra load. Peeters and Jordan (1999) draw on experience to characterise the qualities needed by an effective educator in ASD, but such assumptions need to be tested.

12.3 Core issues in learning in ASD

This section will examine some of the key differences and difficulties in ASD to explore their effect on education. The list is in no way comprehensive but demonstrates some of the core issues that need to be addressed.

12.3.1 Sensory difficulties

Difficulties in sensory processing are commonly attributed to people with ASD, and autobiographies of individuals with ASD often give them a key role in their disorder, especially hypersensitivities to sound and sharp contrasts in light (Grandin and Scariano, 1986; Lawson, 2003; Shore, 2003). Some professionals also support the notion of abnormal sensory responsiveness having a key role in ASD (Bogdashina, 2003). Yet the research evidence is not clear. Rogers and Ozonoff (2005) in a review found more evidence for hyposensitivity than hypersensitivity.
Hyposensitivity to pain (or at least an extreme delay in response to pain) is often reported in the literature but is not supported by well-conducted studies (Nader et al. 2004). This is at odds with the common experience that pain is not a deterrent in many children with ASD, who may return repeatedly to hold their hands in the steam from a kettle, in spite of what appears to be painful scalding, or will return to climbing a surface from which they have recently fallen with apparently painful outcomes (broken limbs) and yet with no apparent fear. Although most parents and teachers will seek to train children to avoid danger, there is inevitably some reliance on the fact that children will learn from their mistakes. Whatever the truth of responsivity to pain, it is clear that learning from it cannot be relied upon in ASD, so greater vigilance is needed to keep individuals with ASD safe.

Theories about attention distribution in ASD (Murray et al. 2005) may offer a partial explanation for inconsistent responses to pain. Other inconsistencies in sensory responsiveness may be due to individual variation; it has been suggested that responsiveness to sensory stimulation may vary across individuals, sense modalities and within an individual over time. If hypersensitivity is caused by a neurochemical imbalance then there is likely to be over adjustment in receptors and contrary responsiveness over time. Thus, for example, a young man detailed his extreme reaction to noise and light (describing sunlight as painful and the teacher’s voice as like bullets hitting him) being replaced a few hours later by extreme under-responsiveness (the view appearing misty and faint and the teacher appearing to whisper indistinctly). There is research showing that individuals with ASD tend to cluster at the extremes of sensory responsiveness (Kientz and Dunn, 1997), which would make some ‘sensory seekers’ and others ‘sensory avoiders’. This has led to programmes designed to assess individuals in terms of their responsiveness to different sensory modalities (seven senses usually being the number chosen – five ‘outer’ senses plus proprioception and vestibular senses), and then design a ‘sensory diet’ to meet their needs. There is a need to research the validity of such analyses and the efficacy of such programmes (American Association of Pediatrics, 2001).

Although the research base may be poor, there is sufficient concern about sensory issues in individuals with ASD themselves, and in educators, for attempts to have been made to adjust educational environments to reduce sensory effects. Whether there is a domain-independent sensory integration disorder is still an empirical question, and there is pressure to get such a disorder recognised in new formulations of the diagnostic manuals (Miller, 2008). Even if such a disorder were established, there would remain the issue of whether it was an integral part of ASD or a separate disorder that may or may not be co-morbid with ASD. Until more and better research provides answers to such questions, sensory issues should be considered:
A deficit in sensory integration has not yet been firmly established. The research gives inconclusive results (Reynolds and Lane, 2008) and undoubtedly more is needed, especially well conducted case studies on the use of sensory integration programmes to tease out variables that would warrant more systematic research. In the UK there is insufficient occupational therapy resource to make such programmes generally available, so it is vital to establish both the evidence base of effectiveness but also a model for their delivery. Are these programmes needed by all with ASD or only some, and what criteria should be used to decide on eligibility? How long and for what intensity should such programmes be given and do they need to be given by specialists such as occupational therapists or physiotherapists, or could such specialists provide management programmes for delivery by parents and professionals in daily contact? At the moment the situation is confused and needs a proper evidence base for treatment. If sensory integration is a significant problem then there are huge implications for the multi-sensory environments that exist in most schools (as elsewhere) so these issues need to be resolved.

What also remains unknown is how sensory reactivity relates to perceptual issues. There are two possibilities. If the sensory problem is core (whether it is one of hypersensitivity or of inability to integrate senses), as some believe, then it would help explain some of the problems in forming concepts and in idiosyncratic perceptions. However, it is possible, as many cognitive psychologists would hold, that the core problem is a perceptual one. This would mean the individual’s primary difficulty would lie in ‘chunking’ environmental stimuli to make sense of the world around them. A failure to do this would leave the individual responding, like a baby, to the ‘booming and buzzing’ (James, 1892) confusion around, interpreted by self and others, perhaps as being hypersensitive to detailed stimulation simply because each detail would need to be responded to, rather than ‘seen’ as part of a more meaningful whole. It is not possible with current knowledge to choose between these ‘chicken and egg’ explanations. At a practical level it appears helpful, and certainly kinder, to work on both aspects: reducing stimulation to
give individuals with ASD a better chance of interpreting their world; and helping individuals make sense of their environment and produce meaningful concepts to reduce the ‘overwhelming’ sensation from the environment and enable them to cope better with different kinds of stimulation.

12.3.2 Perceptual understanding

Regardless of the validity of the different theories about the underlying mechanisms in ASD, there is evidence of differences in making sense of the world. Perceptual understanding typically develops under social tutorage (Vygotsky, 1962) where mechanisms of joint attention, social referencing and social imitation give a framework for both understanding and acting on the world. What this means is that the child with ASD is literally on his/her own in making sense of the environment and thus is liable to develop very idiosyncratic perceptions. The child (like his/her parent or teacher) will be unaware of the idiosyncracy of those perceptions and, exacerbated by problems with communication, those differences may remain unrevealed. Educators need to use careful observation and investigation to try to uncover the child’s perspective or initial confusion may be further compounded.

In particular, educators need to compensate for the lack of natural intuitive mechanisms such as joint attention by teaching meaning explicitly. Without this understanding, educators may continue to refer to items they are holding up or pointing to without checking that the child knows how (and when) to direct attention to the appropriate item. Words and phrases used by the child with an ASD may have a particular meaning tied to a particular context and this also needs to be investigated and the meaning expanded, where necessary. In the same way, the child may attach particular meaning to certain sequences of events in a ‘superstitious’ way so that the occurrence of one event comes to mean a particular outcome; there is then extreme distress if the expected outcome does not materialise or, even more likely, the child is unable to recreate the events she or he believes are necessary for the next event to occur. Gerland (1999), an adult with Asperger syndrome, describes such a situation when, as a child, an arrangement of objects on a table had coincided with the longed-for arrival home of her sister from school. Thereafter she had struggled to recreate that arrangement to bring about her sister’s arrival and had experienced extreme distress when these efforts were thwarted. In a similar way a child with ASD, without social guidance, may not know which perceptual feature is the relevant one in any given situation and may easily attend to some irrelevant detail. In education systems social signals are used rapidly and continuously to direct and redirect attention to different aspects of events and, without the educator understanding the child’s potential problems with this, and allowing for it by specific instruction and time
for attention switching, the child with ASD may become confused and distressed or switch attention to something better understood (some repetitive action, perhaps).

Finally, there is the perception of novelty. There is some research (Plaisted et al. 1998) that shows that individuals with ASD have a particularly strong response to novelty and anecdotal evidence suggests that this can be experienced as aversive. The consequence is that almost all new situations (unless introduced with considerable preparation) are likely to give rise to a negative response at first, and that the child or young person will need time to adjust to new situations before they can be expected to learn in them. New experiences need to be introduced with knowledge (usually presented as a visual schedule) of how many of these experiences there will be, and when they will end. If the new experience is of a situation (such as a new school or class) that is not responsive to the individual’s choice, or to a fixed number of occasions, then a somewhat different strategy is needed of helping the individual find the familiar within the new setting and making clear what aspects can be changed or adapted and what has to be endured (perhaps with additional support).

12.3.3 Conceptual understanding

It is often reported in the literature that individuals with ASD have problems with ‘abstract’ concepts, although it is not always clear what is meant by this and to what research evidence it refers. Certainly it would be difficult to defend this empirically as applying to all with an ASD, since subjects which many individuals with ASD excel in and enjoy utilise numerous abstract concepts: science, mathematics, music, for example. If it is only meant to apply to those with learning difficulties alongside their ASD, then it has little meaning, since it does not distinguish people with ASD from those with learning difficulties and, since learning difficulties are partly defined by difficulties in understanding and using abstract concepts, it becomes a tautology.

There is a problem in concept formation, however, in ‘abstracting’ (the verb, not the adjective) the ‘essence’ of experiences to give the ‘prototypes’ on which typical concept formation depends (Klinger and Dawson, 2001). Typical human perception is characterised by an ability to ‘gloss over’ insignificant differences when ‘chunking’ information into meaningful wholes, paying attention to what unites rather than divides members of a category. Thus, typically, human processing gives a fast ‘good enough’ categorisation of the world, and has to be trained to go beyond that perception to identify those differences that discriminate when necessary. Typical processing is speedy, enabling everyday efficient functioning. In ASD, the focus on detail makes it easier for individuals to detect difference rather than similarity and they find it hard to ignore what they see as pronounced differences, in order to group items into a single category or concept. One consequence
of this is ‘concepts’ that consist of a single exemplar. De Clercq (2003) describes her son with Asperger syndrome as having three separate ‘concepts’ of a bicycle: ‘wheels in the mud’, ‘keep your feet on the pedals’ and ‘off you go’, respectively.

Grandin (1995a) (an intellectually able person with autism) recognised her own differences in concept formation, which in the beginning were also single exemplars, so that ‘old’ meant a particular old man she knew, ‘cat’ a particular cat, ‘red’ a particular red object. She recognised the restrictions on her thinking brought about by this method of conceptualisation, and also that other people’s concepts were not tied to particular items or events in this way. Not having access to the typical process of concept formation, she claims to have devised her own, very closely related to methods used in artificial intelligence. She describes this as a process of constructing mental ‘libraries’ of common objects against which she would assess objects she came across, searching for a match. Thus, if what might be a chair was found not to be represented in her library she would decide it was not a chair unless told it was, whereupon she would add it to her library. This is clearly cognitively inefficient and time consuming and could only work in someone with her high level of intelligence and exceptional powers of memory.

Paradoxically, Grandin has no problems with the truly abstract concepts she encounters in her daily work as an animal scientist and designer, since scientific concepts are defined by criterial features in a way that everyday concepts are not. It might seem then, that educators could attack the problem with concept formation in ASD by giving explicit criterial features for all concepts, but in practice this is unlikely to succeed. Every-day concepts are referred to by psychologists as ‘fuzzy’ concepts, since they are characterised by their relationship to other things in a functional world, not by set definitional criteria. We only ‘know’ what a chair is because we have had experience of chairs and of treating them in the same functional way, not because anyone has defined a chair. Grandin’s strategy would also have limited application, given the high cognitive load entailed. Using discrimination training to pick out concepts works with identifying particular items but does not address the problem of ‘single exemplar’ categories; in fact, it is likely to reinforce the idea that this one object is ‘red’, only to lead to confusion when other objects or hues of red are used. The answer lies in ‘general case programming’, more generally known in education as ‘sorting’. This enables the child to gain practice in paying attention to the one feature (say, the colour ‘red’) that unites a large collection of items as against a similarly large collection of objects that lack this attribute. Computer programs have made such sorting activities more accessible to educators and should also make their effectiveness easier to evaluate. It is not clear how widespread this difficulty with concept formation is in ASD; interest levels and motivation appear to be key determinants of success, but this also needs more research.
The problem with ‘fuzzy’ concepts may also relate to the fact that people with ASD appear to have conceptual boundaries that are less amenable to modification. This also applies to action schema. Peterson (2002) proposes that there are difficulties in ASD with ‘dialogical processing’, which typically allows concepts in working memory to act together, influence one another and thus be flexible and amenable to context. Vermeulen (2001) has offered a similar account of ‘context blindness’ to account for many of the problems in ASD. At the current state of understanding, there are no simple solutions to this other than explicit strategies to draw attention to contextual features when concepts or schema are being activated. A cumbersome, but worthwhile, alternative for educators is to try to teach all possible contextual variations during the initial teaching of the schema, but this is far from easy or satisfactory.

12.3.4 Motivation

One of the hardest issues for educators to resolve in relation to children with ASD is whether failure to perform in acceptable ways is due to difficulties in cognition or conation (i.e. is it that they can’t or won’t?). Of course, ‘willing’ does not happen in a cognitive vacuum and undoubtedly what a person can or cannot do is hugely influenced by motivational factors; in practice, both aspects must be considered. Certainly, nearly all specialist techniques for educating children with ASD give a high profile to motivation. Applied Behaviour Analysis (ABA) claims to be able to override ‘within child’ factors by providing a suitably high level of external motivation, delivered in a highly contingent way for desired responses. In principle, if not always in practice, the reinforcers used to deliver such motivation move from materialistic towards social, as training progresses, although Tauber (1986) gives a useful warning of the dangers of using social reinforcement contingently in educational settings. ‘Structured teaching’, as developed under the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) programme (Mesibov and Howley, 2003), uses the Premack and Collier (1962) principle of more preferred activities rewarding less preferred ones in a motivational chain (often made explicit to the child in a visual schedule), and this has been shown to be adaptable to most educational settings. There is much talk about using the child’s interests and strengths as motivators in education, and some systematic use of special talents is beginning to develop (Clark, 2005).

The need for predictability is so strong in ASD that that alone has been suggested as a way of developing motivation in the ‘hard to motivate’ child (Jordan, 2001). Many of the factors that motivate children in general also apply to those with ASD: active engagement, meaningfulness, time to complete activities, knowing what to do and when it is finished, and what will happen next (Peeters, 1997). The biggest difference is that individuals with ASD are likely to be less aware of how to please
Autism spectrum disorders in current educational provision

12.3.5 Memory

The issue of memory in ASD is complex (Boucher and Bowler, 2008; see Bowler et al. Chapter 10 of this volume), but it is clear that what is sometimes presented as a strength is in fact a reaction to a problem with memory. Children and young people with ASD often rely on single strategies for memorising, which work well for rote learning tasks but are less efficient and even unhelpful for other educational situations. Such strategies often entail exact repetition of experiences (even including the non-verbal soundtrack of memorised films, for example) with the inability to give the gist of the event or to select memories that have relevance to the current situation. The apparently impressive feat of remembering the full soundtrack of a movie is usually without meaning for the individual and is not available to recall unless prompted in some way. Educators can help the child with ASD make use of their memories by teaching cues to the key aspects at the time of encoding and rehearsing the ‘gist’ of the memory, using these cues. The reconstruction of memories from the gist and from general semantic knowledge, that typically takes place naturally, can be taught explicitly, using these same cues and prompts to access stored knowledge. More able individuals with ASD do seem to develop ways of recalling personal events, at least where there is emotional involvement, but may need training in how to relate the event as a narrative and when it is appropriate to do so. Children with ASD also need to be taught that memories relate to actual events rather than learning routines to respond to certain questions, such as ‘what did you do at school today?’ Visual cues can be helpful but have the danger of suggesting a memory, which may not be accurate.

12.3.6 Language

Although it is communication rather than language problems per se that characterise ASD, language development is important for the child expressively as an educational tool and receptively to help make sense of the educational world (see Chapter 9 in this volume for a discussion of the relationship between language deficits and ASD). The minority of children with ASD who do not develop any useful spoken language have a poorer prognosis, but suffer less from being misunderstood and being the subject of unhelpful pressure at school. Faced with a child who is not speaking, all staff will have a natural response of slowing down their own speech and speaking in shorter sentences – both helpful strategies in enabling the child with ASD to process the language. Educators are also less likely
to assume that a failure to speak is wilful and will appreciate, if not fully understand, that the child is likely to have cognitive and linguistic problems. Sometimes this can lead to unnecessarily low expectations of the child, but usually it leads to helpful support, often extending to the use of visual forms of communication.

For the child with an ASD who has speech, but otherwise has very similar difficulties to non-verbal children with ASD, the response of educators and peers can be very different. It is harder for educators to recognise that the speaking child may be unable to communicate, deficiencies are often thought to be wilful and the child said to be suffering from a behavioural disorder. Problems in processing language are similarly often unrecognised, with the educator failing to slow down to the rate the child needs in order to understand. Nor do educators realise that the language the child has may not be available as language for thought, and that visual modes of thinking are still likely to dominate (Grandin, 1995b). The child’s capacity to ‘hold the floor’ (and, even more tellingly, reluctance to ‘yield the floor’) is seldom recognised as a strategy to avoid the difficult task of participating in conversation or relating to the topics raised by others. Being able to talk about one’s own interests is very different from being able to adjust to the interests of others. The child also will need specific training in pragmatics and conversational skills and peers will need to be shown how to support the individual in interactions in which both parties have an interest.

‘Educational’ language can also prove a particular barrier to understanding in children and young people with ASD. It is a particular genre of language based on the assumption that children will already know about how language is used for everyday communication, and introducing particular forms geared to particular educational purposes. This is particularly puzzling for the child with an ASD, who may be trying to learn about communication for the first time in the educational setting and be thus trying to use and understand this special genre as a means of everyday communication. As was discussed above, educators will often assume early communication skills such as the capacity to follow a point or realise that the object of attention is that held in the teacher’s hand, but the child may have no, or a completely wrong, idea of what is being discussed if he or she is absorbed by something else. Educators will often introduce topics by asking questions, usually ones to which they already know the answer, but the child who copies this strategy is bewildered to be told that ‘I’m not answering that; you know the answer to that’. Given the role of theory of mind difficulties in ASD, children on the spectrum are unlikely to realise that others may know things they do not and so are only likely to ask questions (like the teacher) to get the desired response. There are many other aspects of educational language that need explicit translation for the child with an ASD, but, for this to happen, educators have to be aware of the genre they are using and the problems this may pose for those with ASD.
On the positive side, having speech makes it possible for the child to learn ways of thinking in language, which may not be the best mode for the child but will help with generalisation; visual modes of thinking are very particular and context bound so language can be useful in freeing events from that context and in drawing attention to commonalities across settings. It can also be used in training the child to ‘self prompt’ to deal with anxiety or to problem solve in ways that are easier to generalise than image-based formats. Written language can provide an ideal compromise, being available to the child in a preferred visual mode but having the language properties that aid generalisation.

12.3.7 Social aspects

Education is both socially and linguistically mediated, at least in its traditional forms. The problems with linguistic mediation were raised above, but social mediation is also often overlooked as an issue, in spite of the recognition of social difficulties lying at the heart of ASD (Hobson, 1993; see also Chapter 8 of this volume). Evidence presented in earlier chapters suggests that individuals with ASD do not respond to (or even notice) social signals as a priority and are only able to understand social stimuli by working them out cognitively (Frith and Happé, 1994). These social difficulties have certain key consequences in relation to education. Children will need to be taught to recognise and respond to social signals (such as their name being called) as a way of gaining their attention. Once this is achieved, the same recognition will have to be developed for all other such attention-getting signals such as ‘Everybody!’, ‘Class x!’ , ‘All the boys!’, an imperious hand clap, a whistle or whatever form these signals take in that particular environment. However, educators have then to remember to use these taught phrases or actions as signals, and not bury them in the middle or at the end of an instruction. Individuals with ASD are not particularly non-compliant (Golding, 1997), as long as they understand the instruction and that it is addressed to them. Having to process social information through general cognitive routes has further implications for the social context of education. If individuals with ASD are required to learn something new, then they are least able to do so when having to cope with social demands at the same time; unfamiliar tasks need to be introduced asocially (by organising the material as in a structured teaching setting, or using computer assisted learning, for example) or, if appropriate, in one to one instruction with a single adult. The corollary of this is that if the child or young person is required to engage socially, or even just take part in a group, then she or he is best able to do this if the task set is a familiar one, so all the cognitive effort can be directed to the social domain. Just as for most people, it will be easier to interact with and understand someone familiar than a stranger.
Children with ASD vary significantly in the extent they wish to engage socially with others; what they have in common is difficulty in doing so. Wing and Gould (1979) and Wing (1996) found different sub-types in the degree of sociability in children with ASD; these were categorised as ‘withdrawn’, ‘passive’, ‘active but odd’ and ‘eccentric’. They pointed out that children might change sub-category with time and training and it has been shown that stress and mental illness can also cause individuals with ASD to move from a more sociable category to a more withdrawn one, at least temporarily. It is also likely that degree of familiarity of the persons and the environment will affect degree of sociability. Given the effect of social engagement on cognitive capacity in individuals with ASD, it is surprising that degree of sociability is seldom considered when deciding on a teaching approach. Based on analysis and experience, rather than research, I suggest the following guide:

1. a ‘withdrawn’ child requires both didactic one to one teaching to engage interest but also desensitisation to enable him/her to work with others
2. a ‘passive’ child needs intensely interactive high stimulation techniques with structure to encourage engagement
3. an ‘active but odd’ child needs to know the social rules (through Social Stories (Gray, 1994) perhaps) and then support to carry them out as in ‘Buddy’ schemes or Circles of Friends (Whitaker et al. 1998)
4. an ‘eccentric’ child may just need help in analysing situations, managing his/her own reactions and good models to imitate or to act as guides

12.4 Features of learning style

The extreme heterogeneity of those with ASD means that there will always be exceptions to most generalisations about learning style. However, research has established certain features of learning style that are more likely to be true across the spectrum.

12.4.1 Visual rather than verbal mediation

As suggested above, many children and young people have problems processing language and are more able to use visual forms of instruction, whether this is written or in diagrammatic form. Grandin (1995b) gives a good analysis of her own very visual learning style and programmes such as TEACCH (Mesibov and Howley, 2003; Peeters, 1997) use visual structure for time and work schedules and to enable the individual to literally see what has to be done, where, with whom, how, when it will be finished and what happens next. TEACCH can be adapted for those with visual impairments (Howley and Preece, 2003; Jordan, 2004) although
even for the visually impaired with ASD, augmented vision may remain a preferred mode, where possible. Jordan (2003a) shows how a visual flow chart can be used with young people with Asperger syndrome to help them understand where they have choices in situations and to take responsibility for the consequences of their own behaviour.

12.4.2 ‘Bottom-up’ processing

Part of typical development is to move from perception and cognition being led by the details of the stimulation experienced, to a learning style that perceives and processes the world through imposed structures and expectations (Piaget, 1929). Although there is evidence that individuals with ASD do develop conceptual thinking, it also appears that the ‘bottom-up’ processing of early childhood persists into adulthood as a preferred mode, at least in many situations (Behrmann et al. 2006). The situation is complex because stress and anxiety can also lead to switching from ‘top-down’ to ‘bottom-up’ processing styles (Smock, 1955), which we are all more likely to use in new and confusing situations where we have not yet established expectations or routines. It may be that it is the effects of stress or lack of understanding that lead to the long term maintenance of this learning style in ASD, rather than a cognitive bias. However, evidence from biology of more local processing in certain brain regions and fewer connections between areas (Belmonte et al. 2004) would suggest that a bottom-up processing style, less influenced by existing knowledge and structures, has a biological substrate.

In the classroom, there is a clear necessity to reduce stress and anxiety to promote more advanced learning styles and to allow time for processing so that existing concepts and schema can be brought into play. There will also be a need to teach about alternative learning styles and to encourage the adoption of strategies to overcome some of the limitations of a very detailed focused learning style, without losing some of its benefits (a ‘fresher’ and unique vision in the arts resulting in valuable skills in poetry and painting in some, the attention to detail which will be an important asset in some professions, and the fine discriminations that not only enable careers but also provide much appreciated leisure pursuits such as astronomy, playing a musical instrument by ear and bird watching).

One debilitating problem that often remains is understanding how details are grouped together and which details to include or exclude when building cognitive structures. It will be obvious to most children when the teacher switches from explaining some aspect of history or mathematics, to reprimanding a child for misbehaving, for example, but that may not be the case in children with ASD. Educators need to develop habits of giving ‘advance organisers’ (Ausubel et al. 1978) to signal the content of the lesson (or part of the lesson) to come, reducing the guess work for the child with ASD, and benefiting many others who also
struggle to be prepared to take in information. At the same time, the child with ASD needs to be helped to recognise the cues that indicate when educators change topic or addressee and to react accordingly.

12.5 Access to the curriculum

Having an ASD carries no automatic entailments about which curriculum subjects will prove easy or difficult to access. There are some predispositions that arise from ASD, but these are overridden by the child’s characteristics of intelligence, interest, particular relevant abilities and experience as well as factors such as the teaching style and mode of presentation of the teacher, the teaching environment and so on. Thus, no general assumptions should be made about which subjects should be taught to individuals with ASD. They have the same entitlement to a ‘broad and relevant’ curriculum as any other child and having a particular marketable skill may do as much for their future adjustment as an adult as participation in social skills classes (Howlin et al. 2004). Decisions need to be made on an individual basis, taking account of both current and likely future needs, in planning a suitable curriculum. Within each subject domain, however, there are some common issues related to certain curriculum subjects and some of these are discussed below.

12.5.1 English

Many children with ASD learn to read through their interest in computer games, just as they may start to speak through copying what is said (in an exact mimicry of the accent and intonation) in favourite television programmes. There are teaching programmes that harness such natural learning processes in, for example, teaching children to read through animated interactive computer programs (Heimann et al. 1995). Some children with ASD may find it easier to learn to read (in a mechanical sense) than to speak and so the child can be taught to communicate through written language before (or sometimes, but rarely, instead of) doing so through speech. This can be helped by the child learning to type on a computer but this must be taught as an independent skill and not by leaving the child to be ‘assisted’ in typing as in Facilitated Communication (Konstantareas and Gravelle, 1998). Later on in development, learning to use a word processor for essays and other school work not only helps overcome some of the dyspraxic problems that may accompany ASD and interfere with handwriting, but may also help anxious ‘perfectionist’ children overcome their fear of getting things wrong in general. By emphasising the role of ‘drafting’ in eventually reaching a ‘perfect’ copy the child can accept the modifications that may be needed to an early draft
as simply part of the process, rather than feeling judged and too anxious to try again.

Children with ASD have some specific problems with narrative forms (Bruner and Feldman, 1993; Jordan, 2008; Losh and Capps, 2003). Some of these problems may arise from early missed experiences and many children will be helped by learning to act out everyday events and so ‘tell a story’ through drama (Sherratt and Peter, 2002). Learning specific story structures by, for example, analysing the key elements of a newspaper story and reporting on events in class ‘newspapers’ can also help. However, as Jordan (2008) found, failing to understand human emotion and intention is the biggest barrier to understanding stories, as it is to understanding life events, so teaching children on the spectrum to analyse frequently watched television ‘soap’ programmes for these aspects underlying people’s words and actions can be a valuable tool. Soap characters are chosen because motivations and intentions are often both exaggerated and stylised and thus form a more advanced version of Thomas the Tank Engine stories, part of whose attraction for children with ASD lies in the characters’ unvarying motivation and clear intentions. Learning from video is becoming a useful tool in the education of children with ASD (Sturmey, 2003) in many ways, allowing the necessary repetition and focus.

### 12.5.2 History

Aspects of the history curriculum that depend on memorising lists of dates of battles or kings and queens have particular appeal to children with ASD. They have more difficulty when they are expected to use their imaginations and show empathy for people living in past times far from their own experiences (Jordan and Guldberg, 2002). This can be tackled by omitting those aspects of teaching for the child with an ASD who can be given an alternative task, perhaps to do with fact-finding and recording events; sometimes this will be the best course of action to take. However, aspects of subjects and lessons that cause problems for children with ASD often do so because they focus on key barriers to learning. This means that they also represent key opportunities to help the children with ASD overcome these barriers. Thus, empathising with a Roman soldier allows the opportunity to investigate what empathy means and how one would go about exploring the thoughts and feelings of another person who has a very different experience to one’s own. This kind of lesson will be valuable for all children, but particularly so for those with ASD because it makes explicit what is usually hidden and assumed.

### 12.5.3 Mathematics

Mathematics is often an area of strength in ASD, but not invariably so. Sometimes individuals do very well in some aspects, but find others a stumbling
block. It has been suggested that algebra presents a particular problem in this respect and so Jordan and Hewett are currently undertaking trials of a visual tool for use in algebra to see if this will help.

12.5.4 Science

A typical early understanding of the physical world is through an anthropomorphised view (Carey, 1985), which can persist at a deep level into adulthood and present problems when counterposed with alternative physical explanations. It is likely, although not yet adequately researched, that individuals with ASD do not share this developmental pathway and use ‘folk physics’ in preference to ‘folk psychology’ (Baron-Cohen, 2004) from the beginning. This should mean they do not have to overcome earlier modes of thinking when tackling science and should find scientific thinking more comfortable. This appears to be the case. However, there are aspects of science that are likely to be more problematic in ASD. Science proceeds through a ‘democratic’ process of empirical work, testing and verification of hypotheses rather than a set of rules laid down by authorities. Even the most venerable laws in science may be subject to modification or even refutation over time and what is ‘true’ is always a temporary state of affairs until disproved. This level of uncertainty about what is the case and the fact that hypotheses may be proved or disproved, can be difficult for people with ASD to accept, adding to the confusion of a very confusing world. One way round, that experience suggests may be helpful, is to introduce statistics. The young person who is very disturbed to learn that the results of an experiment are uncertain in advance may take comfort in being able to put a number to that level of uncertainty and also when given numbers to show the degree of certainty in a ‘fact’. This has sometimes led to a lifetime’s fascination with, and a career in, statistics.

12.5.5 Modern foreign languages

When looking for subjects that may be regarded as less ‘suitable’ for children and young people with ASD (perhaps to replace them with social skills classes) it is common for educators to select modern foreign languages. Since all such decisions should be made on an individual basis, there are cases where this is appropriate, but the benefits of modern foreign language teaching in ASD are often overlooked. In a mainstream curriculum, this is often the only time when children are taught everyday social skills, how to use common facilities, how to conduct conversations and how to leave them. The fact that all this is being taught in a foreign language is in reality a minor point compared with the explicit learning opportunities provided. In addition the fact that it is a foreign language means that idioms, metaphors, sarcasm are all explained and the child gains some meta-awareness of how language is used. Many children with ASD enjoy this opportunity
to have clarified what has been puzzling before, and again may pursue languages as further study or even as a career. If they have access to dead languages such as Latin, they often enjoy that even more, because the structure remains unchanged, but there are few opportunities to learn (or use) Latin in the UK now.

12.6 Parental support, homework and the ‘24 hour’ curriculum

Since so much that has to be learnt concerns understanding of people, relationships and daily living, the involvement of parents as educators is an important contributor to educational success in ASD. At the lowest level of involvement, parents will be needed to support and extend the teaching begun at school and will inevitably become involved over issues such as homework. Parents may have to explain to teachers the necessity for clear (preferably written) instructions for all homework, and for extra support in lessons to draw the attention of the child with ASD to relevant aspects that will form part of his/her homework. Parents may also need to advocate on behalf of the child who is becoming over-stressed at school (usually through excess social demands or perhaps bullying), even if the effects of the stress build-up are not apparent until the child ‘relaxes’ at home. Just as the education of a child with an ASD cannot be confined to school hours or premises, nor can the stress. Whenever there are problems they are likely to reflect factors at home and school and so a common approach needs to be adopted. The child who explodes in a rage each night on returning from school is unlikely to be reacting solely to something at home, but may be responding to unreleased tensions that have built up during the day. By working together, schools and parents can identify times or occasions when the child needs a respite break to calm down or escape a difficult situation before re-entering the situation as she/he has been taught to do. This may avoid episodes where the child loses control and enable the child (and peers) to be taught better ways of coping with stress.

As the child with ASD gets older, and sometimes even for younger children, parents find it increasingly difficult to manage this 24 hour curriculum at the same time as providing a reasonable quality of life for the rest of the family. Families need a break, as does the child with ASD, both at crisis points and also regularly, as a planned strategy for meeting needs. Preece and Jordan (2007) reinforce the need to relieve stress in families but also demonstrate the inadequacy of provision, even in a well resourced county in the UK that has a long history of specialist provision for children with ASD. The problem seems to lie in the view of social service planning that short breaks services are by their nature a ‘last resort’, to prevent crises in families and to be given only when all else has failed. In fact, well trained staff and well resourced provision should be part of a planned service to meet the child’s 24 hour educational needs, apart from the side benefits that may accrue
from relief of care for families. Failure to get this right may result in residential schooling being sought and/or in family breakdown (Randall and Parker, 1999).

### 12.7 Anxiety and stress

In respect of schooling, it is important to recognise the debilitating effects of stress and anxiety on the child’s capacity to learn and so reducing stress needs to be a top curriculum aim. Sources of stress will be very individual but are likely to include the following:

1. **Endogenous stress arising with hormone changes at the onset of puberty.** Exercise, both aerobic and anaerobic, can help reduce this stress (Campbell, 2007; Campbell and Jordan, unpublished data) as can specific relaxation techniques and periods of quiet enjoyable activity.
2. **Sensory overload in the environment, particularly noise, seems to cause the most stress.** Local solutions might include putting pads on the bottom of chair legs on a vinyl floor, or the child may be given a proximal block such as earphones.
3. **Frustration from not understanding or not being able to communicate needs.** Educators should watch for the signs of communicative need so it can be addressed before frustration sets in, and the child or young person needs to be taught a system of communication.
4. **Anger or panic at having routines disrupted, especially when these routines are themselves indicators of a high level of stress.** Staff and peers may need to be taught to respect routines once they have started. Equally, the child or young person with ASD needs to learn to identify early signs of their own stress and to learn to engage in safe activities that reduce stress, rather than resorting to open-ended routines that may fail to resolve the underlying anxiety. It is important that the child is taught to act on early signs of stress as just drawing attention to them may exacerbate the anxiety in a transactional way.
5. **Having to leave tasks incomplete or being unable to put items back in what the child regards as a ‘proper’ relation to one another (e.g. the chair exactly parallel to the table, the pencils all facing the same way in parallel rows, etc.) often leads to extreme stress.** It may be that the child needs a programme so that in the longer term he/she can learn to tolerate slight deviations from the ‘ideal’ situation with less stress. In the meantime it is best to reduce the size of tasks to allow completion, and to allow the child extra time for packing up, to allow for the exact arranging of materials.
6. Not understanding one’s own emotional states and so being unable to control them leads to further stress. Children need to become aware of their own emotions if they are to understand what they are, to recognise them in themselves and in others, and then learn to manage them. Greig and MacKay (2005) have recently developed a programme for children and young people with Asperger syndrome, based on the idea of ‘little men in the head’ – ‘homunculi’. Children are taught to name these ‘men’ as mental states in a representation of their own heads and to manipulate them in ways that help control their activities. This is ‘Cognitive Behavioural Therapy’ but in a form that is accessible to young children and does not require clinical psychologists to administer.

12.8 Relationships with peers

One of the key benefits in attending school, rather than being educated at home or in a clinic based setting, is that it allows opportunities to engage with and learn with and from peers. Research shows that when individuals with ASD interact in positive ways with peers, all benefit in terms of development and social maturity (Roeyers, 1995; Yang et al. 2003). If children with ASD can interact happily with others all three aspects of impaired or atypical development are likely to be affected: the child will engage more socially, communicate more and become more flexible as others’ thoughts, feelings and intentions ‘interfere’ with one’s own. One feature of the Young Autism Project (Lovaas, 1987) was that children were taught ‘entry’ skills to their local nursery and the most successful children were those who engaged in the group from an early age. There have also been successful programmes targeting the development of peer interaction through pivotal response training (Odom and Strain, 1986) or other proactive techniques (Strain and Hayson, 2000). Peers can also be part of support teams for the child through Buddy schemes or Circles of Friends. A recent suggested remodelling of the diagnostic criteria for ASD (van Lang et al. 2006) has play as a key aspect of the definition of the disorder, in acceptance of its key role in development. Jordan (2003b) has analysed the benefits of teaching both cognitive and social aspects of play to children with ASD, to bring them into successful relationship with their peers, so this too should form a vital part of the educational curriculum.

12.9 Information and communication technologies (ICT)

Engagement with computers has a vital role to play in the education of children and young people with ASD, and in their quality of life thereafter
(Jordan, 2007a; 2007b; Murray, 1997; Murray and Aspinall, 2006). Computer assisted learning can help take the place of social or linguistic mediation of learning, allowing the child or young person to work at their own pace and work to their strengths. Information technology can also provide tools to teach aspects of learning that are otherwise difficult to attempt, such as the use of virtual reality to teach about thinking and imagination (Herrera et al. 2008). Use of laptops with interactive white boards allows teachers to individualise class teaching and monitor the child with ASD, who is working at his/her own pace, at the same time as giving class instruction. The increased use of such 'laboratory' classrooms will help make schools considerably more 'autism friendly'. It is also clear that at least some people with ASD do like to engage socially with others and share ideas and views when they can do so at their own pace in a 'safe' environment, and for many, computer social network sites provide such an opportunity (Biever, 2007).

12.10 Kinds of placement

Alongside growing understanding of ASD and specialist educational approaches to meet their needs has come a worldwide movement for inclusion, where many argue that inclusion should be the default position (as a right) and that it is exclusion or segregation that has to be justified by evidence of a 'greater good' (UNESCO, 1994). There is no evidence (and little research) on which kind of educational provision is 'best' for children with ASD and little agreement on the criteria for 'best' practice. The Department for Education and Skills, UK (2002) has produced consensual (rather than research-based) recommendations for good practice in ASD, but this is based on policies and processes rather than types of provision. Nevertheless, a recent research review in England (Jones et al. 2008) has identified some positive examples of good inclusive practice, while also identifying the common view of all stakeholders that the main barrier to effective inclusion was the lack of understanding among school staff. A new initiative on inclusive practice in ASD (National Strategies Schools Development Programme, 2009) that provides an interactive resource for mainstream schools, may help to remedy this.

The role of research in evaluating broader kinds of educational entitlement is almost invisible. It is rare for the outcome measures of educational placement to be specified, let alone monitored. Thus, there is some evidential base to the policy of inclusion in education in that large international surveys found that segregated schooling made social inclusion as an adult more difficult (Hegarty, 1993). However, given the very atypical experiences of children with ASD in supposedly 'inclusive' settings (e.g. Jordan and Powell, 1994) it is not clear that this is also true for them (Chamberlain et al. 2007; Simpson et al. 2003). Children with ASD in mainstream schools, when there is no or inadequate specialist support, often
Table 12.1 *Comparative benefits of single curricula versus eclectic curricula for pupils with ASD*

<table>
<thead>
<tr>
<th>Single curriculum</th>
<th>Eclectic curriculum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enables staff expertise</td>
<td>Can match to goal</td>
</tr>
<tr>
<td>Better monitoring &amp; easier evaluation</td>
<td>All needs can be addressed</td>
</tr>
<tr>
<td>Builds staff &amp; parent confidence</td>
<td>Needs compatibility checks &amp; child perspective</td>
</tr>
<tr>
<td>Enables positive views</td>
<td>Takes strengths from each approach</td>
</tr>
</tbody>
</table>

feel isolated rather than included, are frequently bullied and are more likely than most other groups to be excluded (Barnard *et al.* 2000; Batten *et al.* 2006). There is anecdotal evidence of a high use of home tutoring among children with ASD (especially at secondary transfer) and it is suggested that this is a response to lack of better options rather than a real choice.

All too often there is conflict between the educational placement that will best meet the child’s therapeutic needs and one that will provide the best access to a broad curriculum and to typically developing peers.

The areas where research evidence would be helpful include:

1. whether being fully included in a mainstream school leads to more social inclusion in society as an adult
2. whether attending specialist provision leads to greater skills, independence and a better quality of life as an adult than either supported mainstream provision or a generic special school
3. whether children with ASD attending mainstream schools have more or fewer positive social contacts with peers than those attending special or specialist schools

Even in specialist provision there is a division between those schools which follow eclectic curricula and those which adopt a single form of intervention, although even in such ‘single approach’ schools there is usually a degree of eclecticism, as other approaches are incorporated. Since, as was shown above, there is no evidence for the value of a single kind of educational intervention to meet all needs, there is equally no evidence for the superiority or otherwise of single approach schools. There are likely to be pros and cons, as illustrated in Table 12.1.

Resource bases appear to provide more flexible provision for children and young people than separate classes or units (Hesmondhalgh and Breakey, 2001). The difference is that in resource bases the child ‘belongs’ to his or her peer group class and the class teacher works with the resource base specialist to plan the
child’s individual educational plan and to work out effective programmes for integrated lessons and for support. This means the child can attend mainstream classes when ready but, if extra stress or particular circumstances mean the child cannot cope on a particular occasion, the resource base is always there to provide a safe working environment. The resource teacher also has a role in advocating for the children with ASD and in arranging training and support for colleagues in the main part of the school and for the children’s peers. Specialist schools may still be needed for some children whose needs or circumstances are extreme, but they should become true centres of excellence, developing innovatory practice, conducting research for evidence-based practice, and supporting mainstream and generic special schools.

Children and young people with ASD who have additional severe (or even profound) learning difficulties also need to have their autism addressed since they are always going to need support and supervision in their daily life. However, specialist teaching is about the understanding and expertise available, not about location. There is no reason why a generic special school for children with moderate or severe learning difficulties could not be an appropriate placement, as long as the conditions for specialist teaching were in place, the school was organised to be ‘autism friendly’ and the peer group was a suitable one for the child with the ASD (Jordan et al. 1999). Just as in mainstream settings, specialist teaching might be available to individuals supported in the ordinary classes in the special school, or there might be a specialist ASD class or a resource base in the school.

Reports from parent surveys, and other research (English and Essex, 2001), show that periods of transition are particularly difficult for children with ASD and their families, and lead to the greatest problems with respect to placement. There are crucial times of transition:

1. from diagnosis to intervention
2. from home and/or pre-school intervention to school
3. from primary to secondary provision
4. from school to adult life/post-school provision

Parents will have a key role at these times but they and students with ASD also need support and guidance to develop transition programmes to ease progress across these boundaries (Emis and Manns, 2004).

12.11 Concluding remarks

In spite of its crucial role in enhancing life opportunities for people on the autism spectrum, education remains poorly researched. This chapter has used
data from other areas of research to draw out the educational implications for
students with ASD, as well as reviewing some of the few studies on educational
provision itself. As other research in ASD illustrates, individual factors remain
key and few specific generalisations can be made. Many areas that would benefit
from further research have been identified, while recognising that the research
question for the educationalist (whether parent or professional) concerns the needs
of an individual, rather than making general statements on the value of particular
interventions.

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Index

Note: The following abbreviations are used: ADHD for attention deficit hyperactivity disorder; ASD for Autism Spectrum Disorders; ASD-LI for autistic spectrum disorders with language impairment; CNVs for copy number variations; EEG for Electroencephalography; fMRI for functional magnetic resonance imaging; HFA for high-functioning autism; MEG for magnetoencephalography; MRI for magnetic resonance imaging.

15q11–13 duplications, 88
16p11.2 locus, CNVs at, 88–91

absence epilepsy, 181
acquired epileptic aphasia, 183
MEG study of epileptiform activity, 162
adaptive functioning and executive skills, 235
measurement of, 29, 354
ADHD, 38, 140–141, 360–361
amygdala and autism, 18
and memory, 334–338
MRI findings, 129–131
animal models
oxytocin studies, 203–204
reelin studies, 201
serotonin dysfunction, 192
anxiety, educational setting, 377, 382–383
Asperger syndrome (AS) as separate diagnostic entity, 3

brain structure differences, 139
diagnostic criteria, 22
language oddities, 286–287
assessment and diagnosis, 19–20
age of onset and diagnosis, 25–26
assessment process, 26–27
behaviour and mental health, 31–32
cognitive assessment, 31
communication, 31
developmental history, 27–29
family assessment, 32
individual profiling, 30–31
medical investigations, 32–33
observations, 29–30
best estimate clinical diagnosis (BECID), 33–34
research procedures, 34–37
diagnostic terminology, 20–24
epidemiology, 24
general population findings, 38–39
atonic seizures, 180
attitudes of others, identifying with, 272–274
auditory processing deficits in speech perception, 303
MEG studies, 163–165
Autism Diagnostic Interview-Revised (ADI-R), 27–28
combined with ADOS, 34–37
Autism Diagnostic Observational Schedule (ADOS), 30
combined with ADI-R, 34–37
Autism Spectrum Disorders (ASD), 1
definitional issues,
20–24
as an evolving concept,
2–3
heterogeneity of, 3–4, 114,
138–139, 190–191
and intellectual disability,
115–116
prevalence, 1, 24
research issues, 4–7
termology issues, 1–2
timing of brain
development, 116–117
Autism Susceptibility Locus 1 (AUTS1), 59
autistic regression
and early onset epilepsy
syndromes, 182–184
pathogenesis of, 186
role of epilepsy, 179–180
Autistic Spectrum Disorder
with Language
Impairment (ASD-LI),
291–299
memory function in, 306
autobiographical episodic
memory, 326–327
basal ganglia, MRI findings,
135
Behaviour Rating Inventory of
Executive Function (BRIEF), 352–354
behavioural assessment,
31–32, 352–354
Behavioural Assessment of
Dysexecutive Syndrome
in Children (BADS-C),
352
best estimate clinical
diagnosis (BECID), 33–34
research procedures, 34

studies using a
combination of
measures, 34–37
biochemistry of autism, 11,
190–191, 207–208
oxytocin, 203–207
reelin, 200–203
serotonin, 191–192
bottom-up processing style,
377–378
brain imaging, see
neuroimaging
brain structure
amygdala and
hippocampus,
129–133, 334–338
basal ganglia, 135
brainstem, 136–137
cerebellum, 135–136
cerebral cortical folding,
129
cerebral hemisphere
abnormalities,
125–129
cingulate cortex, 127
corpus callosum, 133
enlarged brain volume,
124–125
females with ASD, 138
frontal lobe regions,
126–127
heterogeneity issues, 114
lateral temporal lobe
sub-regions, 128
Medial temporal lobe (MTL),
139, 334–338
and memory, 334–338
parietal and occipital
regions, 128–129
thalamus, 133–135
timing of development,
116–117
white/grey matter and lobar
volumes, 125–126
brainstem, MRI findings,
136–137
broader autism phenotype, 3,
38–39, 222
broadly-defined HFA, language
impairments, 289–291
Broca’s area, reversal of
asymmetry, 127
causal precedence criterion,
222
central coherence theory,
241–242
executive dysfunction
hypothesis, 232–234
theory of mind hypothesis,
226–227
central coherence theory,
236–238
causal precedence criterion,
241–242
explanatory power
criterion, 240–241
research, 238
uniqueness criterion,
239
universality criterion,
238–239
cerebellum, structural
abnormalities, 135–136
and memory, 334
reelin levels, 201
cerebral hemisphere
abnormalities, 125–129
childbirth, oxytocin induced,
206–207
cholesterol, 192–193, 203
cingulate cortex, structural
abnormalities, 127
classification systems, 2,
21–22
CNTNAP2 gene and autism,
71–72
cognitive deficits, 20
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page References</th>
</tr>
</thead>
<tbody>
<tr>
<td>executive dysfunction hypothesis</td>
<td>228–236</td>
</tr>
<tr>
<td>explanations of language impairments</td>
<td>301–306</td>
</tr>
<tr>
<td>role of neuropathology</td>
<td>268–269</td>
</tr>
<tr>
<td>search for primary</td>
<td>219–222</td>
</tr>
<tr>
<td>and theory of mind hypothesis</td>
<td>222–228</td>
</tr>
<tr>
<td>weak central coherence</td>
<td>236–242</td>
</tr>
<tr>
<td>cognitive flexibility</td>
<td>266–268</td>
</tr>
<tr>
<td>congenital blindness features of autism in</td>
<td>277</td>
</tr>
<tr>
<td>connectivity of brain regions in ASD</td>
<td>7, 123, 137–138</td>
</tr>
<tr>
<td>continuum concept</td>
<td>3, 19</td>
</tr>
<tr>
<td>copy number variations (CNVs)</td>
<td>81</td>
</tr>
<tr>
<td>15q11–13 duplication</td>
<td>88</td>
</tr>
<tr>
<td>16p11.2 deletion</td>
<td>88–91</td>
</tr>
<tr>
<td>detection methods</td>
<td>81–83</td>
</tr>
<tr>
<td>in schizophrenia</td>
<td>91</td>
</tr>
<tr>
<td>in the general population</td>
<td>83–84</td>
</tr>
<tr>
<td>whole genome studies in ASD</td>
<td>84–88</td>
</tr>
<tr>
<td>corpus callosum, MRI findings</td>
<td>133</td>
</tr>
<tr>
<td>cortical folding, increased in ASD</td>
<td>129</td>
</tr>
<tr>
<td>creativity</td>
<td></td>
</tr>
<tr>
<td>imaginative deficit</td>
<td>278–279</td>
</tr>
<tr>
<td>and symbolic play, 276–277</td>
<td></td>
</tr>
<tr>
<td>cued recall</td>
<td>317, 321, 330</td>
</tr>
<tr>
<td>curriculum subjects</td>
<td></td>
</tr>
<tr>
<td>declarative memory</td>
<td>306, 318–319</td>
</tr>
<tr>
<td>Deese, Roediger, Mc Dermott DRM paradigm</td>
<td>321</td>
</tr>
<tr>
<td>Developmental Diagnostic and Dimensional Interview (3di)</td>
<td>29</td>
</tr>
<tr>
<td>developmental history, assessment of</td>
<td>27–29</td>
</tr>
<tr>
<td>developmental regression in early onset epilepsy syndromes</td>
<td>182–184</td>
</tr>
<tr>
<td>autism</td>
<td>6–7</td>
</tr>
<tr>
<td>Diagnostic Interview for Social and Communication Disorders (DISCO)</td>
<td>28–29</td>
</tr>
<tr>
<td>diagnostic issues</td>
<td>2</td>
</tr>
<tr>
<td>defining the spectrum</td>
<td>20–24</td>
</tr>
<tr>
<td>epilepsy–autism link</td>
<td>179</td>
</tr>
<tr>
<td>diffusion tensor imaging (DTI) studies</td>
<td>123, 137–138</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>78–79</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>183–184</td>
</tr>
<tr>
<td>DSM-IV, proposed change to diagnostic sub-groups</td>
<td>2</td>
</tr>
<tr>
<td>Dysexecutive Questionnaire for Children (DEX-C)</td>
<td>352</td>
</tr>
<tr>
<td>education</td>
<td>12–13, 364</td>
</tr>
<tr>
<td>anxiety and stress</td>
<td>382–383</td>
</tr>
<tr>
<td>curriculum subjects</td>
<td>378–381</td>
</tr>
<tr>
<td>ICT, value of</td>
<td>383–384</td>
</tr>
<tr>
<td>learning issues</td>
<td>366</td>
</tr>
<tr>
<td>conceptual understanding</td>
<td>370–372</td>
</tr>
<tr>
<td>language</td>
<td>373–375</td>
</tr>
<tr>
<td>memory</td>
<td>373</td>
</tr>
<tr>
<td>motivation</td>
<td>372–373</td>
</tr>
<tr>
<td>perceptual understanding</td>
<td>369–370</td>
</tr>
<tr>
<td>sensory difficulties</td>
<td>366–369</td>
</tr>
<tr>
<td>social aspects</td>
<td>375–376</td>
</tr>
<tr>
<td>learning styles</td>
<td>376–378</td>
</tr>
<tr>
<td>parental support &amp; homework issues</td>
<td>381–382</td>
</tr>
<tr>
<td>placement types</td>
<td>384–386</td>
</tr>
<tr>
<td>problems for the ASD child</td>
<td>365–366</td>
</tr>
<tr>
<td>problems for the teacher</td>
<td>366</td>
</tr>
</tbody>
</table>
education (cont.)
relationships with peers, 383
therapeutic role of, 364–365
EEG for epilepsy and autism, 179, 185
Electric Status Epilepticus in Slow Sleep (ESES), 183
emotionally charged stimuli, recall of, 321–323
empathy, 273–274, 379
English curriculum, 378–379
environmental risk factors, 4–5, 24
epidemiological studies, 24, 178
epigenetic mechanisms, 78–81
epilepsy and autism, 5, 10–11, 176–177
autistic regression, 179–180
pathogenesis of, 186
diagnostic aspects, 179
ey early onset epilepsy syndromes, 182–184
EEG, 178–179, 185
gender issues, 178–179
investigation and treatment, 185
phenotype of ASD with epilepsy, 184–185
prevalence, 177–178
seizure types, 180–181
epileptic encephalopathy, 177
epileptiform activity in children, 162–163
episodic memory, 323–324
autobiographical, 326–327
spatio-temporal context, 325–326
epistatic action of genes, 56
ITGB3 and SLC6A4, 197–198
event related fields (ERFs), MEG analysis, 159–160
executive dysfunction case study, 348–350
behavioural assessments, 352–354
neuropsychological assessment, 351–352
executive dysfunction hypothesis, 228–229, 268–269
alternative perspective, 278–280
causal precedence criterion, 232–234
explanatory power criterion, 234–236
uniqueness criterion, 230–232
universality criterion, 230
link to adaptive functioning, 235
real life demands, 359–360
see also executive dysfunction
explanatory power criterion central coherence theory, 240–241
executive dysfunction hypothesis, 234–236
theory of mind hypothesis, 227–228
extreme male brain, 242
eye contact impairment, link to amygdala, 131
face processing evidence of dysconnectivity, 138
MEG studies, 166–169
false belief tasks, see theory of mind (ToM) hypothesis
familial inheritance, genetic studies, 54–55, 56–57
Families and Communication Training and Support (FACTS trial), 35
family assessment, 32
females with ASD epilepsy risk, 178–179
neuroanatomical findings, 138
foreign language learning, benefits of, 380–381
fractional anisotropy (FA), reduction of, 137–138
free recall, 317, 319–320, 321
frontal lobe involvement in memory, 334–335
structural abnormalities, 126–127
functional MRI (fMRI), 138, 157
fusiform face area (FFA), 128, 167–168
GABRB3 gene and autism, 70–71
gamma oscillations, synchronisation of, 161
gender issues, 116
brain structure, 138
epilepsy risk in girls, 178–179
in genetic/epigenetic aetiology, 55–56
reporting bias, 360–361
sex-specific linkage analysis, 61
general population epilepsy–autism link, 179
presence of CNVs (copy number variations) in, 83–84
traits of ASD in, 19, 23, 38–39
generalized tonic–clonic seizures, 182
genetics, 9–10
aetiological models, 56–57
association studies, 61–63
CNTNAP2 gene, 71–72
GABRB3 gene, 70–71
genome-wide, 72–74
RELN gene, 63–69
SLC6A4 gene, 69–70
copy number variations (CNVs), 81
15q11–13 duplication, 88
16p11.2 deletion, 88–91
in the general population, 83–84
methods of detecting, 81–83
in schizophrenia, 91
whole genome studies in ASD, 84–88
epigenetics, 78–81
family studies, 54–55
future research goals, 91–93
IMGSAC study, 34
linkage studies, 57–61
oxytocin studies, 205–206
rare single gene mutations, 74–78
reelin studies, 203
serotonin, 195–198
transmission mode, 55–56
twin studies, 55
genome-wide association studies, 72–74
grammatical impairments children with ASD-LI, 295–297, 299
in narrowly-defined HFA, 288–289
grand mal seizures, 182
grey/white matter and lobar volumes, 125–126
heterogeneity of ASD, 3–4, 114, 138–139, 190–191, 316–317
high-functioning autism (HFA), 20–21
brain structure differences, 139
language impairment in broadly-defined HFA, 289–291
in narrowly-defined HFA, 287–289
see also executive dysfunction case study
hippocampus role in memory, 335–338
structural abnormalities, 131–133
histone modification, 79–81
history teaching, 379
homework issues, 381–382
hyperserotonaemia, 193–195
role of ITGB3 gene, 197
identification with others, 272–273, 274, 275–276
imaginative deficits, 278–279
imitation, 25
and identification with others, 275–276
neural basis of, 169–170
incidence rates, 191
inclusive practice, educational provision, 384–385
individual profiling, 30–31
infantile spasms (West syndrome), 182–183
information and communication technology (ICT), 383–384
intellectual disability and memory, 317
issues for brain imaging, 115–116
see also cognitive deficits International Molecular Genetic Study of Autism Consortium (IMGSAC), 34 interventions, 8
educational, 365
for epilepsy, 185
oxytocin replacement therapy, 206
serotonergic, 198–200
item-specific processing, 330–331
ITGB3 gene, 197–198
Landau-Kleffner syndrome (LKS), 183
MEG study of epileptiform activity, 162
language, 12, 284–285
abilities/impairments across the spectrum, 285
ASD-LI, 291–299
Asperger syndrome, 286–287
broadly-defined HFA, 289–291
narrowly-defined HFA, 287–289
causes of impairments, 299–300
cognitive deficit explanations, 301–306
social deficit explanations, 300–301
and education, 373–375
lateral temporal lobe abnormalities, 128  
learning styles of ASD children, 376–378  
lexical-semantic abnormalities in ASD-LI, 292–293, 297  
linkage studies, genetics, 57–61  
logarithm of the odds (LOD) scores, linkage studies, 58  
low-functioning autism (LFA), brain structure differences, 139  
magnetic resonance imaging (MRI)  
see structural MRI  
functional MRI (fMRI), 157  
magnetoencephalography (MEG), 10, 156  
analytical approaches, 159–161  
ASD studies, 161–162  
auditory processing, 163–165  
epileptiform activity, 162–163  
face processing, 166–169  
mirror neuron system, 169–170  
semantic processing, 165–166  
discussion, 170–171  
instrumentation and measurement, 156–159  
mathematics teaching, 379–380  
MeCP2 gene, 78–79  
medial temporal lobe (MTL) amygdala abnormalities, 129–131  
and atypical memory in ASD, 334, 335  
hippocampus abnormalities, 131–133  
medical assessment, 32–33  
Medical Research Council Autism Imaging Multi-Centre Study (MRC-AIMS), 140  
memory, 12, 316–317  
and the brain, 334–338  
and the self, 326–327  
declarative in ASD-LI, 306  
educational context, 373  
épisodic, 323–324  
spatio-temporal context, 325–326  
standard experimental procedures, 319–323  
types and theories of, 317–319  
wider concepts of, 327–328  
relational processing, 329–333  
task support, 328–329  
mental health assessment, 31–32  
meta-analyses, genetic linkage studies, 60  
metarepresentational ability, 223, 323, 332  
methodeological issues, 4  
methylation of DNA, 78–79  
mirror neuron system, MEG studies, 169–170  
motivational issues, education, 372–373  
MRI, see structural MRI  
multiagency assessment (MAA), 27  
multiple deficits view of autism, 243–245  
applying criteria to, 245–246  
links between cognitive domains, 246–248  
need for longitudinal studies, 248–249  
myoclonic seizures, 180–181, 183–184  
narrowly-defined HFA, language impairments, 287–289  
National Autism Plan for Children, 26, 348  
NEPSY (A Developmental Neuropsychological Assessment), 351–352  
nurexin genes, single mutations in, 75–77  
neuro-cognitive assessment, 31  
neuroimaging, 10, 112  
background, 112–113  
future directions, 140–142  
methodological issues distinguishing between different groups, 138–139  
gender disparity, 116  
heterogeneity of ASD, 114  
intellectual disability, 115–116  
timing of brain development, 116–117  
neuroimaging techniques diffusion tensor imaging (DTI) studies, 123  
other shape-based approaches, 123  
region of interest (ROI) approaches, 119–121  
voxel-based morphometry (VBM), 121–122
Index 399

see also structural MRI, functional MRI
neuroligin genes, single mutations in, 74–75
neuropsychological assessment tools, 351–352
neurotransmitters, 7–8, 191 oxytocin, 203–207 serotonin, 191–192 non-specific pervasive developmental disorders, 23
savant abilities, 6, 236, 242
schizophrenia
  copy number variations (CNVs) in, 91
  oxytocin levels, 204
school curriculum subjects, 378–381
science education, 380
seizures, types of, 180–181
selective serotonin reuptake inhibitors (SSRIs), 198–199
self-concept
  and memory, 326–327
  normal development of, 271–272
self-referential memory, 327
semantic processing
  in ASD-II individuals, 298
  and declarative memory impairment, 306
  during recall, 321
  MEG studies, 165–166
  in narrowly defined HFA, 288
need for task support, 329–330
sensory difficulties, 5–6, 366–369
serotonin and noradrenaline reuptake inhibitors (SNRIs), 199
serotonin neurochemistry, 191–192
dysfunction of serotonin system, 192–193
  elevated blood serotonin levels, 193–195
  genetic factors, 195–198
  positron emission tomography (PET) synthesis, 193
serotonergic interventions, 198–200
SHANK3 gene mutations and ASD susceptibility, 77–78
single gene mutations, 74–78
SLC6A4 gene, 69–70, 195–196, 197–198
SNRIs (serotonin and noradrenaline reuptake inhibitors), 199
social behaviour
  measures of, 38
  mindreading deficit and language impairments, 300–301
  rat hyperserotonemia model, 192
  role of oxytocin, 203–207
  social interaction and task setting, 375
  teaching approaches, 376
  social referencing, 272–273
  social signals used by educators, 375
serotonin neurochemistry, 191–192
dysfunction of serotonin system, 192–193
  elevated blood serotonin levels, 193–195
  genetic factors, 195–198
  positron emission tomography (PET) synthesis, 193
serotonergic interventions, 198–200
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page/Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced in congenitally blind children</td>
<td>277</td>
</tr>
<tr>
<td>systemising-empathising theory</td>
<td>242</td>
</tr>
<tr>
<td>task support, memory</td>
<td>328–329</td>
</tr>
<tr>
<td>temporal lobe abnormalities</td>
<td>128, 129–133, 186</td>
</tr>
<tr>
<td>terminology issues</td>
<td>1–2, 20–24</td>
</tr>
<tr>
<td>thalamus, MRI findings</td>
<td>133–135</td>
</tr>
<tr>
<td>theory of mind (ToM) hypothesis</td>
<td>222–223</td>
</tr>
<tr>
<td>causal precedence criterion</td>
<td>226–227</td>
</tr>
<tr>
<td>and executive function</td>
<td>229, 247</td>
</tr>
<tr>
<td>explanatory power criterion</td>
<td>227–228</td>
</tr>
<tr>
<td>false belief tasks</td>
<td>223</td>
</tr>
<tr>
<td>uniqueness criterion</td>
<td>225–226</td>
</tr>
<tr>
<td>universality criterion</td>
<td>223–225</td>
</tr>
<tr>
<td>executive dysfunction hypothesis</td>
<td>230</td>
</tr>
<tr>
<td>time-frequency analysis, MEG</td>
<td>161</td>
</tr>
<tr>
<td>treatments, see interventions</td>
<td></td>
</tr>
<tr>
<td>triad of impairments</td>
<td>243–244</td>
</tr>
<tr>
<td>tryptophan interventions</td>
<td>199</td>
</tr>
<tr>
<td>twin studies</td>
<td>38, 55, 244</td>
</tr>
<tr>
<td>UBE3A gene</td>
<td>79</td>
</tr>
<tr>
<td>uniqueness criterion</td>
<td></td>
</tr>
<tr>
<td>central coherence theory</td>
<td>239</td>
</tr>
<tr>
<td>executive dysfunction hypothesis</td>
<td>230–232</td>
</tr>
<tr>
<td>theory of mind hypothesis</td>
<td>225–226</td>
</tr>
<tr>
<td>West syndrome (infantile spasms)</td>
<td>182–183</td>
</tr>
<tr>
<td>white/grey matter and lobar volumes</td>
<td>125–126</td>
</tr>
<tr>
<td>Williams syndrome, local processing bias</td>
<td>239</td>
</tr>
<tr>
<td>Vineland Adaptive Behaviour Scale (VABS)</td>
<td>29, 354</td>
</tr>
<tr>
<td>visual learning style</td>
<td>376–377</td>
</tr>
<tr>
<td>voxel-based morphometry (VBM)</td>
<td>121–122</td>
</tr>
<tr>
<td>weak central coherence (WCC) theory</td>
<td>236–242</td>
</tr>
<tr>
<td>see also central coherence theory</td>
<td></td>
</tr>
<tr>
<td>central coherence theory</td>
<td>238–239</td>
</tr>
</tbody>
</table>