NEW TOOLS TO ENHANCE POSTTRAUMATIC STRESS DISORDER DIAGNOSIS AND TREATMENT
NATO Science for Peace and Security Series

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New Tools to Enhance Posttraumatic Stress Disorder Diagnosis and Treatment

Invisible Wounds of War

Edited by

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Preface

The organizers and attendees of the NATO-funded “Wounds of War” Advanced Research Workshop series realized the need for the 2012 NATO Advanced Study Institute: Invisible Wounds – New Tools to Enhance PTSD Diagnosis and Treatment (IW2012) due to the increased rates of PTSD in combat veterans and survivors of armed conflict. Exposure to traumatic events have led to this increased risk of PTSD and often, the serious consequences of this disorder lead to impulsive and destructive behaviours such as drug abuse, uncontrollable anger, and even suicide. Combat-related PTSD is one of the strongest contributing factors to high suicide risk in returning troops. IW2012 disseminated knowledge, emboldened skill sets, fostered collaborations and trained attendees to help counter this aforementioned internal threat to our countries’ security.

In comparison to a traditional conference, IW2012 allowed for greater collaboration among established and emerging research leaders in the field of PTSD, and provided an in depth presentation of this unique material. IW2012 afforded participants a solid grounding in the latest PTSD research; review of the latest science related to theoretical constructs and associated neuroscience; and presentation of the latest psychotherapy and pharmacotherapy for intervention, treatment, and management of this disorder.

Brenda K. Wiederhold, Ph.D, MBA, BCIA
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Editorial

Brenda K. Wiederhold, Ph.D, MBA, BCIA
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Introduction

Fifty-six scientists and representatives from NATO and Partner countries met in Ankara, Turkey from June 18-28, 2012 for the ten-day NATO Advanced Study Institute (ASI) titled “Invisible Wounds New Tools To Enhance Posttraumatic Stress Disorder Diagnosis And Treatment. (IW2012)” Formal scientific presentations were delivered by experts from nine different countries who were invited to take part in the ASI.

The meeting was divided into four scientific sessions:

1. Session I - “Review of the Latest Science Related to Theoretical Constructs and Associated Neurosciences”
2. Session II – “Screening”
3. Session III – “Stress Inoculation Training”
4. Session IV – “Co-morbid Issues: Considering the Whole Person in Treatment”

Papers and Presentations

In addition to their presentations, presenters submitted papers for publication in this volume in order to inform readers who were not in attendance at this year’s study institute about the latest research and rehabilitative techniques in the study of Combat-related PTSD.

The first section, “Review of the Latest Science Related to Theoretical Constructs and Associated Neurosciences,” discusses the latest PTSD research in “Brain Systems and Circuits in PTSD: Overview of Clinical Research Models.” The opening paper by Colonel Eric Vermetten and Dr. Ruth Lanius presents different methods that contributed to the working model of the neural circuitry of PTSD. The chapter focuses on the functional neuroimaging research conducted in PTSD by highlighting various techniques (SPECT, PET, and fMRI) and differing paradigms (resting, active tasks, stimulus presentation) which provides the reader a global overview of the current findings of these studies.

The second paper, “Biomarkers as New Tools to Improve the Diagnosis and Treatment of PTSD” by Professor Nela Pivac et al., discusses their research which attempts to determine different neurobiological, genetic and environmental risk factors which might be involved in the vulnerability and/or resilience to PTSD using Croatian male war veterans. The results indicate that specific PTSD biomarkers, associated with
the narrow clinical features, might be indicators of PTSD traits, state or progression, and might be used to improve the diagnosis and treatment of PTSD.

The second section continues with a discussion on PTSD screening. In “Early Identification of Risk for Posttraumatic Stress Disorder after Military Deployment,” Colonel Michael Roy reports on his iterative effort to educate military family members to recognize symptoms and facilitate intervention. In addition, preliminary results are discussed from direct longitudinal assessment of returning service members for development of PTSD. Their direct assessment of service members is unique in its comprehensiveness, and holds great promise for risk stratification.

Next, Professor Dragica Kozaric-Kovacic and Dr. Andrea Jambrosic Sakoman present results of previous PTSD studies as well as original research in search for psychophysiological indicators of PTSD in their paper “Psychophysiological Indicators and Biofeedback Treatment of Stress Related Disorders: Our Experience.” In addition, their promising experience with applied psychophysiology (biofeedback) as an add-on therapy is discussed.

In “Multimodal Paradigm for Mental Readiness Training and PTSD Prevention”, Professor Krešimir Cosić’s et al. proposes that a multimodal paradigm for cognitive-emotional elicitation, estimation and regulation may strengthen military training and enhance selection process. The paradigm includes multiple sessions involving mission-relevant audio-visual stimulation and simultaneous measurement of the trainee’s multimodal physiological, facial and vocal response.

Another paper led by Professor Krešimir Cosić’s et al. “Extreme Political Attitudes and Emotionally Based Strategic Communications” proposes using Emotionally Based Strategic Communications (EBSC) as a soft power for restoring political stability, security and prosperity in turbulent societies. The authors propose that emotional transformation based on the concept of dominant emotional maps may assist targeted groups or even entire societies to overcome their challenging political, social and security problems.

The third section, “Stress Inoculation Training”, begins with “Our Experiences in the Use of VR Technology in Therapy and Prevention of Combat Related Stress Disorders in the Polish Army” By Stanislaw Ilnicki et. al. This paper is a report on 5-year partnership between the Department of Psychiatry and Combat Stress (DP&CS) of the Military Institute of Medicine in Warsaw with the Virtual Reality Medical Center (VRMC) of San Diego, USA in implementation of VR technology in the area of protection of mental health of Polish Military Contingent’s (PMC) soldiers and veterans who participated in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).

The next chapter, “VR Stress Inoculation Training Results for Polish ISAF Soldiers – A Study of 4 Cases” by Ludmila Kosinska et al. evaluated the results of VR Stress Inoculation Training (SIT) for four soldiers preparing for their first mission in Afghanistan (ISAF) and assessed if their temperamental structure was related to successful training.

Justyna Maciolek’s et al. paper titled, “The Influence of Pre-Deployment VR Computer-Assisted Stress Inoculation Training on the Anxiety Level in the Polish ISAF Soldiers” evaluates the influence of Stress Inoculation Training (SIT) on the anxiety level measured by State-Trait Anxiety Inventory (STAI), both as temporary/emotional state anxiety (X1) and stable personality trait anxiety (X2) in soldiers preparing for their mission in Afghanistan (ISAF). It concludes that given the
equivocal results of the experiment, there is a need for a further study or a deeper analysis.

Next, in “Personality and Stress-Coping Factors in VR Computer-Assisted Stress Inoculation Training of Polish ISAF Soldiers” Maciej Zbyszewski et al. discuss a study that evaluated the impact of personality, temperament and stress coping factors in Stress Inoculation Training (SIT) in soldiers preparing for their first deployment to Afghanistan (ISAF). The results shown could be taken into account when analyzing individual susceptibility to SIT.

The fourth and final section is called “Co-morbid Issues: Considering the Whole Person in Treatment”. “Recent Advances in the Treatment of Comorbid PTSD and Substance Use Disorder” by Professor Mehmet Sofuoglu et al. conducted two clinical trials testing the safety and efficacy of medication treatments for comorbid PTSD and alcohol dependence (AD). The study suggested that norepinephrine uptake inhibitors may have efficacy for the treatment of comorbid PTSD and AD.

In “Secondary Traumatic Stress Among Wives of War Veterans”, Professor Tanja Frančišković et al. present a study that compares the level of present psychological symptoms and perceived quality of life between the wives of veterans with PTSD, without PTSD, and wives of non-veterans. They conclude that when planning the future interventions for PTSD affected veterans, a systemic approach should be considered not only to prevent secondary traumatic stress in partners of war veterans but also to enhance individual functioning of each partner and functioning as a couple.

The ultimate aim of IW2012 was to enhance attendees’ knowledge of the latest advances in assessment, diagnosis, prevention and treatment of posttraumatic stress disorder (PTSD) and related comorbid disorders in military populations. Overall, the conference was successful in increasing knowledge, disseminating information and communicating research results within the group of participants.

We are also grateful to Chelsie Boyd from the Virtual Reality Medical Institute for collecting and coordinating the chapters for this volume.
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Introduction to the 2012 NATO Advanced Study Institute  
*Professor Dr. Kresimir Cosic*

Introduction to the 2012 NATO Advanced Study Institute  
*Captain U. Feyyaz Aydogdu*

Introduction to Posttraumatic Stress Disorder  
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State of the Art: Brain Imaging  
*Colonel Dr. Eric Vermetten*

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Psychophysiological Indicators and Biofeedback Treatment of Stress-related Disorders: Our Experience  
*Professor Dr. Dragica Kozaric-Kovacic*

Multimodal Paradigm for Mental Readiness Training and PTSD Prevention  
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Extreme Political Attitudes and Emotionally Based Strategic Communications  
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Professor Dr. Mehmet Sofuoglu

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Supervised Practice of Attentional Retraining, Psychophysiology and VR
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Workshop organizers Interactive Media Institute and Virtual Reality Medical Institute would like to thank the sponsors of this Advanced Study Institute listed below. Without their support, this event could not have taken place:

- Centre of Excellence-Defence Against Terrorism
- Interactive Media Institute
- International Association of CyberPsychology, Training & Rehabilitation
- North Atlantic Treaty Organization (NATO)
- University of Zagreb
- Virtual Reality Medical Center
- Virtual Reality Medical Institute
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Section 1

Review of the Latest Science Related to Theoretical Constructs and Associated Neurosciences
Brain Systems and Circuits in PTSD: Overview of Clinical Research Models

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Abstract. One of the goals in research in the clinical neuroscience of trauma-related disorders is to apply findings related to the effects of traumatic stress in the brain on animals and patients with trauma and stressor-related disorders, e.g. PTSD. The paradigm of translational neuroscience has been an avenue that has contributed much to a model of the neural circuitry of PTSD that is currently used in studies. In general, the neural circuits and systems mediating symptoms of all PTSD, trauma and stressor-related disorders can be studied by registering and assessing behavioral and biochemical responses to environmental/pharmacological challenge to specific neurochemical systems measuring neurotransmitters and hormone levels in blood, urine, and saliva; measuring key brain structures with neuroimaging (Magnetic Resonance Imaging, MRI); provoking disease-specific symptoms in conjunction with (functional) neuroimaging (functional MRI, fMRI), or using imaging (Positron Emission Tomography, PET) to measure neuroreceptors. The findings of the studies (research designs, methodologies, and some of the techniques) will be discussed in this chapter varying to a great extent. Three key mechanisms seen in PTSD are: stress sensitization, fear conditioning and failure of extinction. This chapter further focuses on the functional neuroimaging research conducted in PTSD. It covers various techniques (SPECT, PET and fMRI) that are used in different kinds of paradigms (resting, active tasks and stimulus presentation) and provides a global overview of the brain circuits that currently are used to explain the phenomenology in PTSD. The disorder showed remarkable heterogeneity in some recent studies. These give consideration to speculate on two models for the disorder that can alternate and coexist together. These two models will be presented, one, in which the amygdala is hyperactive, in line with fear circuitry, being the most common and dominant situation. In another model the amygdala is hypoactive, in line with predominance of symptoms of derealisation and depersonalization symptoms that are accompanying the other PTSD symptoms. Finally, the need for longitudinal studies is emphasized. Studies that assess patients before as well as after treatment are the paradigm that will be new and promising.

Keywords. PTSD, brain, circuits, stress, trauma, MRI, amygdala, hippocampus

Introduction

PTSD is of particular interest in the 21st century, when the entire world is filled with the spectre of terrorism—a stress of great magnitude that can strike any time and anywhere. Also, a time when we again have many young soldiers returning from yet another war: the treacherous combat experience in Iraq and Afghanistan. Moreover, society is increasingly affected by various other types of human violence including, killing, rape, robberies and assault. To add, other psychological traumas such as, large-
scale natural disasters (hurricanes, floods), man-made disasters, train, plane and other accidents. These events can leave the individual with intense terror, fear, and paralyzing helplessness.

Over the last three decades there has been an expansion of studies on PTSD that have resulted in a significant increase in our knowledge of the prevalence, phenomenology and neurocircuitry of PTSD (e.g. [1], [2], [3]. The literature on this diagnosis is now vast. It goes far beyond the descriptive psychopathology upon which the original DSM-III definition was based. There are a multitude of papers covering topics such as, neural mechanisms (as revealed in imaging studies), risk factors, prevalence, comorbidity, symptom patterns, and outcome. Over 15000 scientific papers have been published on PTSD in the last 40 years, as well as numerous books and dissertations. This chapter will highlight the contribution from a neurobiological perspective and provides a brain circuitry that can contribute to an understanding of the symptomatology in cases of PTSD.

1. Towards DSM-5

The imminent redefinition of DSM-5 criteria for PTSD should reflect new advances in the science, conceptualization of the disorder and address the need of patients. The A1 Criterion was criticized about definition of ‘traumatic’. The new definition tightens up the A1 criterion to make a better distinction between ‘traumatic’ and events that are distressing but which do not exceed the ‘traumatic’ threshold. New findings do not support the inclusion of A2 as diagnostic requirement for DSM-V, so this will be likely left out of the new definition [4]. A new diagnostic cluster dividing C criterion will be introduced based on confirmatory factor analytic studies in: 1. Persistent avoidance of stimuli associated with the traumatic event(s) (that began after the traumatic event(s)), and: 2. Negative alterations in cognitions and mood that are associated with the traumatic event(s) (that began or worsened after the traumatic event(s)) [5] [6]. It is increasingly understood and recognized that PTSD is a heterogeneous disorder, which is resembled by a dissociative subtype for DSM-5 [7].

For DSM5, the proposed symptoms of PTSD are divided into four discrete and different categories:

A. Definition of the traumatic event;
B. Intrusion symptoms that are associated with the traumatic event(s) (that began after the traumatic event);
C. Persistent avoidance of stimuli associated with the traumatic event(s) (that began after the traumatic event(s));
D. Negative alterations in cognitions and mood that are associated with the traumatic event(s) (that began or worsened after the traumatic event)
E. Alterations in arousal and reactivity that are associated with the traumatic event(s) (that began or worsened after the traumatic event).
2. A Working Model for a Neural Circuitry in PTSD

Based on studies of the effects of stress on animals and emerging work in clinical neuroscience of PTSD, a working model for a neural circuitry of anxiety and fear that is also applicable to PTSD can be described. This model heavily leans on the work of Charney and Bremer [8, 9]. The brain structures that constitute a neurological working model for traumatic stress should have several features:

(1) Sufficient afferent input should be provided to permit assessment of the fear-producing nature of the event.
(2) The neuronal interactions among the brain structures must be capable of incorporation of a person's prior experience into the cognitive appraisal of stimuli.
(3) It is critical to effectively lay down memory traces related to a potential threat.
(4) Efferent projecting from the brain should be able to mediate an individual's neuroendocrine, autonomic and motor responses.

In the developmental trajectory of human fear or anxiety, afferent sensory input enters through the eyes, ears, nose, sense of touch, the body's own visceral information or any combination of these. These sensory inputs are relayed through the dorsal thalamus to cortical brain areas such as primary visual (occipital), auditory (temporal), or tactile (postcentral gyrus) cortical areas. Olfactory sensory input, however, has direct inputs to the amygdala and entorhinal cortex [10]. Input from peripheral visceral organs is relayed in the brainstem to the locus coerules, the site of the majority of the brain's noradrenergic neurons and from here to central brain areas.

These brain areas have projections to multiple areas including amygdala, hippocampus, entorhinal cortex, orbitofrontal cortex, and cingulate are involved in mediating memory and emotion [11]. Cognitive appraisal of potential threat is also an important aspect of the stress response. The cognitive response to threat involves placing the threatening object (man-knife) in space and time. Specific brain areas are involved in these functions (such as localizing an object in space, visuospatial processing, memory, cognition, action, or planning). The anterior cingulate gyrus (Brodmann area 32) is involved in selection of responses for action as well as emotion [12]. This area and other medial portions of the prefrontal cortex including area 25 and orbitofrontal cortex modulate emotional and physiological responses to stress and are discussed in more detail below.

In a prospective study with fMRI, we investigated central processes of exposure (appraisal) to war-related stress in soldiers before and after deployment to a combat zone. As expected, combat stress increased amygdala and insula reactivity to biologically salient stimuli across the group of combat exposed individuals. Yet, in contrast, its influence on amygdala coupling with the insula and dorsal anterior cingulate cortex (dACC) was dependent on perceived threat rather than actual exposure, which suggested that threat appraisal affects interoceptive awareness and amygdala regulation. Interestingly, combat stress had sustained consequences on neural responsiveness, which, suggested there is a key role for the appraisal of threat on an amygdala-centered neural network in the aftermath of severe stress [13].

Another important aspect of the stress response is incorporation of a person's prior experience (memory) into the cognitive appraisal of stimuli. For example, if you are approached in a potentially threatening situation, it will be important to determine whether the face of the person is someone known to you or is a stranger who may be
more threatening. In addition, it is important to place the situation in time and place. Entering a dark alleyway may trigger prior memories of being robbed, with associated negative emotions and physiological arousal. These memories may have survival value, in that the individual will avoid the situation where the previous negative event took place. Finally, it is critical to effectively lay down memory traces related to a potential threat in order to avoid this type of threat in the future.

Critical brain structures involved in mediating anxiety and fear behavior resulting from traumatic stress are locus coeruleus (LC) (the ‘alarm bell’ of the central nervous system), the hippocampus (the memory and stress regulator), the amygdala (the ‘significance’ provider), the prefrontal cortex (the execution and planning station), the thalamus and hypothalamus (central relaying and integrative limbic structures), the periaqueductal grey nervous matter (PAG), that will contribute to three basic neural mechanisms, (see figure 1) discussed below:

1. Behavioral sensitization or stress sensitisation
2. Fear conditioning
3. Failure of extinction

Figure 1. Schematic overview of major biological circuits and systems in PTSD. The three to three basic neural mechanisms of fear conditioning, extinction and behavioral or stress sensitization are projected in the major contributing brain structures.

2.1. Behavioral Sensitization (Stress Sensitisation)

Insomnia, poor concentration, hypervigilance, and exaggerated startle response are traits related to the increased susceptibility to stimuli in patients with PTSD. Sensitization may be defined as an increase in a certain response due to the presentation
of a specific stimulus [14]. It refers to ‘the observation that individuals that are repeatedly exposed to an environmental risk factor may develop progressively greater responses over time, finally resulting in a lasting change of response amplitude’ [15]. Furthermore, sensitisation is a biological term that can explain common mechanisms linking multiple environmental effects. In other words, factors in the behavioural, physical and neurochemical areas can all induce such changes. Therefore, the repeated presentation of a stimulus has the capacity to progressively increase the amplitude of the response of a particular physiological system.

In military, veterans with PTSD for example witnessed a traumatic event, or series of events they thought to cause the onset of PTSD. The typical PTSD patients becomes more aroused and hypervigilant, among other characteristics than a healthy or control individuals when presented with trauma-related stimuli. It is the prior experience or the recurrent experience of traumatic occurrences that facilitates or sensitized this process. It is therefore possible to state that PTSD is a certain type of behavioral sensitization in which, trauma exposure causes the onset of increased stress sensitivity. The kindling hypothesis has been used by Post and Weiss in 1998 to explain the underlying pathophysiological mechanisms during the emergence of progressive limbic abnormalities and diseases such as, depression and posttraumatic stress disorder [16].

The neural circuitry underlying the increased sensitivity to stress is not centralized to a specific anatomical or functional neurological component because sensitization is a very broad concept and even occurs at cellular levels throughout the body. In patients with PTSD, the (over-)sensitization is more vivid in the structures and mechanisms involved in the stress response as described earlier. An example of this is, the glucocorticoid mechanism- a well investigated model in PTSD of sensitization in patients with PTSD [17, 18], making them more sensitive or susceptible to stress.

2.2. Fear Conditioning

Among the most characteristic feature of PTSD is that ‘anxiogenic’ memories (e.g. traumatic experience) can remain indelible for years or decades and can be reawakened by various sorts of stimuli and stressors. The strength of traumatic memories relates in part to the degree to which certain neuromodulatory systems, particularly catecholamines and glucocorticoids, are activated by the traumatic experience [19]. Release of these stress hormones modulates the encoding of memories of the stressful event. Experimental and clinical investigations provide evidence that memory processes remain susceptible to modulating influences after information has been acquired. Long-term alterations in these catecholaminergic and glucocorticoid systems may also be responsible for symptoms of fragmentation of memories but also for hypermnesia, amnesia, deficits in declarative memory, delayed recall of trauma or abuse and other aspects of the wide range of memory distortions in anxiety disorders. With long-term storage, memories are shifted from hippocampus to the neocortical areas where the initial sensory impressions take place. The shift in memory storage to the cortex may represent a shift from conscious representational memory to unconscious memory processes that indirectly affect behavior. ‘Traumatic cues’ such as a particular sight or sound reminiscent of the original traumatic event can trigger a cascade of anxiety and fear-related symptoms will ensue often without conscious recall of the original traumatic event [20], [21]. In patients with PTSD, however, the traumatic stimulus is always potentially identifiable. Symptoms of anxiety in panic or
phobic disorder patients however, may be related to fear responses to a traumatic cue (in individuals who are vulnerable to increased fear responsiveness, either through constitution or previous experience), where there is no possibility that the original fear-inducing stimulus will ever be identified.

Thus, patients with PTSD have symptoms that reflect a more or less continuous perception of threat with unconscious processed fear responses. The animal model of contextual fear conditioning represents a good model for these symptoms. Preclinical data suggest that the hippocampus (as well as BNST and periaqueductal grey) plays an important role in the mediation of contextual fear and that increased responding to CS- is due to hippocampal dysfunction. Hippocampal atrophy in PTSD therefore provides a possible neuroanatomical substrate for abnormal contextual fear conditioning and chronic symptoms of feeling of threat and anxiety. Interestingly, in light of studies showing abnormal noradrenergic function in PTSD, the BNST has some of the densest noradrenergic innervation of any area in the brain.

The startle reflex has been the subject of the few fear conditioning studies that have been performed in humans [22]. Startle is a useful method for examining fear responding in experimental studies involving both animals and humans that is mediated by the amygdala and connected structures. Patients with combat-related PTSD were found to have elevated baseline startle compared to controls in some studies but not others. In the patients group there was asymmetry of baseline startle response and increased heart rate responses during measurement of startle. From other studies, it becomes quite clear that unconscious emotional processes are involved in fear conditioning (e.g. patients with anxiety disorders) have demonstrated greater resistance to extinction of conditioned responses to angry facial expressions but not to neutral facial expressions compared to controls. In the neural circuitry, damage to the amygdala does not prevent patients from learning the relationship between the CS and the UCS, but it abolishes conditioned autonomic responses. In contrast, damage to the hippocampus does not affect conditioned autonomic responses but does prevent learning of the CS-US association. Further evidence for unconscious processes stems from backward masking techniques which prevents conscious awareness of a stimulus. Using such a technique, fear conditioning to a certain class of stimuli called fear-relevant stimuli (e.g., spiders and snakes) proves to be mediated by pre-attentive automatic information processing mechanisms. These automatic mechanisms may be mediated in part by direct thalamic-amygdala connections. Thalamo-amygdalar pathways that bypass the cerebral cortex may trigger conditioned responses before the stimulus reaches full awareness, providing an explanation for unconscious conditioned phobic responses to fear-relevant stimuli.

2.3. Failure of Extinction

The process of fear extinction is closely linked to the conditioning of fear. When a person is exposed to a normally dangerous situation from which no aversive events result, this situation elicits a smaller fear response than before. In patients with PTSD, this process does not occur efficiently and fear of certain situations fails to extinguish. In military veterans this may be identified by persistent, fearful responses to large, noisy crowds, fireworks and doors slamming among other forms of traumatic recall. Therefore, some permanence in fear conditioning in patients is strengthened by a dysfunction in the extinction of fear. Ultimately, this can be the cause of the persistence of the traumatic memories. The neural mechanisms involved in the extinction of fear
greatly overlap with those involved in fear acquisition as just described[23]. In fact, the main structures involved in the extinction of fear are the medial prefrontal cortex and the amygdala. NMDA receptors and voltage-gated calcium channels are essential to extinction processes. Other systems include the neurotransmitters gamma-aminobutyric acid (GABA), norepinephrine, and dopamine. During a fearful response of the amygdala, the mPFC is activated and modulates the initial response to the threat. In this manner, fear is contained and managed accordingly. If this prefrontal activation is absent or occurs to a lesser extent, the amygdala does not receive sufficient inhibitory feedback resulting in higher autonomic arousal and exaggerated responses, as we see in patients with PTSD (see figure 2) [24]. The amygdala–mPFC connection (feedback process) is thought to be mediated by GABA interneurons, which may be malfunctioning in PTSD [25].

Figure 2. Sequential slices of PET study showing a mPFC dysfunction in a traumatic recall paradigm. There is a decreased function in medial prefrontal cortical areas, the anterior cingulate cortex (BA 25, BA 32) in veterans with PTSD compared to veterans without PTSD during viewing of combat-related slides and sounds (Bremner et al., 1999).

3. Functional neuroimaging techniques contributing to a brain neurocircuitry in PTSD

The advent of modern structural and functional imaging techniques has opened a great window of opportunity for conducting neurological research in human patients. As stated before, in the past years such techniques have been used to reveal whether the hypotheses about changes in the brain in PTSD, made in the 1990s by Charney et al. [9] and Bremner et al. [25] were accurate. In later publications by the same authors, hypotheses supported by preclinical data are discussed in relation to research findings in human subjects [26] [27]. These updates include neural structures, circuits, and functions that are altered in patients with PTSD. Although there is no definitive pathophysiology for PTSD and its biological cause, many theories that have been developed remain closely tied to the mechanisms from the preclinical findings.

Functional neuroimaging techniques are a relatively recent development in the field of neurological research. There are various ways to measure the activity that takes place in the brain, all based on different principles. Such techniques include SPECT, PET, and fMRI. These three techniques derive brain function indirectly from physiological measures such as cerebral blood flow, blood oxygen levels, and energy consumption. The assumption related to these techniques is that glucose metabolism and blood flow, among other parameters, alter when certain brain areas become activated or inhibited. When neural cells fire, their increase in activity requires a
restoration of the energy they used. It is thought that the metabolic demands by such neurons result in an increased blood flow to these areas. Hence, these methods interpret physiological measures to deduce brain activity. Both SPECT and PET make use of rCBF and neuroreceptor concentration, whereas fMRI makes use of the blood oxygen level–dependent (BOLD) signal to show patterns of activity in the brain.

3.1. Structural Neuroimaging with Magnetic Resonance Imaging

Over the last decade a significant number of studies have reported smaller hippocampal volume in individuals with symptoms of post-traumatic stress disorder (PTSD) relative to control groups [28, 29] (see figure 3). This line of research was prompted by studies in animals showing that high levels of cortisol seen during times of stress are associated with damage to the hippocampus. These studies we first reported when spatial resolution of MRI was still low. Frist studies were repeated in veterans with PTSD [30], and females with sexual abuse related PTSD [31]. Interesting was that the magnitude of the reduction in hippocampal volume was associated with magnitude of deficits in short-term verbal memory [30], and observation that has been made by other later as well [32, 33]. Since then studies have improved accuracy and subject composition. Smith performed a meta-analysis and found on average that PTSD patients had a 6.9% smaller left hippocampal volume and a 6.6% smaller right hippocampal volume compared with control subjects [34]. These volume differences were smaller when comparing PTSD patients with control subjects exposed to similar levels of trauma, and larger when comparing PTSD patients to control subjects without significant trauma exposure.

![Figure 3](image.png)

**Figure 3.** Comparison of two MRIs of sections through brain, showing hippocampal volumes (left a healthy subject, right a patient with PTSD). The presumed hypothesis is that stress results in decreased hippocampal neurogenesis resulting in a loss of branching and decreased volume. Hippocampal volume is strongly correlated with verbal declarative memory. Recent meta-analyses showed associations between PTSD and memory impairment, stronger for verbal than visual memory.

3.2. Functional Neuroimaging

Sophisticated techniques have been developed for the measurement of cerebral activity, such as single photon emission tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), and to a lesser extent electro-encephalography (EEG), an earlier technique for monitoring brain activity. Each technique has its own advantages and each provides different information about brain function. Advances in all these techniques have enabled us to produce detailed images of brain structures, and observe neurochemical changes that occur in the brain as it processes information, or responds to various stimuli such as recollections of traumatic events.
With fMRI, it can be determined with greater precision when brain regions become active and how long they remain active. As a result, it can be seen whether brain activity occurs simultaneously or sequentially in different brain regions as a patient responds to experimental conditions. FMRI scans can produce images of brain activity as fast as every second, whereas the temporal resolution of PET is much larger. Thus, with fMRI, it can be determined with greater precision when brain regions become active and how long they remain active. As a result, it can be seen whether brain activity occurs simultaneously or sequentially in different brain regions as a patient responds to experimental conditions. An fMRI scan can produce high-quality images that can pinpoint in detail which areas of the brain are being activated. So far data obtained with fMRI and PET have been very similar. PET has a number of limitations, such as a low temporal resolution due to signal averaging during 1 minute, the need for group analysis pooling the data of at least five to eight subjects to obtain meaningful results, the need for a nearby cyclotron to prepare short-lived radioactive tracers, and the need to give intravenous injections to subjects. Compared to PET, fMRI provides superior image clarity along with a noninvasive ability to assess blood flow and brain function in seconds. On the other hand, PET has less technical problems related to noise and claustrophobia (due to a larger opening of the PET gantry). In addition, another drawback of fMRI is the requirement of MRI-compatible equipment, restricting the ability to perform simultaneous psychophysiology measurements, as well as creating the need for strict timing between stimuli and acquisition in rapidly alternating conditions.

Positron emission tomography (PET) requires the injection of radioactive compounds into the blood circulation of the subject to measure blood flow, glucose uptake, or receptor availability. In PET studies $H_2^{15}O$ provides a good measure of immediate changed to cerebral blood flow. Cerebral blood flow has been shown to be highly correlated with local cerebral glucose metabolism. Since neurons almost exclusively utilize glucose for cell processes, glucose utilization provides a measure of local neuronal activity. Studies in PTSD have begun to use PET during pharmacologic and cognitive provocation of symptom states in order to identify neural correlates of PTSD symptomatology and of traumatic remembrance.

PET and fluorodeoxyglucose (FDG) was also used in the measurement of cerebral glucose metabolic rate following administration of yohimbine and placebo in Vietnam combat veterans with PTSD and healthy controls. Since the Vietnam was veterans returned with a clinical presentation of agitation, arousal and anxiety one of the first biological models of PTSD was an increased noradrenergic function to underlie many of the symptoms of PTSD [35]. Administration of the $\alpha_2$-antagonist yohimbine, which stimulates brain norepinephrine release, resulted in increased PTSD symptoms and anxiety in the PTSD group [36]. Norepinephrine has a U-shaped curve type of effect on brain function, with lower levels of release causing an increase in metabolism, while very high levels of release actually cause a decrease in metabolism. It was hypothesized that yohimbine would cause a relative decrease in metabolism in patients with PTSD in cortical brain areas which receive noradrenergic innervation. Indeed, yohimbine resulted in differences in metabolism in orbitofrontal, temporal, parietal, and prefrontal cortex in PTSD patients relative to controls, with PTSD patients showing a pattern of decreased and normal subjects a pattern of increased metabolism in these areas. PTSD patients (but not normal subjects) had decreased hippocampal metabolism with yohimbine [36].
Later, several studies have started using PET H2[15O] and also with fMRI techniques in challenge paradigms. These include traumatic scripts, presentation of sounds, images, or smells [37]. In a classical study of combat-related PTSD using PET and H2[15O] measurement of cerebral blood flow, ten Vietnam veterans with PTSD and ten Vietnam veterans without PTSD were studied during exposure to combat-related and neutral slides and sounds. Vietnam veterans with combat-related PTSD (but not non-PTSD veterans) demonstrated a decrease in blood flow in the medial prefrontal cortex (Brodmann's area 25, or subcallosal gyrus) and middle temporal cortex (auditory cortex) during exposure to combat-related slides and sounds. A failure of activation was found in anterior cingulate (area 32 and 24), and increased activation in posterior cingulate, motor cortex, and lingual gyrus in PTSD veterans [24]. In a similar study, cerebral blood flow correlates of exposure to personalized scripts of childhood sexual abuse were looked at in women with histories of childhood abuse with (n=10) and without (n=12) PTSD. PTSD women showed decreased blood flow in medial prefrontal cortex (area 25) and failure of activation in anterior cingulate, with increased blood flow in posterior cingulate and motor cortex (replicating findings in combat-related PTSD) and anterolateral prefrontal cortex. PTSD women also had decreased blood flow in right hippocampus and parietal and visual association cortex [38]. Other studies of traumatic imagery in combat-related PTSD found alterations in orbitofrontal and temporal cortex in PTSD [39, 40], see review [41].

Another field is receptor imaging in PTSD. Based on findings of decreased benzodiazepine binding in frontal cortex in animal models of stress, we measured benzodiazepine binding with PET and found reduced [11C]-flumazenil binding throughout most of the cortex [42]. This was consistent with an earlier [123I]-iomazenil SPECT study in Vietnam veterans with PTSD [43]. This may be indicative of an a priori difference in subunit composition of GABA_\_A - benzodiazepine receptors, a lower expression of the GABA_\_A receptor in PTSD patients, or a disease or trauma induced modulation or downregulation of the GABA_\_A receptor complex. These explanations are consistent with other clinical studies that have suggested altered GABA-ergic function in PTSD [44, 45].

4. Heterogeneity of Response to Traumatic Reminders

It was Bremner (1999) who proposed the presence of two subtypes of acute trauma response that represent unique pathways to chronic stress-related psychopathology: one is primarily intrusive and hyperaroused with a concomitant increase in heart rate and can be seen as a form of emotional undermodulation. The other is predominantly dissociative [46]with no concomitant increase in heart rate and can be viewed as a form of emotional overmodulation. Data from psychophysiological and neuroimaging studies have shown that a variety of response types can persist in individuals with chronic PTSD and are associated with distinct neural correlates in response to recalling traumatic memories [47-54].

Approximately 70% of patients in studies typically report experiencing their traumatic event in response to traumatic script-driven imagery concomitant with psychophysiological hyperarousal [7, 55, 56]. Yet, there is often minority, the remaining 30% of PTSD subjects, that experiences depersonalization, derealization and a feeling of emotional detachment while evidencing no significant increase in heart rate. We emphasize the state-related nature of these response patterns, specifically, that
individuals with PTSD may show both types of responses during different episodes or even distinct time points within a single episode. Nevertheless, PTSD patients with histories of prolonged trauma, such as occurs in childhood maltreatment or combat trauma often show a clinical syndrome that is characterized by chronic symptoms of dissociation as opposed to patients who have suffered from more acute traumatic experiences during adulthood.

4.1. Emotional Undermodulation: Failure of Corticolimbic Inhibition

PTSD individuals who re-experienced their traumatic memory and showed concomitant psychophysiological hyperarousal exhibited abnormally low response in brain regions that are implicated in arousal modulation and emotion regulation, including the medial prefrontal- and the rostral anterior cingulate cortex. Consistent with impaired top-down cortical modulation, decreased response within the ventromedial prefrontal cortex and increased response within the limbic system, especially the amygdala has been one of the most replicated findings in individuals with PTSD after exposure to traumatic script-driven imagery, as well as to masked fearful faces [57].

When taking a dimensional approach to individual differences in re-experiencing symptoms and associated neural response patterns in response to trauma reminders, results have shown that severity of state re-experiencing was positively correlated with response in the right anterior insula, a brain region that is involved in the neural representation of somatic aspects of emotional states and interoception of feeling states. In contrast, state re-experiencing was negatively correlated with response of the rostral portion of the anterior cingulate cortex (BA 32) [49]. This finding further supports the top-down cortical modulation model because, as discussed above, rostral anterior cingulate reactivity is a powerful modulator of regions involved in conditioned emotional responses.

The findings described above are consistent with the phenomenology and clinical presentations of individuals with PTSD who exhibit pathological emotional undermodulation during re-experiencing states. Such re-experiencing states often also include a wide variety of negative emotional states, such as anger and guilt. We conceptualized this group of individuals as experiencing emotional undermodulation in response to traumatic memories leading to subjective reliving experiences of the traumatic events, such as experiencing a flashback or acting or feeling as if the traumatic event was recurring. Re-experiencing/ hyperarousal reactivity and related emotional states such as anger and guilt can therefore be viewed as a form of emotion dysregulation that involves emotional undermodulation, mediated by failure of prefrontal inhibition of limbic regions [7].

4.2. Emotional Undermodulation and Failure of Corticolimbic Inhibition: Implications for Generalized Affective Disturbance in PTSD

Neuroimaging studies in PTSD have begun to move beyond solely focusing on fear-specific stimuli and situations and have begun to encompass other affective disturbances. Responses to recall imagery of non traumatic sad and anxious memories in PTSD was first associated with decreased response in the rostral anterior cingulate cortex and thalamus similar to what was found during recall of traumatic memories [58]. A further study reported decreased ventromedial prefrontal cortex response and
decreased amygdala response during viewing of negatively valenced/aversive pictures [59]. A recent study examining deliberate emotion regulation in PTSD showed that deliberate successful attempts to downregulate emotional responses to negative pictures was more successful in non-traumatized healthy controls as compared to subjects with a history of sexual assault with and without PTSD, and that success was associated with increased response of prefrontal regions in the non-traumatized group [60]. These studies therefore not only provide support for failure of cortical inhibition during the processing of non traumatic stimuli, but also suggest affective disturbances and emotion dysregulation extend to non-trauma-related stimuli in trauma-exposed individuals with and without PTSD. Future psychobiological research will have to closely examine the neural correlates underlying grief, anger, guilt, and shame in PTSD and their relationship to the neural circuitry involved in adaptive emotion regulation.

4.3. Emotional Overmodulation: Excessive Corticolimbic Inhibition

In contrast to the re-experiencing/hyperaroused group of chronic PTSD patients, the dissociative group exhibited abnormally high response in brain regions involved in arousal modulation and emotional regulation, including the rostral anterior cingulate cortex and the medial prefrontal cortex. It is interesting to note that the medial prefrontal cortex cluster (peak MNI 4, 54, 12) that shows increased response during states of dissociation is in close proximity to the medial prefrontal cortex cluster (peak MNI 10, 52, 2) that was associated with decreased cerebral blood flow during trauma imagery and found to be negatively correlated with amygdala response in the study by Shin and colleagues [61, 62]. Consistent with the corticolimbic disconnection model of depersonalization [63], the findings of increased medial prefrontal cortex response during states of dissociation in PTSD may reflect medial prefrontal inhibition of the amygdala and other limbic activity. The dissociative PTSD patients can be conceptualized as experiencing emotional overmodulation in response to exposure to traumatic memories. This can include subjective disengagement from the emotional content of the traumatic memory through depersonalization, derealization, and emotional numbness mediated by midline prefrontal inhibition of the limbic regions (see figure 4).

<table>
<thead>
<tr>
<th>Dissociative subtype of PTSS</th>
<th>PTSD</th>
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<tbody>
<tr>
<td>Etiology</td>
<td>More often complex, chronic, multiple trauma, early life trauma as well as adult trauma</td>
</tr>
<tr>
<td>Reaction after exposure to traumatic reminder</td>
<td>- dissociation, numbing ('zone out') - decreased autonomic arousal - decreased heart frequency - cortisol production dampened</td>
</tr>
<tr>
<td>Phenomenology</td>
<td>Dissociation (derealisation/depersonalisation)</td>
</tr>
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Dimensionally, dissociative responses to trauma reminders are negatively correlated with right anterior insula response [49]. Interestingly, the right anterior insula positively correlated with state re-experiencing symptoms. Dissociative response positively correlated with response in the medial prefrontal cortex and dorsal anterior cingulate cortex. The left medial prefrontal cortex cluster (peak MNI -12, 50, 4) that was positively correlated with state dissociative symptoms is, aside from laterality, in very close proximity to the right medial prefrontal cluster (peak MNI 10, 52, 2) previously negatively correlated with amygdala activity during script-driven imagery [61]. This finding thus provided support for hypothesized hyperinhibition of limbic regions by medial prefrontal areas in states of pathological overmodulation; i.e., during dissociative states in response to trauma-related emotions.

A study by Felmingham et al. [64] gave further support to the corticolimbic inhibition model. Using fMRI, these investigators examined the impact of dissociation on fear processing in two groups of PTSD patients, one with high, and the other with low dissociation scores. Felmingham et al. compared brain response during the processing of consciously and non-consciously perceived fear stimuli. Patients with PTSD who experienced higher levels of dissociation showed enhanced response in the ventral prefrontal cortex during conscious fear processing, as compared to patients with PTSD and low levels of dissociation. The authors suggest that these data support the theory that dissociation is a strategy invoked to cope with extreme levels of arousal in PTSD through hyperinhibition of limbic regions, with this strategy most active during conscious processing of fear.

Additional evidence for hyperinhibition of the limbic system, including the amygdala, during dissociative states stems from an examination of the neural correlates underlying pain processing in healthy and disease states. In a study examining healthy individuals, Roder et al. ([65]2007) demonstrated decreased amygdala response in response to painful stimulation during hypnosis-induced states of depersonalization. These findings are also consistent with amygdala response to thermal pain stimuli in patients with PTSD as well as in patients with Borderline Personality Disorder and
comorbid PTSD, who generally show high levels of dissociation and analgesia to painful stimuli [66-69] (Schmah et al., 2008; Geuze et al., 2007; Kraus et al., 2009). A recent study revealed a similar pattern of increased mid-cingulate and insula response in patients with borderline personality disorder and comorbid PTSD in conjunction with reduced pain sensitivity during script-induced dissociative states (Ludaescher et al., in press). Future research will need to examine to what extent hyperinhibition of limbic regions underlies reduced pain sensitivity/analgesia to painful stimuli often observed in patients with PTSD.

5. Concluding Remarks

Three decades of PTSD research have placed it on the map. This calls for an orientation where the new research investments should go. Future studies will need to focus on estimating age-at-onset distributions, cohort effects, and the conditional probabilities of PTSD from different types of trauma. These future epidemiologic studies will also need to assess PTSD for all lifetime traumas rather than for only a small number of retrospectively reported "most serious" traumas. As for the neurobiology and treatment of the disorder, the wealth of laboratory research and animal models has helped us understand the pathophysiology of the disorder.

Preclinical and clinical investigations provide strong evidence for linking several brain structures to the signs and symptoms of anxiety and fear associated with trauma. Critical structures are the amygdala, hippocampus, thalamus, periaqueductal gray, and orbitofrontal cortex. Although there were no published studies on imaging in PTSD as recently as 15 years ago, since that time there has been a rapid growth of studies in this area. This is in part due to a growing appreciation of the neurobiological contributions to PTSD. Also, technical developments have enabled complex designs. Spatial resolution has improved much, and structures that before 10 years were not able to be visualized, e.g. amygdala, have now led to a new focus in many studies. It is predicted that the field is becoming saturated in terms of demonstrating the validity as well as the neural circuitry of the disorder, and that the focus in the next decade will be on longitudinal studies that enable phenotypical comparison with functional imaging findings.

The increased capabilities of the imaging techniques, including improved spatial resolution but also by the increased availability of scanning equipment in smaller research institutes, the knowledge of the altered brain function in PTSD increase. Given the specific role of the prefrontal cortex in (neuro-) psychological functions in patients with PTSD (i.e., attention and cognitive interference) will play the role of the prefrontal cortex in interest increase significantly. Increased multidisciplinary with inclusion of genetics, endocrinology, immunology, (neuro-) psychology and psychopathology is essential to find consistency between biological, emotional and cognitive dysfunction in PTSD. Related to this, longitudinal studies are essential to assess the relationships between stress parameters and clinical phenotype of PTSD. This is true for the DST super suppression e.g., stress reactivity, hypocortisolaemia, and hippocampal (neuro-genetic) changes, but also for memory function and neuro-cognitive mechanisms. The deployment of new and existing drugs in PTSD, including specific serotonergic agents such as 5-HT1A antagonists, NA-blockers, CRF antagonists, GC-receptor antagonists, prazosin and α1-adrenergic blocker with nightmares, use of β-blockers early after trauma exposure will be investigated [70]. Treatment options such as D-cycloserine and cortisol seem to offer opportunities to the
memory of traumatic experiences to influence, in timed and careful therapeutic dosage in relation to exposure. Finally, the mechanisms of exposure therapy and cognitive therapy in influencing neurobiological markers should be further investigated. The same goes for emerging therapies such as EMDR, virtual reality exposure, Internet therapy and neurofeedback [71].

The first three decades since inclusion in DSM-III have been characterized by the urge to seek acknowledgement for those suffering from the consequences psychotrauma through biological validation of the disorder. Yet, cross-sectional studies do not qualify for causal relationships no matter how carefully the health of trauma control populations is matched. The field has also taken some hits e.g. by weak study designs not controlling for trauma exposure, and the unreliability of memory recollections about exposure and symptoms.

This paper has not focused on peripheral regulation of stress. Yet, one of the major and earliest postulates in PTSD has been the HPA axis hypersensitivity hypothesis, namely a failure to mount sufficient levels of circulating cortisol at the time of the traumatic event to the occurrence of PTSD. Essentially no studies have looked at this proposition in a true prospective design. To test this, our group prospectively looked if GR expression could be a risk factor for the development of post-traumatic stress disorder symptoms. We assessed whether pre-deployment GR binding capacity differed between soldiers with and without PTSD symptoms after deployment to a combat zone. Included were soldiers who reported high levels of PTSD symptoms a half-year after deployment (n=34) and an equal number of soldiers without high levels of PTSD or depressive symptoms. Highly interesting was our finding that before deployment, GR expression in PBMCs was significantly increased in participants with high levels of PTSD symptoms after deployment as compared to matched controls. The risk for a high level of PTSD symptoms after deployment increased 4.8-fold with each increase of 1000 GR binding sites, demonstrating that increased pre-trauma GR binding capacity of PBMCs is a vulnerability factor for subsequent development of PTSD symptoms [72, 73]. Additionally, the predeployment GR number positively correlated with amygdala reactivity post deployment in a fMRI study [74].

6. Perspective

The field of psychiatry appears to be finally coming to terms with the fact that traumatic stress can result in chronic psychiatric disorders, including PTSD. We may be ready to go beyond the thinking inherent in the gross stress reaction of DSM-I, which described a reversible mental response to stress that can affect anyone and does not constitute a true psychiatric disorder. These changes have been partially driven by the finding, surprising to many, that events, which enter the eye, and the ear (trauma) can have lasting effects on the brain and physiology. In PTSD, we are still at the crossroads between mind and brain, and this field is challenging the breakdown between the artificial distinctions between psychology and biology. This will bring us back to the viewpoint originally encompassed by DaCosta in 1871 and Kraepelin in 1919 that mental disorders have their basis in the brain.

The more traumatic stress is examined, the more it becomes apparent that traumatic stress may have also far-reaching influences on all of the major psychiatric disorders. This has led to a tendency for PTSD and the stress response to become like a fast-moving train that threatens to take along everything in its path. In fact, workers in the
field of PTSD are now in danger of being victimized by their own success. Once again, psychiatrists may be asked to bear the responsibility for the unfairness and discrepancies of our society. The challenge in the future will be to determine the most appropriate way to use our psychiatric nomenclature to describe the relationship between environmental events such as extreme stress and psychopathology.

It is for future studies to translate these findings into models for optimal pharmacotherapeutic interventions that can be combined with psychological treatments for alleviation of symptoms, reduction of medical consumption, and better quality of life for patients currently suffering from PTSD -- since it is not likely that traumatic stress will be eliminated from our society.

References


Biomarkers as New Tools to Improve the Diagnosis and Treatment of PTSD

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Abstract. PTSD is a serious and debilitating psychiatric disorder that can develop in individuals who were exposed to one or more intense traumatic event(s). Since not all people exposed to traumatic experience develop PTSD, it is assumed that different neurobiological, genetic and environmental risk factors are involved in the vulnerability and/or resilience to PTSD. PTSD biomarkers, defined as characteristics that objectively measure and evaluate normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, might improve the diagnosis and treatment of PTSD.

Determined biomarkers were peripheral biochemical markers such as platelet serotonin (5-HT) concentration, platelet monoamine oxidase type B (MAO-B) activity, plasma dopamine-beta-hydroxylase (DBH) activity, and genetic markers MAO-B intron 13, -1021C/T DBH, catechol-o-methyltransferase (COMT) val158/108met, brain-derived neurotrophic factor (BDNF) val66met, 102T/C serotonin receptor type 2A gene (5HT2A) polymorphism and serotonin transporter (5HTT) gene-linked polymorphic region (5HTTLPR). Study participants were Croatian male war veterans with or without current and chronic combat-related PTSD, recruited from the Referral Centre for the Stress-related Disorders of the University Hospital Dubrava, Zagreb. Only plasma DBH activity, but not other markers, differed significantly between war veterans with or without PTSD. When veterans were subdivided according to the narrow clinical symptoms (such as psychotic features, sleep disturbances, suicidal behavior), platelet 5-HT concentration, platelet MAO-B activity, and val66met BDNF were significantly different among these groups. The results indicate that specific PTSD biomarkers, associated with the narrow clinical features, might be indicators of PTSD traits, state or progression, and might be used to improve the diagnosis and treatment of PTSD.

Keywords. PTSD; War veterans; Biochemical markers; Genes; Narrow clinical features; Polymorphisms, Risk factors
Introduction

PTSD

Post-traumatic stress disorder (PTSD) is classified as an anxiety disorder, or as a stress related disorder, depending on the classification used (DSM-IV; ICD-10). It is the only mental disorder that occurs following an exposure to a traumatic event or a series of traumatic events. PTSD is highly comorbid with other psychiatric disorders such as depression, anxiety disorders, alcohol or drug abuse and dependence [1, 2]. In addition, PTSD is comorbid with various somatic diseases such as cardiovascular diseases, headaches, diabetes, respiratory diseases /asthma/, gastrointestinal problems, and musculoskeletal disorders [1, 3-10]. These comorbid psychiatric and somatic disorders add to higher morbidity and mortality in PTSD subjects. It is a serious and debilitating disorder associated with the significant social and functional impairments, financial burden to the affected families and to the whole society. In the vulnerable individuals who develop PTSD, the traumatic experience is associated with a fearful reaction, which lasts more than 30 days and is accompanied by the presence of symptom clusters: re-experiencing the trauma, numbing and avoidance, and persistent hyperarousal. Although the diagnostic criteria for PTSD include an exposure to one or more traumatic events, PTSD occurs only in some of the persons exposed to trauma [11-13]. Therefore, the dysregulation of several biological systems, together with complex interactions between environmental, psychological and neurobiological factors, have been implicated in the abnormal response underlying the pathophysiology of PTSD. In addition, genetic background might add to increased vulnerability for PTSD [14, 15]. The etiology of PTSD, like of other complex disorders, is believed to be elicited by multiple factors and multiple genes. Although PTSD represents an exaggerated reaction to a traumatic experience, it has been reported that PTSD might indicate stress vulnerability [16, 17]. Most often studied biological systems involved in the etiology of PTSD are neuroendocrine systems /corticotrophin releasing hormone (CRH) and hypothalamic–pituitary–adrenal axis activity/, neurotransmitter systems /noradrenergic, serotonergic, glutamatergic/ and neurotrophic (brain derived neurotrophic factor) systems that are thought to be dysregulated and abnormal in vulnerable individuals exposed to traumatic events.

Psychotic features

The occurrence of the psychotic symptoms is a frequent complication in PTSD, especially when combat-related [18-24], with a 30–40% rate of patients showing secondary psychotic symptoms [2, 25]. These symptoms might worsen the clinical presentation of PTSD. This psychotic subtype of PTSD is characterized by the occurrence of auditory and visual hallucinations, delusional thinking, paranoia and violent thoughts. Therefore this psychotic subtype of PTSD is more severe than PTSD without psychotic symptoms [23-25]. These two subtypes of PTSD differ in biological background and treatment response [19-21,24-28].
Suicidal behavior

Besides the core PTSD symptoms, such as re-experiencing of the trauma, numbing and avoidance, and persistent hyperarousal, PTSD is frequently associated with aggression and suicidal behavior [29]. Suicidal behavior in combat related PTSD, often related to availability of weapons, might lead to a completed suicide [30]. Suicide is defined as the act of intentionally ending one's own life; suicide ideation are thoughts of engaging in behavior intended to end one's life; suicide plan is a formulation of a specific method through which one intends to die; and suicide attempt is an engagement in potentially self-injurious behavior in which there is at least some intent to die [31]. Almost 2% of deaths in the world are a consequence of suicide [30, 32].

Sleep disturbances

Sleep disturbances, including disrupted, broken or unsatisfactory sleep, insomnia, nightmares, night terrors, difficulties in falling asleep or staying asleep, waking up frequently during night or too early in the morning, occur in a large proportion (10%) of general population, but also in mental patients. Insomnia is a devastating symptom that affects physical and social performances, and quality of life. Patients with PTSD, schizophrenia, depression, or alcoholism frequently have insomnia, which is assumed to be a core symptom in these disorders [33-42]. Insomnia is the perception of complaint of inadequate sleep, which can be transient, intermittent or chronic. It is unclear whether insomnia develops as a secondary symptom of these psychiatric disorders, or precedes the development of depression, anxiety disorders, or PTSD [42].

1. Aims of the Study

The aims of these studies were to assess biomarkers (peripheral biochemical as well as genetic markers) as new tools to improve the diagnosis and treatment of PTSD. Investigated biomarkers were platelet serotonin (5-HT) concentration, platelet monoamine oxidase type B (MAO-B) activity, plasma dopamine-beta-hydroxylase (DBH) activity, and genetic markers, i.e. polymorphisms of MAO-B gene, DBH gene, catechol-o-methyltransferase (COMT) gene, brain-derived neurotrophic factor (BDNF) gene, serotonin transporter (5HTT) gene and receptor type 2A gene (5HT2A), in male Croatian war veterans with current and chronic combat-related PTSD. Veterans with PTSD were subdivided into those with, or without suicidal behavior, psychotic features and sleep disturbances. The objectives were to determine platelet 5-HT concentration, platelet MAO-B activity and plasma DBH activity and to determine the distribution of the genotypes or alleles for MAO-B intron 13, -1021C/T DBH, COMT Val158/108, Met, BDNF Val66Met, 102T/C 5HT2A polymorphisms and 5HTTLPR gene-linked polymorphic region (5HTTLPR) in veterans with or without PTSD, with or without presence of suicidal behavior, psychotic features and sleep disturbances, and to explore the relation between these peripheral biomarkers and gene variants and PTSD, suicidal behavior, psychotic features and sleep disturbances. The hypothesis was that these biomarkers would differ between veterans with or without PTSD, with or without suicidal behavior, psychotic symptoms or sleep disturbances and insomnia, and that some of
these biomarkers (peripheral biochemical as well as genetic markers) might be used as new tools to improve the diagnosis and treatment of PTSD.

2. Materials and Methods

2.1. Participants and clinical measures

The study included 576 unrelated, medication-free male Caucasian subjects of Eastern European (Croatian) origin. The study participants were male war veterans with current and chronic combat-related PTSD, older than 18 years (mean age 42.3 ± 7.1 years), who were active duty soldiers between 1991-1995 in the Croatian armed forces, with comparable traumatic combat experience (3.0 ± 1.0 years). Veterans were diagnosed as having current and chronic PTSD. Diagnoses were made using the Structured Clinical Interview (SCID) for DSM-IV [43] based on DSM-IV Disorders [44], the Clinician Administered PTSD Scale (CAPS) [45], The Hamilton Depression Rating Scale (HDRS) [46] and The Hamilton Rating Scale for Anxiety (HAMA) [47]. Psychotic symptoms were evaluated using Positive and Negative Syndrome Scale (PANSS) [48]. Psychiatric comorbidity was assessed by means of the Mini-International Neuropsychiatric Interview [49]. All participants were recruited from 2002-2008 at the Referral Centre for the Stress-related Disorders of the University Hospital Dubrava in Zagreb, Croatia. Veterans were seeking treatment in Veterans PTSD program at the Referral Centre for the Stress-related Disorders of the University Hospital Dubrava. Psychiatrists conducted the assessments and ratings with extensive experience in stress-related disorders. Veterans were categorized as those with PTSD (N=370). Among veterans with PTSD, 76 veterans had secondary psychotic features while 294 veterans had PTSD without psychotic symptoms. Combat exposed veterans with comparable combat experience who did not develop PTSD served as a control group (N=206). The groups did not differ in age (average age 40.75 ± 4.55 years, range 34-59).

2.1.1. Inclusion/exclusion criteria

Inclusion criteria for all patients: medication-free male combat veterans between 18-65 years old. All participants fulfilled the questionnaire answering the questions about their medical history, drinking and smoking habits. Groups did not differ in mean age, education, combat experience and drug status. Exclusion criteria: a family history of psychosis or PTSD, a prior episode of any psychosis, a positive history of schizophrenia spectrum disorders, bipolar disorder, neurodegenerative disorders, history of cognitive dysfunction or mental retardation, alcohol dependence, past or current alcohol or other substance abuse within 3 months, serious concomitant medical condition, clinically significant abnormalities in electrocardiogram or laboratory findings and positive urine screen for illicit drugs and alcohol. Written informed consent was obtained from all participants, after explaining the aims and procedures of the study, under procedures approved by the Ethics committee of the Dubrava University Hospital, Zagreb, Croatia. All human studies have been carried out with the full cooperation of participants, adequate understanding, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.
2.1.2. Suicidal behavior

2.1.2.1. The Hamilton Depression Rating Scale (HDRS)

Veterans were categorized according to the suicidal behavior into those with or without suicidal behavior. The subdivision into suicidal and non-suicidal veterans with PTSD was done based on the scores in item 3 (suicide) from the HDRS 17-item scale [46], as proposed by Roggenbach et al. [50]. Non-suicidal subjects had 0 scores (which indicates absence of any suicidal thoughts or ideation), while suicidal subjects had ≥ 1 scores. Suicidal patients included patients with scores 1-4, i.e. patients with score 1 (a person feels life is not worth living), score 2 (a person wishes he/she was dead or has any thoughts of possible death to him/herself), score 3 (a person has suicide ideas or gestures), and score 4 (a person attempted suicide).

2.1.3. Psychotic features

2.1.3.1. Positive and Negative Syndrome Scale (PANSS)

Veterans were also categorized according to the presence of psychotic symptoms into veterans with psychotic and nonpsychotic PTSD. As previously described [20, 21, 28], veterans with a psychotic PTSD subtype had psychotic combat-related symptoms, which were secondary to the primary PTSD. Psychotic symptoms were more strongly associated with characteristics of PTSD than with characteristics of psychotic disorders or major depressive disorder with psychotic features, and were defined as evidence of hallucinations or delusions during the mental status examination, with a score of at least 4 (moderate severity) on the 4 critical positive items on the PANSS (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution), 2 negative items (emotional withdrawal, and passive/apathetic social withdrawal), 8 items out of the general psychopathology subscale (guilt feelings, depression, motor retardation, unusual thought content, disorientation, disturbance of volition, poor impulse control and active social avoidance) and 2 items on the supplementary subscale (anger and affective liability).

2.1.4. Sleep disturbances

2.1.5. Clinical measures of sleep disturbances

Veterans were also categorized according to the sleep disturbances into those with or without insomnia and other sleep disturbances (nightmares, interrupted sleep) according to HAMA, HDRS and CAPS. Participants included in the study were 236 unrelated male veterans with combat-related PTSD. The diagnosis of PTSD was done using the Structured Clinical Interview (SCID) for DSM-IV [43] based on DSM-IV Disorders [44], the Clinician Administered PTSD Scale (CAPS) [45], and the Hamilton Rating Scale for Depression-17 (HDRS) [46] and Anxiety [47].

2.1.5.1. The Hamilton Anxiety Rating Scale (HAMA)

According to the item 4 of the HAMA, all patients with PTSD were subdivided into veterans without insomnia (with score 0), which indicates that symptoms of insomnia
(difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors) were not present, and in patients with insomnia, with scores (with scores \( \geq 1 \)). These groups included patients with score 1 (with mild symptoms), score 2 (with moderate symptoms), score 3 (with severe symptoms), and score 4 (with very severe symptoms). The groups were also subdivided into patients without (with score 0) or with insomnia (with scores 1-4). Insomnia was presented as difficulties in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

### 2.1.5.2. The Hamilton Depression Rating Scale (HDRS)

According to item 4 (early insomnia) of the HDRS, all participants were subdivided into veterans without early insomnia and veterans with early insomnia (i.e. insomnia early in the night). Veterans without early insomnia had score 0 on the item 4 of the HDRS, indicating that they experienced no difficulties falling asleep. Veterans with early insomnia had \( \geq 1 \) scores on the item 4. These veterans might have 1 score on the item 4 (with complains of occasional difficulty falling asleep), or 2 scores on the item 4 (with complains of nightly difficulty falling asleep). Veterans were additionally subdivided into those without (with score 0), or with early insomnia (with scores 1-2). According to the item 5 (middle insomnia) of the HDRS, veterans were also categorized into those without middle insomnia (with score 0). These veterans did not have any difficulties with sleep, and no insomnia in the middle of the night. Veterans with middle insomnia had more than 1 score on the item 5 of the HDRS. These veterans had 1 score on the item 5 (having complains of being restless and disturbed during the night) or 2 scores on the item 5 (with waking during the night – any getting out of bed rates 2, except for purposes of voiding). Veterans were additionally subdivided into patients without (with score 0) or with middle insomnia (with scores 1-2). Veterans were also subdivided into those with or without late insomnia (according to item 6 on the HDRS). Late insomnia is insomnia that occurs in the early hours of the morning. Veterans were subdivided into those without late insomnia (with score 0), and these veterans did not have any difficulties with sleeping, and no late insomnia. Veterans with late insomnia had more than 1 score on the item 6 of the HDRS. These groups included veterans with 1 score (persons waking in early hours of the morning but going back to sleep), and with 2 scores of the item 6 (veterans who were unable to fall asleep again after getting out of bed). Veterans were also additionally subdivided into patients without (with score 0) or with late insomnia (with scores 1-2).

### 2.1.5.3. Clinician-Administered PTSD Scale (CAPS)

According to the item B2 of the CAPS, veterans were additionally subdivided into patients without recurrent distressing dreams of the event (item B2) or veterans with recurrent distressing dreams of the event. In addition, veterans were categorized into those with or without acting or feeling as if the traumatic events were recurring (includes a sense of re-enactment the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated), according to item B3 of the CAPS. Veterans were also subdivided into those with or without difficulty falling or staying asleep (item D1 of the CAPS).
2.2. Blood Collection

Blood samples (8 ml) were drawn in a plastic syringe with 2 ml of acid citrate dextrose anticoagulant at 08.00 h. Genomic DNA was extracted from peripheral blood using a salting out method [51].

2.3. Biochemical Analyses

2.3.1. Platelet Serotonin Determination

Platelet 5-HT concentration was determined by the spectrofluorimetric method, as described previously [52]. Platelet protein concentration was determined by the method of Lowry et al. [53].

2.3.2. Platelet Monoamine Oxidase Determination

Platelet MAO-B activity was determined by the spectrofluorimetric method, using kynuramine as a substrate, by a slight modification of the method of Krajl [54], as previously described [55].

2.4. Genotyping

2.4.1. Genotyping of 5HTTLPR

Polymerase chain reaction (PCR) amplification of polymorphic loci of the 5HTT gene was performed in total volume of 15 μL containing 150 ng DNA, 0.5 μM of each specific primer (Sigma Aldrich, USA), 250 μM of each dNTP (Invitrogen, USA), 0.5 units Taq polymerase (Qiagen, Germany) and 1X PCR buffer (67 mM Tris-HCl, pH 8.8, 6.7 mM MgCl2, 16.6 mM (NH4)2 SO4, 0.01% Tween-20) (Qiagen, Germany). The primers used for amplification of 5HTTLPR were 5’-GGCGTTGCCGCTCTGAATGC-3’ and 5’-GAGGGACTGAGCTGGACAACCAC-3’. Cycle conditions consisted of an initial denaturation at 95°C for three minutes, followed by 40 cycles of denaturation at 95°C for 30 seconds, 30 seconds annealing at 55 °C, extension at 72°C for one minute as well. A final extension was carried out at 72°C for five minutes. PCR products were separated in 2% agarose gel and visualized with ultraviolet light after ethidium bromide staining. All laboratory procedures were performed blind to subject status. The method was described in detail before [56].

2.4.2. Genotyping of COMT Val¹⁵⁸/¹⁰⁸Met

In DNA samples COMT Val¹⁵⁸/¹⁰⁸Met polymorphism was genotyped in ABI Prism 7000 Sequencing Detection System apparatus (ABI) using Taqman-based allele-specific polymerase chain reaction assay, according to the procedure described by the Applied Biosystems (Applied Biosystems, Foster City, CA, USA). The primers and probes were purchased from Applied Biosystems. The method was described in detail previously [57].
2.4.3. Genotyping of BDNF Val<sup>66</sup>Met

BDNF Val<sup>66</sup>Met polymorphism was genotyped in ABI Prism 7000 Sequencing Detection System apparatus (ABI) using Taqman-based allele-specific polymerase chain reaction assay, according to the procedure described by the Applied Biosystems (Applied Biosystems, Foster City, CA, USA). The primers and probes were purchased from Applied Biosystems. The method was described in detail in our previous work [58].

2.4.4. Genotyping of DBH-1021C/T

DNA was amplified using primers for polymerase chain reaction (PCR): 5′–GGAGGGACAGCTTCTAGTCC-3′ and 5′–CACCTCTCCCTGCTCCTTCGC-3′ (5). PCR reaction conditions and reagents (total volume 15μl) followed the protocol described by Kohnke et al. [59]. The Taq polymerase used was Taq DNA GOLD (Applied Biosystems, Foster City, CA). PCR reaction aliquots of 10 μl were digested for three to four hours with three units of HhaI (Takara, Japan), in a final volume of 20 μl. The digested products were separated on 2% agarose gels and visualized with ethidium bromide under UV light. For the estimation of fragment sizes a 50 bp ladder DNA (Takara, Japan) was used. The method was described in detail before [60].

2.4.5. Genotyping of MAO-B Intron 13 G/A

DNA samples were genotyped for the MAO-B intron 13 G/A polymorphism in the ABI Prism 7000 Sequencing Detection System apparatus (ABI, Foster City, USA) using Taqman-based allele-specific polymerase chain reaction assay, according to the procedure described by the Applied Biosystems. The primers and probes were purchased from Applied Biosystems (ABI, Foster City, USA). The method was described in detail previously [27].

2.4.6. Genotyping of 102T/C 5HT2A

The DNA samples were genotyped using ABI Prism 7000 Sequencing Detection System apparatus using Taqman-based allele-specific polymerase chain reaction assay, according to the procedure described by the Applied Biosystems. The primers and probes were purchased from Applied Biosystems (ABI, Foster City, USA).

2.5. Statistical Analysis

The results, expressed as means ± standard deviations (SD), were evaluated with Sigma Stat 3.5 (Jandell Scientific Corp. San Raphael, California, USA) using one-way analysis of variance (ANOVA), followed by the multiple comparison tests. The correlations were determined by a Pearson’s coefficient of correlation (r). The Hardy-Weinberg analysis was used to test the equilibrium of the population. The differences in the genotype and allele frequencies were evaluated using a χ² test. The power of performed tests was given for all comparisons, while the desired power should be alpha ≥ 0.800. The significance was accepted when p<0.05.
3. Results

Investigated biomarkers were 5-HT concentration, MAO-B activity, plasma DBH activity, and genetic markers, i.e. polymorphisms of MAO-B gene, DBH gene, COMT gene, BDNF gene, 5HTT gene, 5HT2A gene (genotypes or alleles for MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, BDNF Val66Met, 102T/C 5HT2A polymorphisms and 5HTTLPR) in veterans with or without PTSD. Veterans with PTSD were additionally subdivided into veterans with PTSD with or without suicidal behavior, evaluated according to the item 3 of the HDRS. Veterans were also subdivided into veterans with PTSD with or without psychotic features, evaluated using the PANSS (defined with a score of at least 4 (moderate severity) on the 4 critical positive items on the PANSS). In addition, veterans were subdivided into veterans with PTSD with or without insomnia, evaluated using the item 4 of the HAMA, and subdivided also according to the items 4 (veterans with or without early insomnia), item 5 (veterans with or without middle insomnia) and item 6 (veterans with or without late insomnia) of the HDRS. Veterans with PTSD with sleep disturbances were subdivided also into those with or without recurrent distressing dreams of the event, flashbacks or difficulties in falling or staying asleep based on the CAPS. They were subdivided according to the item B2 of the CAPS into veterans with or without the recurrent distressing dreams of the event, or according to item B3 of the CAPS into veterans with or without flashbacks, and according to the item D1 of the CAPS into veterans with or without difficulties in falling or staying asleep.

3.1. Biochemical (platelet and plasma) markers and genetic markers in veterans with or without PTSD

Platelet 5-HT concentration was determined in war veterans with or without combat related PTSD. One-way ANOVA revealed that platelet 5-HT concentration did not differ significantly ($F=2.707; df=1; 604; P=0.100$) between veterans with or without PTSD.
PTSD (Figure 1). These results showed similar values of platelet 5-HT between veterans with PTSD and veterans who did not develop PTSD.

![Figure 2](image.png)

Figure 2. Platelet MAO-B activity in war veterans with or without PTSD, subdivided into smokers and non-smokers

Platelet MAO-B activity was determined in war veterans with or without combat related PTSD, who were subdivided according to the cigarette smoking into smokers and non-smokers. One-way ANOVA showed that MAO-B activity differed significantly ($F=9.910; df=3, 390; P=0.001$) between veterans with or without PTSD (Figure 2). Tukey’s multiple comparison test revealed that platelet MAO-B activity was significantly lower in veterans without PTSD (referred as healthy male subjects) who smoked than in healthy male nonsmokers ($P=0.015$) and also in veterans with PTSD who smoked compared to veterans with PTSD who were non-smokers ($P=0.002$). Platelet MAO-B activity was significantly higher in non-smoking veterans with PTSD compared to nonsmokers in healthy groups ($P=0.010$). Platelet MAO-B activity was also significantly higher in veterans with PTSD smokers compared to healthy smokers ($P=0.024$). These results revealed that platelet MAO-B activity was significantly higher in veterans with PTSD compared to values in veterans without PTSD.

![Figure 3](image.png)

Figure 3. Plasma DBH activity in war veterans with or without PTSD
Plasma DBH activity was determined in war veterans with or without combat related PTSD. One-way ANOVA revealed that plasma DBH activity differed significantly (F=16.984; df=1, 214; P=0.001) between veterans with and without PTSD (Figure 3). Plasma DBH activity was significantly (Tukey’s multiple comparison test) lower in veterans with PTSD than in veterans without PTSD (P=0.001). These results suggested lower plasma DBH activity in veterans with PTSD compared to values in veterans without PTSD.

5HTTLPR genotypes (LL, LS or SS) were determined in veterans with or without PTSD. No significant differences (Figure 4) were detected in the frequency of the 5HTTLPR genotypes (LL, LS or SS) in veterans with or without PTSD ($\chi^2=0.080; \text{df}=2; P=0.961$; power of performed test with $\alpha=0.050$: 0.179; $\chi^2$ =test). These results showed a lack of significant association between 5HTTLPR genotypes (LL, LS or SS) and PTSD.

MAO-B intron 13 genotypes in veterans with or without PTSD

Figure 4. 5HTTLPR genotypes in veterans with or without PTSD

Figure 5. MAO-B intron 13 genotypes in veterans with or without PTSD
The gene for MAO-B is located on the X chromosome and the most common polymorphism is an A to G substitution, present in intron 13 of MAO-B gene. The frequency of the MAO-B A or G genotypes was determined in veterans with or without PTSD (Figure 5). The frequency of A or G genotypes of the MAO-B intron 13 did not differ between veterans with or without PTSD ($\chi^2 = 9.235; df = 1; P = 0.628$; power of performed test with alpha = 0.050: 0.073). These results showed a lack of significant association between MAO-B intron 13 genotypes (A or G) and PTSD.

The frequency of the CC, CT and TT DBH genotypes was determined in veterans with or without PTSD (Fig. 6). No significant differences were found in the distribution of the DBH genotypes (CC, CT and TT) in veterans with or without PTSD ($\chi^2 = 0.711; df = 2; P = 0.701$; power of performed test with alpha = 0.050: 0.103). These results showed a lack of significant association between DBH genotypes (CC, CT or TT) and PTSD.

The gene for MAO-B is located on the X chromosome and the most common polymorphism is an A to G substitution, present in intron 13 of MAO-B gene. The frequency of the MAO-B A or G genotypes was determined in veterans with or without PTSD (Figure 5). The frequency of A or G genotypes of the MAO-B intron 13 did not differ between veterans with or without PTSD ($\chi^2 = 9.235; df = 1; P = 0.628$; power of performed test with alpha = 0.050: 0.073). These results showed a lack of significant association between MAO-B intron 13 genotypes (A or G) and PTSD.

The frequency of the CC, CT and TT DBH genotypes was determined in veterans with or without PTSD (Fig. 6). No significant differences were found in the distribution of the DBH genotypes (CC, CT and TT) in veterans with or without PTSD ($\chi^2 = 0.711; df = 2; P = 0.701$; power of performed test with alpha = 0.050: 0.103). These results showed a lack of significant association between DBH genotypes (CC, CT or TT) and PTSD.
The distribution of the 5HT2A genotypes (CC, CT and TT) was determined in veterans with or without PTSD. As shown in Figure 7, slight but significant difference in the frequency of 5HT2A genotypes was detected between veterans with or without PTSD ($\chi^2 = 6.070; \text{df} = 2; P = 0.048$; power of performed test with alpha $= 0.050$: $0.582$; $\chi^2$ =test). These data revealed a significant association between 5HT2A genotypes and PTSD.

Frequency of the COMT genotypes (Met/Met or AA, Met/Val or AG and Val/Val or GG) was determined in veterans with or without PTSD. There were no significant differences (Figure 8) in the frequency of COMT genotypes in veterans with or without PTSD ($\chi^2 = 1.598; \text{df} = 2; P = 0.450$; power of performed test with alpha $= 0.050$: $0.054$; $\chi^2$ =test). These results showed a lack of association between COMT genotypes and PTSD.

The distribution of the BDNF genotypes (Met/Met or AA, Met/Val or AG and Val/Val or GG) was determined in veterans with or without PTSD. As shown in Fig. 9, no
significant differences in the frequency of BDNF Met/Met, Met/Val and Val/Val genotypes in veterans with or without PTSD were found ($\chi^2 = 2.140$; df= 2; $P = 0.343$; power of performed test with alpha = 0.050: 0.228; $\chi^2$ = test). These results showed a lack of significant association between BDNF genotypes and PTSD.

3.2. **Biochemical (platelet and plasma) markers and genetic markers in veterans with psychotic PTSD compared to veterans with PTSD without psychotic features**

![Figure 10. Platelet 5-HT concentration in war veterans with psychotic PTSD, non-psychotic PTSD and in veterans without PTSD](image)

Platelet 5-HT concentration was determined in war veterans with psychotic symptoms secondary to combat related PTSD, veterans with PTSD without psychotic features and in veterans without PTSD. One-way ANOVA revealed that platelet 5-HT concentration differ significantly ($F=19.539$; df=2,602; $P=0.001$) between veterans with or without psychotic symptoms and veterans without PTSD (Figure 10). Namely, war veterans with psychotic PTSD had significantly higher platelet 5-HT concentration ($P=0.009$, Tukey’s test) than war veterans with non-psychotic PTSD. Veterans with PTSD without psychotic symptoms had significantly ($P=0.001$, Tukey’s test) lower platelet 5-HT concentration than veterans without PTSD.

![Figure 11. Platelet MAO-B activity in war veterans with psychotic PTSD, non-psychotic PTSD and in veterans without PTSD](image)
These results showed that platelet 5-HT concentration was significantly increased in psychotic PTSD compared to non-psychotic PTSD.

Platelet MAO-B activity was determined in smoking and non-smoking war veterans with or without psychotic symptoms secondary to PTSD and in war veterans without PTSD (Fig. 11). One-way ANOVA revealed that platelet MAO-B activity was significantly (F=5.957; df=5,310; P=0.001) different between veterans with or without psychotic symptoms and veterans without PTSD (Fig. 10), additionally subdivided according to the smoking status. Between smokers, war veterans with psychotic PTSD had significantly higher platelet MAO-B activity (P=0.036, Tukey’s test) than the corresponding (smoking) veterans with non-psychotic PTSD (P=0.005, Tukey’s test) or veterans without PTSD (P=0.036, Tukey’s test). Between non-smokers, veterans with psychotic PTSD had significantly higher platelet MAO-B activity (P=0.050, Tukey’s test) than the corresponding (non-smoking) veterans without PTSD (Figure 11). These results showed that platelet MAO-B activity was significantly increased in psychotic compared to non-psychotic PTSD.

Figure 12. Plasma DBH activity in war veterans with psychotic PTSD, non-psychotic PTSD and in veterans without PTSD

Plasma DBH activity was determined in war veterans with psychotic symptoms secondary to combat related PTSD, war veterans with non-psychotic PTSD and in veterans without PTSD (Figure 12). Due to the abnormal distribution of data, plasma DBH activity was evaluated using Kruskall Wallis one-way ANOVA, which showed significant differences in plasma DBH activity (H=14.300; df=3,602; P=0.025) between veterans with or without psychotic symptoms and veterans without PTSD. Both groups of war veterans with PTSD, i.e. those with psychotic PTSD (P=0.009, Mann Whitney U test) and those with non-psychotic PTSD (P=0.001, Mann Whitney U test) had significantly lower plasma DBH activity than war veterans without PTSD. These results showed that plasma DBH activity was significantly decreased in both psychotic and non-psychotic PTSD veterans compared to values in veterans without PTSD, and that plasma DBH activity was not associated with psychotic features in PTSD.
Figure 13. 5HTTLPR genotypes in veterans with or without PTSD, with or without psychotic symptoms

5HTTLPR genotypes (LL, LS or SS) were determined in veterans with PTSD with or without psychotic symptoms and in veterans without PTSD (Fig. 13). No significant differences (Figure 13) were found in the frequency of the 5HTTLPR genotypes (LL, LS or SS) in veterans with psychotic PTSD, veterans with non-psychotic PTSD and veterans without PTSD ($\chi^2 = 0.484; \text{df}= 4; P = 0.975$; power of performed test with alpha $= 0.050$: 0.074; $\chi^2 = \text{test}$). These results showed a lack of significant association between 5HTTLPR genotypes and psychotic PTSD.

Figure 14. MAO-B intron 13 genotypes in veterans with or without PTSD, with or without psychotic symptoms

MAO-B intron 13 genotypes (A or G) were determined in veterans with PTSD with or without psychotic symptoms and in veterans without PTSD (Figure 14). The frequency of the MAO-B genotypes did not differ significantly between veterans with psychotic
PTSD, veterans with non-psychotic PTSD and veterans without PTSD ($\chi^2 = 1.572; \text{df} = 2; P = 0.456$; power of performed test with alpha $= 0.050$: $0.176$; $\chi^2 = \text{test}$). These results showed a lack of significant association between MAO-B intron 13 genotypes and psychotic PTSD.

Figure 15. DBH genotypes in veterans with or without PTSD, with or without psychotic symptoms

DBH genotypes (TT, CT or CC) were determined in veterans subdivided according to the presence of PTSD and presence of psychotic features (Figure 15). The distribution of the DBH genotypes was not significantly different between veterans with psychotic PTSD, veterans with non-psychotic PTSD and veterans without PTSD ($\chi^2 = 1.461; \text{df} = 4; P = 0.834$; power of performed test with alpha $= 0.050$: $0.174$; $\chi^2 = \text{test}$). These results showed a lack of significant association between DBH genotypes and psychotic PTSD.

Figure 16. 5HT2A genotypes in veterans with or without PTSD, with or without psychotic symptoms

The distribution of the 5HT2A genotypes (TT, CT or CC) was determined in veterans with or without PTSD and with or without psychotic symptoms (Figure 16). The frequency of the DBH genotypes did not differ significantly ($\chi^2 = 9.201; \text{df} = 4; P = 0.056$; power of performed test with alpha $= 0.050$: $0.670$; $\chi^2 = \text{test}$) between veterans with psychotic PTSD, veterans with non-psychotic PTSD and veterans without PTSD,
however, the TT genotype was most frequently found in all veterans, while the CC genotype was the rarest. These results showed a lack of association between 5HT2A genotypes and psychotic PTSD.

Figure 17. COMT genotypes in veterans with or without PTSD, with or without psychotic symptoms

The frequency of the COMT Met/Met, Met/Val and Val/Val genotypes was determined in veterans with PTSD, with and without psychotic features, and in veterans without PTSD (Figure 17). We have found the lack of significant differences in the frequency of the COMT Met/Met, Met/Val and Val/Val genotypes between veterans with or without PTSD and veterans with psychotic PTSD ($\chi^2 = 3.840; df = 4; P = 0.428$; power of performed test with alpha = 0.050: 0.299; $\chi^2$ =test). These results showed a lack of significant association between COMT genotypes and psychotic PTSD.

Figure 18. BDNF genotypes in veterans with or without PTSD, with or without psychotic symptoms

The distribution of the BDNF Met/Met, Met/Val and Val/Val genotypes was determined in veterans with PTSD, with and without psychotic features, and in veterans without PTSD. As shown in Figure 18, there were significant differences in the frequency of BDNF Met/Met, Met/Val and Val/Val genotypes between veterans...
with or without PTSD and veterans with psychotic PTSD ($\chi^2 = 10.082; df = 4; P = 0.039$; power of performed test with alpha = 0.050: 0.718; $\chi^2 =$test). These results showed a significant association between BDNF genotypes and psychotic PTSD.

3.4. Biochemical (platelet and plasma) markers and genetic markers in veterans with PTSD with or without insomnia and other sleep disturbances

Figure 19: Platelet 5-HT concentration in veterans with PTSD, who were subdivided according to the item 4 from the HAMA into veterans without insomnia and veterans with different degrees of insomnia

Platelet 5-HT concentration did not differ significantly ($F=2.281; df=4,231; p=0.061$, ANOVA) between male veterans with PTSD who were subdivided into veterans with different scores (1-4 scores) of insomnia or without (with 0 score) symptoms of insomnia (Figure 19), according to the item 4 from the HAMA. Although not significant, all veterans with PTSD with different scores in the symptoms of insomnia had marginally lower platelet 5-HT concentration than veterans with PTSD without insomnia (Fig. 19). Symptoms of insomnia included difficulties in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, and night terrors. These results showed a trend towards an association between platelet 5-HT concentration and insomnia.

Figure 20: Platelet 5-HT concentration in veterans with PTSD with or without insomnia, determined according to the item 4 from the HAMA
Platelet 5-HT concentration was significantly different ($F=4.901; \text{df}=1,234; p=0.028$, ANOVA) between male veterans with PTSD who were subdivided into veterans with (with scores 1-4) or without (with 0 score) insomnia (Figure 20). Namely, male veterans with PTSD with 1-4 scores of insomnia on the item 4 of the HAMA had significantly lower ($P=0.028$, Tukey’s test) platelet 5-HT concentration than veterans without insomnia. These results showed a significant association between platelet 5-HT concentration and insomnia.

![Figure 21: Platelet 5-HT concentration in veterans with PTSD, subdivided further according to the item 4 from the HDRS into veterans without early insomnia and veterans with different degrees of early insomnia](image)

When early insomnia was determined by the item 4 of the HDRS scale, there were no significant differences in platelet 5-HT concentration ($F=1.729; \text{df}=2,233; p=0.180$, ANOVA) between veterans with PTSD with or without the presence of early insomnia (i.e. veterans with early insomnia with 1 score or with 2 scores on the item 4 of the HDRS) and veterans without early insomnia (Figure 21). These results showed a lack of significant association between platelet 5-HT concentration and early insomnia.

![Figure 22: Platelet 5-HT concentration in veterans with PTSD with or without early insomnia, determined according to the item 4 from the HDRS](image)
Platelet 5-HT concentration did not differ significantly ($F=1.322; \text{df}=1,234; p=0.251$, ANOVA) between veterans with 1-2 scores of early insomnia compared to veterans with 0 scores of early insomnia (Figure 22). These results showed a lack of significant association between platelet 5-HT concentration and early insomnia.

![Figure 23: Platelet 5-HT concentration in veterans with PTSD, subdivided further according to the item 5 from the HDRS into veterans without middle insomnia and veterans with different degrees of middle insomnia](image)

Veterans with middle insomnia, assessed by the item 5 of the HDRS scale, had similar platelet 5-HT concentration (Figure 23). Namely, platelet 5-HT concentration was not significantly different ($F=0.679; \text{df}=2,233; p=0.508$, ANOVA) between male veterans with PTSD with or without the presence of middle insomnia, and there was no significant difference between veterans with 1 or 2 scores of middle insomnia compared to veterans with 0 scores of middle insomnia (Figure 23). These results showed a lack of significant association between platelet 5-HT concentration and middle insomnia.

![Figure 24: Platelet 5-HT concentration in veterans with PTSD with or without middle insomnia, determined according to the item 5 from the HDRS](image)

Platelet 5-HT concentration did not differ significantly ($F=0.465; \text{df}=1,234; p=0.496$, ANOVA) between male veterans with PTSD with or without middle insomnia, since
veterans with 1-2 scores on the item 5 of the HDRS had similar platelet 5-HT concentration as veterans with 0 scores on the item 5 of HDRS (Figure 24). These results showed a lack of significant association between platelet 5-HT concentration and middle insomnia.

Figure 25: Platelet 5-HT concentration in veterans with PTSD, subdivided further according to the item 6 from the HDRS into veterans without late insomnia and veterans with different degrees of late insomnia

There was no significant difference in platelet 5-HT concentration (F=1.703; df=2,128; p=0.186, ANOVA) between veterans with PTSD without late insomnia, and veterans with 1 or 2 scores. Veterans with late insomnia (with 1-2 scores on the item 6 of the HDRS) did not differ in their platelet 5-HT values from veterans with 0 scores on the item 6 of HDRS (Figure 25). These results showed a lack of significant association between platelet 5-HT concentration and late insomnia.

Fig. 26: Platelet 5-HT concentration in veterans with PTSD with or without late insomnia, determined according to the item 6 from the HDRS

No significant difference was found in platelet 5-HT concentration (F=0.330; df=1,128; p=0.567, ANOVA) between veterans with PTSD without or with late insomnia.
Veterans with 1-2 scores on item 6 of the HDRS had similar platelet 5-HT as veterans with 0 scores on the Item 6 of the HDRS (Figure 26). These results showed a lack of significant association between platelet 5-HT concentration and late insomnia.

![Figure 27. Platelet 5-HT concentration in veterans with PTSD, subdivided according to the item D-1 from the CAPS](image)

Since the core symptoms of PTSD are sleep disturbances such as difficulties in falling or staying asleep, these sleep disturbances were evaluated also using D-1 item from the CAPS. There were no significant differences in platelet 5-HT concentration (F=0.362; df=2,76; p=0.697, ANOVA) between veterans with PTSD with difficulties in falling or staying asleep, subdivided into those with 5, 6 or 7 scores on the D1 of the CAPS. These results showed a lack of significant association between platelet 5-HT concentration and difficulties in falling or staying asleep.

![Figure 28. Platelet 5-HT concentration in veterans with PTSD, subdivided according to the item B-2 from the CAPS](image)

Platelet serotonin concentration was determined in male veterans with PTSD, subdivided further according to the recurrent distressing dreams of the event (item B-2
from the CAPS) into veterans with recurrent distressing dreams of the event with 4, 5, 6, 7 or 8 scores (Figure 28). Platelet 5-HT concentration was not significantly different (F=2.089; df=3,74; p=0.109, ANOVA) between veterans with PTSD who were subdivided according to the item B-2 from the CAPS into veterans with recurrent distressing dreams of the event with different scores (4-8 scores), (Figure 28). All veterans with recurrent distressing dreams of the event, i.e. with scores 5-8 on the B-2 of the CAPS had marginally lower platelet 5-HT concentration than veterans with distressing dreams with the lowest score (score 4). These results showed a trend of an association between platelet 5-HT concentration and recurrent distressing dreams.

Figure 29: Platelet 5-HT concentration in veterans with PTSD, subdivided according to the item B-3 from the CAPS

After flashbacks were evaluated using CAPS item B-3, platelet 5-HT concentration did not differ significantly (F=2.763; df=2,75; p=0.070, ANOVA) between veterans with PTSD who were subdivided into veterans without flashbacks (with score 0) and with flashbacks (i.e. scores 2, 3 and 5). All veterans with flashbacks with 2-5 scores had slightly lower platelet 5-HT concentration than veterans without flashbacks (Figure 29). These results showed a trend of an association between platelet 5-HT concentration and flashbacks.

Figure 30: Platelet 5-HT concentration in veterans with PTSD, subdivided according to the item B-3 from the CAPS into veterans without (score 0) flashbacks and with flashbacks (with 2-5 scores)
Platelet 5-HT concentration was significantly different ($F=6.551; \text{df}=1,77; p=0.012$, ANOVA) between veterans with PTSD with or without flashbacks. Veterans with flashbacks (item B-3 from the CAPS with 2-5 scores) had significantly lower platelet 5-HT concentration than veterans without flashbacks ($P=0.012$, Tukey test). These results showed a significant association between platelet 5-HT concentration and flashbacks (Figure 30).

Platelet MAO-B activity was determined in veterans with PTSD, evaluated according to the item 4 from the HAMA and subdivided into those with or without insomnia (different scores in symptoms of insomnia: difficulties in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors), and according to the smoking status (Figure 31). There were significant differences in platelet MAO-B activity ($F=3.392; \text{df}=6,104; p=0.004$, ANOVA) between veterans with PTSD without insomnia (with score 0), and veterans with insomnia, who had more than 1 score (i.e. with 1 score, 2 scores, 3 scores and 4 scores on the item 4 of the HAMA), and according to the smoking status. Insomnia did not affect platelet MAO-B activity, since no differences were detected within veterans with or without insomnia. Smoking status, but not insomnia, was responsible for these differences detected by one-way ANOVA. Smokers had marginally lower platelet MAO-B activity than non-smokers. These results showed a lack of association between platelet MAO-B activity and insomnia.
There was a significant difference in platelet MAO-B activity (F=11.917; df=2,109; p=0.001, ANOVA) between smoking and non-smoking veterans with PTSD without insomnia (with 0 score) and with insomnia (1-4 scores). Non-smokers with insomnia had significantly higher (P=0.002, Tukey’s test) platelet MAO-B activity than smokers with insomnia (Figure 32). These results showed that smoking, but not insomnia, affected platelet MAO-B activity.

Platelet MAO-B activity differed significantly (F=3.909; df=4,107; p=0.005, ANOVA) between veterans with or without different degrees of early insomnia, determined by a HDRS item 4. Platelet MAO-B activity was significantly (p=0.049) higher in nonsmokers than in smokers with early insomnia who had 1 score. Smoking status, but not early insomnia, affected platelet MAO-B activity in veterans (Figure 33). These results showed that platelet MAO-B activity was not associated with early insomnia.
There were significant differences in platelet MAO-B activity (F=7.312; df=2,109; p=0.001, ANOVA) between veterans with PTSD who were subdivided according to smoking status and early insomnia (according to the item 4 from the HDRS). Nonsmokers with early insomnia with 1-2 scores on the item 4 had significantly higher (P=0.005, Tukey’s test) platelet MAO-B activity than smokers with early insomnia (Figure 34). These results showed that smoking, but not insomnia, affected platelet MAO-B activity, and therefore platelet MAO-B activity was not associated with early insomnia.

Figure 34. Platelet MAO-B activity in veterans with PTSD with or without early insomnia, determined according to the item 4 from the HDRS, and according to the smoking.

Figure 35. Platelet MAO-B activity in veterans with PTSD, who were subdivided according to the item 5 from the HDRS into veterans without middle insomnia and veterans with different degrees of middle insomnia, and according to the smoking.
Significant differences were detected in platelet MAO-B activity (F=3.183; df=5,196; p=0.010, ANOVA) between veterans with PTSD with or without different degrees of middle insomnia. There were no significant differences between groups of veterans subdivided according to the presence or absence of different degrees of middle insomnia, and only smoking status, affected platelet MAO-B activity (Figure 35). These results indicate that platelet MAO-B activity was not associated with middle insomnia.

Platelet MAO-B activity (F=4.306; df=3,108; p=0.007, ANOVA) differed significantly between veterans with PTSD with or without middle insomnia (according to the item 5 from the HDRS). Nonsmokers with middle insomnia who had 1-2 scores had significantly higher (P=0.003, Tukey's test) platelet MAO-B activity than smokers with middle insomnia (Figure 36). These results showed that platelet MAO-B activity was not associated with middle insomnia.

Platelet MAO-B activity differed significantly (F=3.271; df=5,106; p=0.009, ANOVA) between veterans with PTSD with or without different degrees of late insomnia. There
were no significant differences between groups of veterans subdivided according to the presence or absence of different degrees of late insomnia. Smoking status only marginally (p=0.058, Tukey’s test) affected platelet MAO-B activity within veterans with 1 score on late insomnia (Figure 37). These results indicate that platelet MAO-B activity was not associated with late insomnia.

Figure 38. Platelet MAO-B activity in male veterans with PTSD with or without late insomnia, determined according to the item 6 from the HDRS, and according to the smoking

Platelet MAO-B activity (F=5.380; df=3,108; p=0.002, ANOVA) was significantly different between veterans with PTSD with or without late insomnia (evaluated according to the item 6 from the HDRS). Nonsmoking veterans with 1-2 scores on the late insomnia had significantly higher (P=0.001, Tukey’s test) platelet MAO-B activity than smokers with late insomnia (Figure 38). Late insomnia did not affect platelet MAO-B activity.

Figure 39: Platelet MAO-B activity in veterans with PTSD, subdivided according to the item D-1 from the CAPS, and according to the smoking

The difficulties in falling or staying asleep, evaluated using D-1 from the CAPS, occurred similarly in veterans with PTSD. Platelet MAO-B activity did not differ significantly (F=1.615; df=4,62; p=0.182, ANOVA) between male veterans with PTSD, subdivided according to their smoking status into smokers and non-smokers,
and according to different degree of difficulties in falling or staying asleep (5-7 scores) (Figure 39). These results suggest that platelet MAO-B activity was not associated with difficulties in falling or staying asleep.

![Figure 40. Platelet MAO-B activity in veterans with PTSD, subdivided according to the item B-2 from the CAPS, and according to the smoking.](image)

Platelet MAO-B activity did not differ significantly (F=1.249; df=6,60; p=0.294, ANOVA) between veterans with PTSD with different scores of recurrent distressing dreams of the event, i.e. between veterans with scores 4, 5, 6, 7 and 8 on the B-2 of the CAPS. All veterans with recurrent distressing dreams of the event (with 5-8 scores on the B-2 of the CAPS) had slightly lower platelet MAO-B activity than veterans with 4 scores on the distressing dreams (Figure 40). These results suggest that platelet MAO-B activity was not significantly associated with recurrent distressing dreams of the event.

![Figure 41. Platelet MAO-B activity in veterans with PTSD, subdivided according to the item B-3 from the CAPS, and according to the smoking.](image)
Flashbacks (a sense of re-enactment of the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated) were evaluated using the item B-3 from the CAPS. Veterans were subdivided into those without flashbacks (with 0 scores) and with flashbacks (with 2 or 3 scores). Platelet MAO-B activity was significantly different (F=3.531; df=3,62; p=0.020, ANOVA) between veterans with or without different scores of flashbacks (Figure 41). This difference was due to the smoking status, since the presence or absence of flashbacks or different cores of the flashbacks did not affect significantly platelet MAO-B activity. These results suggest that platelet MAO-B activity was not significantly associated with flashbacks.

![Figure 42. Platelet MAO-B activity in veterans with PTSD, subdivided according to the item B-3 from the CAPS into veterans without (score 0) flashbacks and with flashbacks (with 2-3 scores), and according to the smoking status. Veterans were subdivided into those without flashbacks (with 0 scores) and with flashbacks (with 2-3 scores) and smoking status. Platelet MAO-B activity was not significantly different (F=2.360; df=3,64; p=0.080, ANOVA) between veterans with or without flashbacks (Figure 42). These results suggest that platelet MAO-B activity was not associated with flashbacks.](image)

Veterans were subdivided into those without flashbacks (with 0 scores) and with flashbacks (with 2-3 scores) and smoking status. Platelet MAO-B activity was not significantly different (F=2.360; df=3,64; p=0.080, ANOVA) between veterans with or without flashbacks (Figure 42). These results suggest that platelet MAO-B activity was not associated with flashbacks.

![Fig. 43. 5HTTLPR genotypes in veterans with PTSD subdivided into those with or without different degrees of insomnia, evaluated according to the scores in the item 4 from the HAMA.](image)
There were no significant differences in the frequency of the 5HTTLPR genotypes (LL, LS or SS) in veterans with PTSD subdivided according to the scores in the item 4 from the HAMA into veterans without insomnia (with score 0), and veterans with different degrees of insomnia, with 1, 2, 3 or 4 scores ($\chi^2 = 4.792; df = 8; P = 0.780$, $\chi^2 = \text{test}$). These results suggest that 5HTTLPR genotypes were not significantly associated with insomnia.

No significant differences in the frequency of the 5HTTLPR genotypes (LL, LS or SS) in veterans with PTSD subdivided according into those without and with (who had 1-4 scores) insomnia, evaluated with the item 4 of HAMA ($\chi^2 = 1.847; df = 2; P = 0.397$, $\chi^2 = \text{test}$). These results suggest that 5HTTLPR genotypes were not significantly associated with insomnia.

Frequency of the 5HTTLPR genotypes (LL, LS or SS) differ significantly (Figure 45) in veterans with PTSD subdivided according to the scores in the item 4 from the HDRS into veterans without early insomnia (with score 0), and veterans with early insomnia,
who had 1, 2, 3 or 4 scores ($\chi^2 = 11.470; \text{df} = 4; P = 0.022$, $\chi^2 = \text{test}$). These results suggest that 5HTTLPR genotypes were significantly associated with early insomnia.

Figure 46. 5HTTLPR genotypes in male veterans with PTSD with or without early insomnia, determined according to the item 4 from the HDRS

Significant difference was found in the frequency of the 5HTTLPR genotypes (LL, LS or SS) in veterans with PTSD subdivided according to the scores in the item 4 from the HDRS into veterans without early insomnia (with score 0), and veterans with early insomnia, who had 1-2 scores ($\chi^2 = 8.432; \text{df} = 2; P = 0.015$, $\chi^2 = \text{test}$), Figure 46. These results suggest that 5HTTLPR genotypes were significantly associated with early insomnia.

Figure 47. 5HTTLPR genotypes in veterans with PTSD, who were subdivided according to the item 5 from the HDRS into veterans without middle insomnia and veterans with different degrees of middle insomnia

When veterans with PTSD were subdivided according to the middle insomnia and using the scores in the item 5 from the HDRS (Figure 47), frequency of the 5HTTLPR genotypes (LL, LS or SS) didn’t differ significantly between veterans without middle
insomnia (with score 0), and veterans with middle insomnia, who had 1 or 2 scores ($\chi^2 = 4.822; df = 4; P = 0.306, \chi^2 = \text{test}$). These results suggest that 5HTTLPR genotypes were not significantly associated with middle insomnia.

![Figure 48. 5HTTLPR genotypes in male veterans with PTSD with or without middle insomnia, determined according to the item 5 from the HDRS](image)

No significant differences in the frequency of the 5HTTLPR genotypes (LL, LS or SS) between veterans without insomnia (with score 0), and veterans with middle insomnia, who had 1-2 scores ($\chi^2 = 2.288; df = 2; P = 0.318, \chi^2 = \text{test}$) was found (Figure 48). These results suggest that 5HTTLPR genotypes were not significantly associated with middle insomnia.

![Figure 49. 5HTTLPR genotypes in veterans with PTSD, who were subdivided according to the item 6 from the HDRS into veterans without late insomnia and veterans with different degrees of late insomnia](image)

After veterans with PTSD were subdivided according to the late insomnia and using the scores in the item 6 from the HDRS (Fig. 49), frequency of the 5HTTLPR genotypes (LL, LS or SS) didn’t differ significantly between veterans without late insomnia (with score 0), and veterans with late insomnia, who had 1 or 2 scores ($\chi^2 =$
4.753; df = 4; P = 0.314, \( \chi^2 = \text{test} \). These results suggest that 5HTTLPR genotypes were not significantly associated with late insomnia.

Figure 50. 5HTTLPR genotypes in male veterans with PTSD with or without late insomnia, determined according to the item 6 from the HDRS

Frequency of the 5HTTLPR genotypes (LL, LS or SS) did not differ significantly between veterans with PTSD subdivided according to the scores in the item 6 from the HDRS (Fig. 50) into veterans without late insomnia (with score 0), and veterans with late insomnia, with 1-2 scores (\( \chi^2 = 3.076; \) df = 2; P = 0.215, \( \chi^2 = \text{test} \)). These results suggest that 5HTTLPR genotypes were not significantly associated with late insomnia.

Figure 51. 5HTTLPR genotypes in veterans with PTSD, subdivided according to the item D-1 from the CAPS
When veterans with PTSD were subdivided according to the difficulties in falling or staying asleep according to the item D-1 from the CAPS (Figure 51), there were no significant, but marginal, differences in the frequency of the 5HTTLPR genotypes between veterans with 5, 6 or 7 scores on the item D-1 from the CAPS ($\chi^2 = 9.270; \text{df}=4; P = 0.055$, $\chi^2 = \text{test}$). These results suggest that 5HTTLPR genotypes were only marginally associated with difficulties in falling or staying asleep.

Figure 52. 5HTTLPR genotypes in veterans with PTSD, subdivided according to the item B-2 from the CAPS

After subdividing veterans with PTSD according to the item B-2 from the CAPS into veterans with recurrent distressing dreams of the event, with scores 4, 5, 6, 7 and 8, no significant differences in the frequency of the 5HTTLPR genotypes (LL, LS or SS) between veterans with different scores on the item B-2 from the CAPS ($\chi^2 = 10.768; \text{df}=8; P = 0.215$, $\chi^2 = \text{test}$) was found (Figure 52). These results suggest that 5HTTLPR genotypes were not significantly associated with recurrent distressing dreams of the event.

Figure 53. 5HTTLPR genotypes in veterans with PTSD, subdivided according to the item B-3 from the CAPS
When veterans with PTSD were subdivided according to the item B-3 from the CAPS into veterans without (score 0) and with flashbacks, with scores 2, 3 or 5 on the B-3 of the CAPS, no significant, but only marginal, differences in the frequency of the 5HTTLPR genotypes (LL, LS or SS) between veterans with different scores on the item B-3 from the CAPS ($\chi^2 = 12.371; \text{df} = 6; P = 0.054$, $\chi^2$-test) were found (Figure 53). These results suggest that 5HTTLPR genotypes were not significantly associated with flashbacks.

Figure 54. 5HTTLPR genotypes in veterans with PTSD, subdivided according to the item B-3 from the CAPS into veterans without flashbacks (score 0) and with flashbacks (2-5 scores)

No significant difference in the frequency of the 5HTTLPR genotypes (LL, LS or SS) between veterans without flashbacks and with flashbacks with 2-5 scores on the item B-3 from the CAPS ($\chi^2 = 3.593; \text{df} = 2; P = 0.166$, $\chi^2$-test) was detected (Figure 54). These results suggest that 5HTTLPR genotypes were not significantly associated with flashbacks.

3.5. Biochemical (platelet and plasma) markers and genetic markers in veterans with PTSD with or without suicidal behavior

Figure 55. Platelet 5-HT concentration in veterans with PTSD, subdivided according to the item 3 of the HDRS into suicidal and on-suicidal veterans

Platelet 5-HT concentration was significantly different ($F=14.299; \text{df}=1,259; p=0.001$, ANOVA) between male veterans with PTSD with or without suicidal behavior.
(evaluated using item 3 of the HDRS). Veterans without suicidal behavior had 0 scores, while veterans with suicidal behavior had 1-4 scores on the item 3 of the HDRS. Non-suicidal veterans with PTSD had significantly higher (P=0.001, Tukey’s test) platelet 5-HT concentration than suicidal veterans (Figure 55). These results suggest that platelet 5-HT concentration was significantly associated with suicidal behavior.

Platelet MAO-B activity was determined in war veterans with combat related PTSD, who were subdivided according to the cigarette smoking and according to the item 3 of the HDRS into suicidal and non-suicidal veterans. One-way ANOVA revealed that MAO-B activity differed significantly (F=2.980; df=3,74; P=0.037) between smoking and non-smoking veterans with or without suicidal behavior (Figure 56). However, Tukey’s multiple comparison test revealed that platelet MAO-B activity was not significantly affected by suicidal behavior. Smoking induced this difference.

Figure 56. Platelet MAO-B activity in veterans with PTSD, subdivided according to the item 3 of the HDRS into suicidal and on-suicidal veterans, and according to the smoking

Figure 57. Plasma DBH activity in veterans with PTSD, subdivided according to the item 3 of the HDRS into suicidal and on-suicidal veterans
Plasma DBH activity was determined in war veterans with combat related PTSD subdivided into suicidal and non-suicidal veterans according to the item 3 of the HDRS. Plasma DBH activity was not significantly different (F=1.347; df=1,87; P=0.249) between veterans with or without suicidal behavior (Figure 57). These results suggest that plasma DBH activity was not associated with suicidal behavior.

The 5HTTLPR genotypes (LL, LS and SS) were determined in veterans with PTSD, who were divided into non-suicidal and suicidal veterans according to the current suicidal behavior (item 3 of the HDRS). The frequency of LL, LS and SS genotypes of the 5HTTLPR did not differ significantly (Figure 58) between non-suicidal and suicidal veterans with PTSD (χ²=4.667; df=2; P=0.096; power of performed test with alpha = 0.050: 0.463; χ² =test). These results suggest that SHTT genotypes were not significantly associated with suicidal behavior.
The frequency of MAO-B genotypes (A or G) did not differ significantly (Figure 59) between non-suicidal and suicidal veterans with PTSD ($\chi^2=1.185; \text{df}=1; P=0.276$; power of performed test with alpha = 0.050: 0.179; $\chi^2$ =test). These results suggest that MAO-B genotypes (A or G) were not significantly associated with suicidal behavior.

Figure 60: The DBH genotype frequency in veterans with PTSD, subdivided according to the item 3 of the HDRS into suicidal and on-suicidal veterans

The frequency of DBH genotypes (CC, CT and TT) was not significantly different (Figure 60) between non-suicidal and suicidal veterans with PTSD ($\chi^2=0.874; \text{df}=2; P=0.646$; power of performed test with alpha = 0.050: 0.117; $\chi^2$ =test). These results suggest that DBH genotypes were not significantly associated with suicidal behavior.

Figure 61: The 5HT2A genotype frequency in veterans with PTSD, subdivided according to the item 3 of the HDRS into suicidal and on-suicidal veterans

Suicidal behavior did not affect the distribution of 5HT2A genotypes (CC, CT and TT). Namely, no significant differences in the frequency of CC, CT or TT genotypes, (Figure 61) between non-suicidal and suicidal veterans with PTSD was detected ($\chi^2=2.235; \text{df}=2; P=0.327$; power of performed test with alpha = 0.050: 0.236; $\chi^2$
These results suggest that 5HT2A genotypes were not significantly associated with suicidal behavior.

The distribution of the AA (Met/Met), GA (Met/Val) or GG (Val/Val) genotypes between non-suicidal and suicidal veterans with PTSD ($\chi^2=3.290$; df=2; $P=0.193$; power of performed test with alpha = 0.050; 0.335; $\chi^2$-test) was similar (Figure 62), and veterans with or without suicidal behavior had similar frequency of the COMT genotypes. These results suggest that COMT genotypes were not significantly associated with suicidal behavior.

The frequency of COMT genotypes in war veterans with PTSD is shown in Figure 62.

The frequency of BDNF genotypes in war veterans with PTSD is shown in Figure 63.
No significant differences in the distribution of the BDNF AA (Met/Met), GA (Met/Val) or GG (Val/Val) genotypes between non-suicidal and suicidal veterans with PTSD ($\chi^2=2.183; \text{df}=2; P=0.336$ power of performed test with alpha = 0.050: 0.3232; $\chi^2 =\text{test}$) was found (Fig. 63). These results suggest that BDNF genotypes were not significantly associated with suicidal behavior.

4. Discussion

4.1. Biochemical (platelet and plasma) markers and genetic markers in veterans with or without PTSD

This study evaluated biomarkers (peripheral biochemical and genetic markers) as new tools to improve the diagnosis and treatment of PTSD. Investigated biomarkers were 5-HT concentration, MAO-B activity, plasma DBH activity, and genetic markers, i.e. polymorphisms of the genes coding for enzymes involved in the catabolism of catecholamines, and genes coding for receptors and transporters of 5-HT, such as MAO-B gene, DBH gene, COMT gene, BDNF gene, 5HTT gene and 5HT2A gene. Some of the biomarkers significantly associated with PTSD might be used as tools to improve the diagnosis and treatment of PTSD.

Our results have shown that platelet MAO-B activity and plasma DBH activity were significantly associated with PTSD. These findings are in line with some previous suggestions of the possible biomarkers for PTSD [11]. According to Zhang et al. [11], biomarkers might be classified as type 0, type 1, type 2 or surrogate end point and risk markers. Type 0 biomarker is related to the natural history of a disease and is in correlation with known clinical indices. Type 1 biomarker is related to therapeutic intervention in accordance with its mechanism of action and surrogate end point (type 2 biomarker) is intended to substitute for a clinical end point. A surrogate end point is expected to predict clinical benefit (harm or lack of benefit) on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence. A risk marker can be measured quantitatively in the subject at risk, it can be used to identify cohorts for prevention, and may also be used as endpoints in prevention studies [11]. These authors proposed potential biomarkers of PTSD: T cell phenotypes, erythrocyte sedimentation rate, white blood cell count, cortisol/dehydroepiandrosterone-sulfate ratio, endothelial dysfunction in plasma, serum interleukin-2 and interleukin-8 levels, platelet 5-HT concentration and platelet MAO activity, circulating cortisol levels, glucocorticoid receptor expression in lymphocyte, WFS1 gene, baseline level of platelet-leukocyte aggregates, platelet CD63 expression, soluble P-selectin concentration, GABA plasma levels, S-100B and neuron-specific enolase, NPY expression, myelin basic protein, C-reactive protein, serum amyloid A, urinary dopamine, thyroid hormone, neopterin, plasma and cerebrospinal fluid interleukin-6 concentrations, REM latency, average heart rate responses to a series of sudden, loud-tone presentations, mixed lateral preference, parental left-handedness, and startle responses [11].

Within these proposed biomarkers, we have confirmed (present study) that platelet MAO-B activity might be used as a biomarker for PTSD. Namely, we have found significantly higher platelet MAO-B activity in veterans with PTSD compared to activity of this enzyme in veterans without PTSD. These results are in agreement with
our previous data [27]. On the other hand, these results are in contradiction with some of our previous data [61]. The differences between the present and previous findings might be explained by the existence of psychotic features in our veterans with PTSD that were shown to increase platelet MAO-B activity [27]. The substrates for MAO-B are beta-phenylethylamine, benzylamine, dopamine, tyramine and tryptamine, and this enzyme is selectively inhibited by deprenyl [62, 63]. In some conditions when MAO-A is missing, MAO-B oxidizes serotonin, noradrenaline and adrenaline [62]. Platelet MAO-B activity has been proposed to represent a biomarker of the altered central 5-HT neurotransmission. Altered platelet MAO-B activity has been found in different psychopathological conditions, neuropsychiatric disorders and altered behaviors [62]. It is assumed that deficits of the 5-HT system are related to development of PTSD [64, 65]. In line with this hypothesis, various behaviors such as impulsivity, hostility, irritability, psychopathic deviance or violence, antisocial, borderline, narcissistic and histrionic personality traits, suicidal behavior, overt aggressive behavior, intermittent explosive disorder, and substance or alcohol abuse are mediated by central 5-HT system [29, 66, 67]. Central 5-HT also regulates cognition and memory systems, and cognitive disturbances and deficits are characteristic symptoms of PTSD [68]. In agreement, our present and previous results [27] showed that platelet MAO-B activity is increased in PTSD, indicating altered serotonergic function in PTSD.

In addition, in agreement with the proposal that urinary dopamine is a biomarker of PTSD [11], we have found significantly lower plasma DBH activity in veterans with PTSD compared to plasma DBH activity in veterans without PTSD. It is assumed that PTSD is associated with abnormalities in dopamine- and noradrenaline-mediated neurotransmission [65]. Dopaminergic abnormalities, such as an increase in plasma [69] and urine [70] were consistently found in individuals with PTSD. The enzyme DBH converts dopamine to noradrenaline. DBH is present within synaptic vesicle, released concurrently and proportionately with noradrenaline and can be found in the cerebrospinal fluid, plasma and serum. There are reports of the altered DBH activity in various psychiatric disorders [71], such as lower plasma DBH activity in paranoid schizophrenic [72], unipolar geriatric delusional depression [73], unipolar depression with psychotic features [74] and alcoholism [59]. Higher plasma DBH activity has been associated with psychotic PTSD [75], and psychotic bipolar depression [76]. Therefore, our present and previous results [60] confirmed that lower plasma DBH activity is a characteristic feature of PTSD.

Other studied biomarkers, such as 5HTTLPR, MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, and BDNF Val66Met were not significantly associated with PTSD. Namely, the present study could not detect any significant difference in the distribution of the gene variants of the 5HTTLPR, MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, and BDNF Val66Met between Croatian war veterans with current and chronic combat related PTSD and veterans, matched for combat experience, who did not develop PTSD. The only significant finding was a significant difference in the frequency of the 102T/C 5HT2A genotypes between veterans with or without PTSD. Since there was only one carrier of the TT genotype of the 102T/C 5HT2A in the group of veterans without PTSD, and this genotype presumably contributed to this significant difference, these results should be confirmed in the larger groups.
4.2. **Biochemical (platelet and plasma) markers and genetic markers in veterans with psychotic PTSD compared to veterans with PTSD without psychotic features**

Since we did not expect that all biomarkers would be associated with PTSD due to its heterogeneity and complexity, biomarkers were evaluated in association with smaller sub-symptoms such as psychotic features, suicidal behavior, and sleep disturbances. Namely, it has been proposed that platelet biomarkers are associated with a single psychological dysfunction [77], or a specific phenotype [78-81], but not with a complex diagnostic entity, such as PTSD [68]. A proportion of our combat exposed veterans have developed a severe “subtype” of PTSD, complicated with psychotic features [19-21, 25, 28, 82], which were manifested in pronounced psychotic symptoms listed on the PANSS. These psychotic symptoms were secondary to the primary PTSD. Psychotic features were more strongly associated with characteristics of PTSD than with characteristics of psychotic disorders or major depressive disorder with psychotic features [20, 21, 28]. Psychotic symptoms were: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, emotional withdrawal, passive/apathetic social withdrawal, guilt feelings, depression, motor retardation, unusual thought content, disorientation, disturbance of volition, poor impulse control and active social avoidance, anger and affective liability.

In veterans with PTSD complicated with psychotic features, platelet 5-HT concentration, platelet MAO-B activity and BDNF Val66Met were significantly associated with psychotic symptoms. Namely, we have found, in line with our previous results [83], that platelet 5-HT concentration was significantly higher in psychotic compared to nonpsychotic veterans with PTSD. Therefore, our present and previous results [83], together with the proposal by Zhang et al. [11], suggest that platelet 5-HT concentration might be used as a biomarker for psychotic subtype of PTSD.

In addition, platelet MAO-B activity also differed significantly between war veterans with or without psychotic features. Veterans with psychotic PTSD had higher platelet MAO-B activity than veterans with PTSD without psychotic features. This finding agrees with the increased platelet MAO-B activity detected in risk-admitting high-risk drivers compared to controls and risk-denying high-risk drivers [80], or in anxious subjects [78, 84], especially after adjusting for the effect of smoking.

From the genetic markers studied, only BDNF Val66Met was significantly associated with psychotic symptoms in PTSD. We have found significant differences in the distribution of the BDNF Val66Met genotypes between veterans with psychotic compared to non-psychotic PTSD. In line with our recent study [26]. BDNF is a neurotrophic factor, with an important role in neuronal function, neuro-development and synaptic plasticity. It affects cognition, memory, learning, and mood. It is involved in molecular and behavioral responsiveness to stress. BDNF regulates serotonergic, glutamatergic, cholinergic, and dopaminergic neurotransmission [85, 86]. Its levels in plasma were found to be lower in the first episode psychosis [87], schizophrenia [88], depression [89] and bipolar disorder [90] associated with childhood trauma, and PTSD [91]. Altered BDNF levels might reflect the impaired neuroplasticity regardless of the diagnosis. BDNF secretion is under influence of the BDNF Val66Met [92]. This polymorphism, with a Met variant of the BDNF Val66Met, has been reported to be associated with decreased activity-dependent BDNF secretion from the cultured hippocampal neurons [92]. BDNF Val66Met was reported to be associated with stressful life events, and suicide victims. Met carriers (i.e. carriers of the combined
Met/Met and Met/Val genotypes) were more frequently found in those victims who experienced stressful life events in childhood than in the group of suicide victims with the homozygous Val/Val genotype [93]. Compared to controls, Met carriers were more frequently detected in suicide victims who committed suicide with violent methods [93]. In addition, patients with Alzheimer’s disease with psychotic symptoms were more frequently Met carriers than patients with Alzheimer’s disease with non-psychotic symptoms [58]. It is assumed that BDNF Val66Met might have a role in the impaired fear extinction, since the Met allele was significantly associated with reduced activation of the ventro-medial prefrontal cortex [94]. BDNF Val66Met was significantly associated with psychotic disorders [86]. Since combat exposed veterans frequently develop PTSD with psychotic symptoms [22], BDNF Val66Met was significantly associated with psychotic subtype of PTSD, although it was not associated with PTSD [present study][26, 95, 96]. These results confirmed a significant association between BDNF Val66Met and psychosis [86].

The higher platelet 5-HT concentration and platelet MAO-B activity and more Met carriers of the BDNF Val66Met found in veterans with psychotic combat related PTSD, confirmed that psychotic PTSD subtype is pharmacologically [19, 21, 25, 28], as well as biologically [2, 18-20, 82] a distinct subtype of PTSD, that differs from nonpsychotic PTSD.

Other studied biomarkers, such as plasma DBH activity, 5HHTLPR, MAO-B intron 13, -1021C/T DBH, and COMT Val158/108Met were not significantly associated with psychotic subtype of PTSD. These results suggested that plasma DBH activity, and gene variants of the 5HHTLPR, MAO-B intron 13, -1021C/T DBH, and COMT Val158/108Met were not related to psychotic PTSD, and could not be used as biomarkers of this specific more severe subtype of PTSD.

4.3. Biochemical (platelet and plasma) markers and genetic markers in veterans with PTSD with or without insomnia and other sleep disturbances

The characteristic symptoms of PTSD include sleep disturbances such as early, middle or late insomnia, nightmares, interrupted sleep, difficulties in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors, recurrent distressing dreams of the event and flashbacks. These sleep disturbances were evaluated according to particular items of the HAMA, HDRS and CAPS. Some of the studied biomarkers, such as platelet 5-HT concentration, were reported to be affected by insomnia [97-99]. The neural pathways involved in the regulation of sleep waking cycle include serotonergic raphe nuclei, noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus and dopaminergic neurons in the ventral periaqueductal gray matter [100], but also the GABA-ergic neurons located in the preoptic area of the hypothalamus, and the adenosinergic system affecting several major areas of the brain [101, 102]. In the present study we have found a significant association between insomnia and other sleep disturbances and platelet 5-HT concentration, platelet MAO-B activity and 5HHTLPR genotypes. Namely, platelet 5-HT concentration was significantly lower in veterans with PTSD with insomnia, determined according to the item 4 from the HAMA, with 1-4 scores on the item 4 of the HAMA, compared to platelet 5-HT concentration in veterans without insomnia. In addition, platelet 5-HT concentration was also significantly reduced in veterans with flashbacks (evaluated according to the item B-3 from the CAPS who had 2-5 scores on the item B-3 from the
CAPS), compared to veterans without (score 0) flashbacks. Although platelet MAO-B activity was significantly different between smoking and non-smoking veterans with or without early, middle or late insomnia and other sleep disturbances, our analyses revealed that the presence of insomnia and other sleep disturbances did not affect significantly platelet MAO-B activity. Smoking status was a significant factor that affected platelet MAO-B activity, and therefore platelet MAO-B activity might not be used as a biomarker of sleep disturbances in veterans with PTSD. On the other hand, the distribution of the 5HTTLPR genotypes was significantly different between veterans with different scores of the early insomnia, evaluated according to the item 4 of the HDRS, compared to veterans without early insomnia, and between veterans with and without early insomnia, evaluated according to the item 4 of the HDRS. The frequency of the 5HTTLPR genotypes was marginally different between veterans with difficulties in falling or staying asleep (evaluated according to the item D1 from the CAPS), compared to frequency in veterans without difficulties in falling or staying asleep. 5HTTLPR genotype frequency was significantly different between veterans with PTSD sub-divided according to the item B-3 from the CAPS into veterans without (score 0) and with flashbacks (2-5 scores). These results are in line with the frequent sleep disturbances, such as flashbacks and insomnia in PTSD [40, 42, 103, 104]. Since 5-HT regulates sleep/waking cycle and arousal, our present and previous data [97, 98] confirmed that peripheral biochemical marker, platelet 5-HT concentration, was significantly lower in veterans with PTSD whom had insomnia or flashbacks compared to veterans without sleep disturbances. These findings suggest that platelet 5-HT concentration might be used as a biomarker of sleep disturbances in PTSD. The genetic marker, 5HTTLPR, was also significantly associated with sleep disturbances. The distribution of the 5HTTLPR genotypes was significantly different between veterans with early insomnia, compared to veterans without early insomnia, and between veterans with and without flashbacks. These data confirm the important role of 5-HT system in sleep/waking state regulation, and show a significant association between 5HTTLPR and sleep disturbances in PTSD. These results also indicate that 5HTTLPR genotypes might be used as biomarkers of difficulties in falling or staying asleep, recurrent distressing dreams of the event, and flashbacks [40, 42], which are frequent in PTSD.

4.4. Biochemical (platelet and plasma) markers and genetic markers in veterans with PTSD with or without suicidal behavior

The objectives were to determine whether biomarkers, platelet 5-HT concentration, platelet MAO-B activity, plasma DBH activity and genotypes of the MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, BDNF Val66Met, 102T/C 5HT2A, and 5HTTLPR are associated with suicidal behavior in veterans with PTSD. Platelet 5-HT concentration, platelet MAO-B activity, plasma DBH activity and genotypes of the MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, BDNF Val66Met, 102T/C 5HT2A, and 5HTTLPR were determined in suicidal and non-suicidal veterans with PTSD.

Psychiatrists using item 3 from the HDRS 17-item scale, assessed current suicidal behavior. It consists of 0-4 scores. Veterans were subdivided into non-suicidal, i.e. with 0 scores (absence of any suicidal thoughts or ideation) and veterans with suicidal
behavior who had 1-4 scores (feelings that life is not worth living, wishes of death, suicide ideas or gestures, and attempts of suicide) [50].

In line with our previous data [52, 105-109], platelet 5-HT concentration was significantly lowered in suicidal compared to non-suicidal veterans with PTSD. These data indicate that in un-medicated psychiatric patients with different diagnoses (except alcoholism, see [110], platelet 5-HT concentration might be used as a biomarker of suicidal behavior. Namely, in suicidal subjects with PTSD [present data][109], depression [52, 105], and acute psychotic episode [108], platelet 5-HT concentration is significantly lower compared to values in non-suicidal patients. These data reveal that platelet 5-HT concentration is significantly associated with suicidal behavior. This proposal is in line with our previous findings [52, 105-109] however the opposite conclusions also exist [77, 111]. Since suicide is a global health problem that is responsible for 2% of the deaths worldwide [30, 31], in order to prevent suicidal attempts and to reduce suicide-induced deaths, our data suggest that using the easy obtainable blood sample and measuring platelet 5-HT concentration might indicate a predisposition to suicidal attempts and help in prevention of suicidal behavior by a proper treatment.

Other biomarkers, such as platelet MAO-B activity, plasma DBH activity and genotypes of the MAO-B intron 13, -1021C/T DBH, COMT Val158/108Met, BDNF Val66Met, 102T/C 5HT2A, and 5HTTLPR were not significantly associated with suicidal behavior in veterans with PTSD.

5. Conclusion

Biomarkers studied differed significantly between veterans with or without PTSD, with or without suicidal behavior, and/or psychotic symptoms and/or sleep disturbances and insomnia, and therefore, some of these biomarkers (peripheral biochemical as well as genetic markers), might be used as new tools to improve the diagnosis and treatment of PTSD.

References


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Section 2
Screening
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Early Identification of Risk for Posttraumatic Stress Disorder after Military Deployment

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Abstract. PTSD is common after combat, but onset is frequently delayed until months after return. This “honeymoon effect” affords opportunities to prevent PTSD if high-risk individuals can be identified. We report our iterative effort to educate military family members to recognize symptoms and facilitate intervention, along with preliminary results from direct longitudinal assessment of returning service members for development of PTSD. We conducted focus groups with military families and incorporated their feedback into an educational website which we piloted before evaluating PTSD-related knowledge with a 25-item questionnaire in 497 military family members before and after their use of the website. We also documented interventions reported by 217 of the family members, who, subsequently, returned to the site. In a separate ongoing study, we are assessing 100 service members within 2 months of return from combat with novel brain imaging, psychophysiology, genetic and neuroendocrine measures, followed by serial evaluations to identify the baseline measures that best predict subsequent PTSD. Our educational website improved PTSD-related knowledge from a mean 13.9 correct responses beforehand to 18.7 after (p < .001; effect size 1.2). Nearly 60% of family members returning to the site had intervened with a service member; 74% of them reported discussion with the service member about their symptoms was helpful, as did 91% who persuaded them to see a healthcare provider. Preliminary analysis of the direct assessment of service members indicates that psychophysiological measures are significantly different between those with subthreshold symptoms of PTSD versus those with very few PTSD symptoms. A web-based intervention can improve PTSD-related knowledge and foster behavioral changes in military family members. Risk stratification of service members via assessment upon their return from deployment also has the potential to facilitate targeted interventions. While others have developed PTSD-related educational websites, we believe we are the first to document their efficacy, both with regard to knowledge and behavioral enhancement. Our direct assessment of service members is unique in its comprehensiveness, and holds great promise for risk stratification.

Keywords. posttraumatic stress disorder, anxiety disorders, combats stress, computer-based education

Introduction

Posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) have been called signature injuries of the wars in Iraq and Afghanistan; in fact, PTSD is approximately 2.5 times more common after deployment to Afghanistan and 5 times more common
after deployment to Iraq, than for non-deployed SMs [1]. PTSD and TBI are associated with more frequent social withdrawal, anger and irritability as well as higher rates of depression and other mental disorders, poor physical health, impaired occupational and social function, and higher healthcare utilization, costing billions in lost wages and medical care. Sequelae may include citations for driving under the influence, domestic violence, divorce, and even suicide or homicide, that may put a dramatic and unfortunate end to a military career or even a life. Mild TBI has been report to account for between 75 and 99% of all TBI experienced by U.S. service members who were deployed to Iraq [2]. Although moderate to severe TBI is readily diagnosed, the diagnosis of both PTSD and mild TBI, as well as depression, relies largely on self-report, can be relatively subjective, and there is considerable overlap between them; the ambiguity that surrounds their diagnosis, prognosis, and long term implications warrants considerable research.

Although TBI is used as an all-encompassing term in the lay media, it is really a point of injury diagnosis, whereas the consequent persistence of symptoms over time, paralleling PTSD, is more accurately characterized as Post Concussive Syndrome (PCS). PCS represents the manifestation of at least 3 symptoms over a three-month period that is believed to be attributable to the prior head injury. We will focus more on PCS than TBI here because it is really the symptoms that linger on over time that have the greatest import.

In conducting research on these challenging post-war conditions, it is important to recognize that the presentations of PTSD and depression are often delayed until months after return from deployment. For example, a study of service members evacuated from Iraq or Afghanistan to Washington, D.C.’s Walter Reed Army Medical Center as inpatients identified PTSD and depression rates of only 3-4% initially, and while more than half of those had resolution over the ensuing 3 months, approximately 10% had a new diagnosis of PTSD or depression at 3-6 months [3]. This honeymoon effect is likely multi-factorial, and highlights the fact that PTSD in military service members has some substantial differences from the disorder that has been described in civilians. As opposed to a single traumatic event, military service members frequently find the need to maintain hypervigilance throughout the entire period when they are in the war zone; the modern battlefield has no safe zone or front line, and it is often unclear whom one can trust within the civilian population, as any vehicle or even a pedestrian woman or child could be carrying an Improvised Explosive Device (IED). Upon return home, many service members remain hypervigilant, have difficulty returning to a normal sleep pattern, and have a variety of other challenges adjusting. However, expectations that these symptoms will subside often lead service members to underreport symptoms when queried early after their return. Moreover, there are many positive aspects as they are reunited with loved ones that may lead service members to overlook symptoms, so that it is only months later that they recognize that they have a variety of symptoms that are not getting better. Thus, we believe that a method for identifying those at high risk for persistent symptoms, especially those associated with impaired function, such as PCS, PTSD, and depression, could be particularly substantial. This is particularly important because currently available treatments for PTSD and depression are at best effective about half the time, and for PCS there are really no well-validated therapies. While improved treatment modalities for full-blown disorders must be pursued simultaneously, it is especially important to focus on ways to identify those at high risk earlier in order to facilitate early intervention. At present, by the time PTSD is diagnosed, service members have often had impairment for so long that retention on
active duty seems unlikely, even with state-of-the-art treatment. Prevention, or early intervention made possible by identifying those at high risk upon return from deployment, may hold much more promise. In this chapter we will discuss two methods for improving early identification.

1. The Impact of Deployment-Related Stress on Military Members

PTSD impairs service members’ functional status in multiple domains, including the home, with significant repercussions for their family members. Marked distress has been documented in female domestic partners of combat veterans with PTSD [4], and rates of mental health problems in spouses have been documented to be comparable to those seen in the deployed [5]. Additional research documents higher symptom rates in spouses who believe the service member is more symptomatic, particularly when spouses view the service members’ symptoms as being more severe than do the service members themselves [6]. Army wives have been identified to have significant increases in rates of depression, anxiety disorders, adjustment disorders, and sleep disorders in relation to their husbands’ deployment, especially with longer deployments [7]. Interventions for military family members have been recommended [8,9], and programs such as SOFAR (Strategic Outreach to Families of All Reservists) and FOCUS (Families Overcoming Under Stress) provide resources to help military families cope with stressors. However, it was only quite recently that we were the first to report the impact of tailored PTSD-related educational efforts on military family members.

Since service members commonly have several weeks of leave shortly after their return from deployment, their family members can generally be expected to have the greatest contact with them during that time, especially in settings where the service member can let their guard down. Thus, family members are ideally positioned to identify warning signals earlier than others, which could enable them to have a role in helping to prevent stress-induced impairment. However, actually being able to recognize such cues and then respond in an effective manner, leading the service member to get the help they need for these symptoms, requires pertinent knowledge on the part of family members. We therefore sought to ascertain what the baseline level of knowledge is in military family members, followed that assessment by fostering their use of an educational website that we developed expressly for military family members, and then determined whether their knowledge of PTSD and related conditions was significantly enhanced by their use of the site.

2. Intervening with Military Families on-Line: Postdeploymenthealth.com

We conducted a three-phase study to try to evaluate the extent to which we could engage military family members in an educational website addressing PTSD, how much this could improve their knowledge, and finally, whether the acquisition of this knowledge would in turn lead them to make behavioral changes that could be beneficial to service members. The first phase involved focus groups to gather the input of family members from diverse military services about what they would like to see in a website; the second phase was a pilot study to assess the experiences of some military family members with our initial draft of the website, and then the final phase was our scientific evaluation of the impact upon the knowledge and behavior of
military family members, of the ultimate version of the website after modifications were made based on the pilot study experience.

2.1 Phase I: Focus Groups

We convened focus groups at three sites across the United States, chosen to attract participation by family members from diverse backgrounds and service branches, since the length and nature of deployments can vary considerably between services. Participants were recruited through local Family Readiness Groups and Family Advocacy Programs. The first focus group was conducted at San Diego Naval Base in California, with 12 family members of active duty sailors and marines. The second was held at Fort Indiantown Gap, Pennsylvania, attracting 13 family members associated with reserve component and National Guard units. A third group was convened at Fort Bragg, North Carolina with eight family members from the Army’s active duty 82nd Airborne Division. Nearly all participants were spouses or significant others of service members, but two children of service members provided a teen perspective. Each focus group lasted approximately 90 minutes; as an Army primary care physician, I co-led each of the groups with a civilian psychologist.

Group facilitators initially sought to elicit participants’ personal experience with deployment-related stressors as well as their current understanding of PTSD and related conditions. Group members provided many vivid examples of stressors impacting service members (e.g., a service member swerving across several lanes of traffic after seeing an abandoned bag on the roadside) as well as family members (e.g., resumption of bedwetting in a child that had been toilet trained). Other topics that were discussed included preferred website content and applications, confidentiality, and the best methods for promoting awareness of the website among military family member populations. Family members of active duty service members, both in San Diego and at Fort Bragg, expressed concerns about confidentiality, worrying that if they used the site and responded to questions or engaged in dialogue, their inquiries and replies pertaining to PTSD, may ultimately, adversely affect the careers of the service member to which they are related. Families of National Guard and reserve component service members at Fort Indiantown Gap did not feel that such issues were of concern. Participants in all three focus groups felt strongly that the site needed to be user-friendly and easily navigable, with clear font and pictures interspersed with text. Many emphasized the importance of being able to easily identify content that would be especially relevant to them based on their personal demographics (e.g., the wife of an active duty service member with young children). Focus group participants desired that information be presented in layman terms, wanted to see information addressing impact of deployment on children across all ages, and felt that local as well as national referral sources would be helpful. They also voiced a preference for interactive features such as moderated forums or blogs where they could post comments and obtain answers to specific questions. Participants were interested in hearing the stories of others, especially families who survived deployment and its aftermath successfully, to both provide an idea of what to expect during and after deployment, as well as a guide for how to navigate these periods. Many focus group participants also felt that it would be best to try to make the website not appear too “military” in color or appearance, as a way of creating an image of independence. Finally, while they thought it was important for psychological health issues to be addressed, they wanted the presentation to be relatively subtle to mitigate stigmatization. As a result of the focus
group input, the site name and URL were changed from “Behavioral Health Readiness System” to “Post Deployment Health” and the primary background color was modified from olive green to teal. The overall website appearance was simplified to promote ease of use, with larger font, more pictures, and implementation of tabs to facilitate reaching targeted content.

2.2 Phase II: Pilot Study of the Website

Educational content for the website was carefully selected from mainstream media articles (e.g. The Washington Post, New York Times, and popular magazines), leading medical journals (e.g., New England Journal of Medicine, Journal of the American Medical Association), and on-line resources from organizations such as the National Institutes of Health. Each article or link was prefaced by summaries of approximately a paragraph in length, oriented toward military family members, emphasizing in readily understandable language why this information might be of interest to the family member. Family members who used the website were afforded the opportunity to rate the quality of the articles as well as to identify the specific audience (e.g., service members, spouses, teenage children) they believed would find the information most relevant.

The 100 military family members who took part in the pilot study answered questions about their demographic backgrounds before using the site, along with a 25-item PTSD-related knowledge questionnaire both before and after their use of the site, with a minimum of 30 minutes required on the site; successful completion was rewarded with a $25 Amazon® gift card. Pilot phase participants were recruited through military Family Readiness Groups and Family Advocacy Programs on military posts. Pilot study participants demonstrated a significant increase in PTSD knowledge scores between pre-test (14.79 ± 5.59) and post-test (19.30 ± 2.49; t (100) = -7.70; p < .001) on the 25-item test. Some pilot phase participants also provided anecdotal feedback such as:

- "Overall, I love the site, and ease of use. Great summary of research articles. It makes them easy for the average person to read in plain language."
- “More information to help with the issue of stigma are [sic] recommended.”
- "I have to say, I am very, very happy that this study is being conducted. This site provides so much information! It definitely makes me feel better knowing that I have a place to turn to obtain information for such a sensitive issue. THANK YOU!"

2.3 Phase III: Primary Study of the Website

Upon completion of the pilot study, several questionnaire items were modified in order to improve their utility. The website content was regularly updated to incorporate new lay press and medical articles throughout both the pilot and main study periods. The main study included 497 military family members who completed questionnaires both before and after using the website for at least 30 minutes, and as in the pilot study, they then were eligible for $25 Amazon® gift cards. In addition, users of the site were asked to return 10 or more days later to complete a returning user questionnaire that included the same 25 questions to assess their knowledge, along with a series of questions that asked about actions they may have taken since their first use of the site. The 217 family
members who completed the returning user questionnaire were also provided with $20 Amazon® gift cards.

2.3.1 Analyses

A paired t-test was conducted to compare the knowledge score obtained on the post-site-use test with that from before the participant used the site. The knowledge score for each time point represents the number of questions answered correctly out of a total of 25 questions pertaining to understanding of PTSD. The McNemar test of dependent proportions was employed to evaluate whether users were more likely to endorse a correct response at posttest versus pretest on the 25-item knowledge questionnaire. A Bonferroni correction was used to adjust for multiple comparisons: .05/25 = .002. In order to assess whether there were significant differences on pre-post test scores based on the reported educational level obtained, a Random Means analysis of variance (RM ANOVA) was performed. All statistical analyses were performed using SPSS (A subsidiary of IBM, Armonk, NY).

2.3.2 Results from the Main Study, Initial Site Use

The demographic characteristics of the 497 valid respondents, those of the military service member in their family, and their beliefs about the health of that member, are presented alongside those of the pilot study participants in Tables 1, 2 and 3, respectively. Not surprisingly, the majority of respondents were wives of service members, particularly Army soldiers. Between 10 and 18% reported that the military service member to which they were related had been told by a medical provider that they had depression, PTSD or TBI, and more than half said the service member was “not the same” as before deployment. Many witnessed significant behavioral changes in the service members, with nearly half reporting greater irritability and forgetfulness, and 30-40% each observing greater social withdrawal, anhedonia, down or depressed mood, sleep problems, being easily startled, and greater alcohol or tobacco use.

Primary study participants demonstrated a significant increase in correct scores on the 25 PTSD knowledge items between pre-test (13.92 ± 4.72) and post-test (18.68 ± 3.12; t (495) = -22.42; p < .001). The proportion of correct responses in the study population significantly increased between pre and post website use administration for 23 of the 25 items on the PTSD Knowledge questionnaire (p < .002). For the other two items, there was not a significant change in the proportion of correct responses. For one of these, which asked the user to identify an example of a PTSD flashback, there was a strong trend (p=.008) favoring improved knowledge, but it did not quite achieve the high standard of statistical significance we required due to the number of comparisons being assessed. For the final item there was no significant change in the percentage answering correctly after use of the site. We examined questionnaire responses by educational background, which showed that those with more years of formal schooling did better on the pretest before using the site, and such individuals then had less of an absolute improvement than did those with less prior formal education with the use of the site. While those with more prior education still performed better on the post-test, use of the site helped to significantly narrow the performance gap, as those with less prior years of schooling saw their scores increase to a greater degree.
2.3.3 Results from the Main Study, Returning Site Use

There were 217 users who returned to the site 10 or more days after their initial use and completed the PTSD Knowledge Questionnaire for a third time. During their return visit, they also answered a series of questions about their use of resources to learn about PTSD, self-reported help-seeking behavior, and questions about their family member symptoms (which were the same as those asked at the pre-test). The average number of days between post-test and returning user visit was 24.5 ± 45.4 (range 11-219).

When users were asked: “Since your initial visit to this site at least 10 days ago, have you, learned more about PTSD and combat stress from any other sources?” 63.6% replied affirmatively, with the most commonly sources being another website (46.5%) or printed material (28.6%). Despite the fact that most sought information about PTSD from other sources, they did not achieve a higher score on the knowledge test, though their scores were stable, indicating retention of the knowledge acquired at the time of their previous use of the website.

A majority of the 217 returning site users (57%) reported taking some sort of action after using the site. Nearly all of these (56% of the entire sample) had a discussion with the service member about their symptoms. Also, 34% of the returning users persuaded the service member to get medical attention for their symptoms. Figure 1 depicts the percentage who persuaded the service member to see a primary care specialist, a mental health specialist, or both. The great majority of those who took some action thought it had a favorable impact, including 74% of those who had a discussion with the service member about their symptoms, 82% of those who persuaded the service member to see a healthcare provider, and 95% who persuaded them to see a mental health specialist.

2.4 Lessons Learned from Postdeploymenthealth.com

We believe our study represents the first reported scientific evaluation of the impact on knowledge levels of military family members regarding a relevant and significant health concern, in this case PTSD. We document that use of our website was associated with highly significant improvements in knowledge as measured on a 25-item questionnaire; in fact, a significant increase in correct answers was seen after the use of the website for nearly every question. Even more notable, we demonstrated that most site users reporting taking action to try to help the service member in their family after only a brief time interval since their first use of the site. The overwhelming majority who did so through their actions was beneficial. We therefore demonstrated that an educational website is not only feasible, but also effective in both improving military family members’ knowledge of PTSD and engendering positive actions. Previous studies of military service members have documented significant concerns about stigma that have prevented military service members from getting help even when they recognized they had problems [1,10], so these are highly relevant behavioral changes. Given such concerns about stigma, web-based content can be particularly valuable as a method for providing information and tools to military service members and their families about psychological health issues after deployment.

The picture of military service members’ health, as portrayed by the family members who participated in our study, is undoubtedly concerning, and complements studies that have focused directly upon service members themselves [1,3,11]. Even
when diagnoses are not made, sleep disturbances and increased alcohol use—reported by a quarter and a sixth of respondents, respectively—can increase motor vehicle accidents and other events that may decrease life expectancy, and symptoms such as the irritability and withdrawal that were reported by a majority of participants increase marital strife contributing to higher rates of separation and divorce, which in turn adversely impact children in military families. It is also interesting to note that in the pilot, we asked family members whether they thought the service member had a particular diagnosis, whereas in the main study we asked whether a medical professional had given them the diagnosis; for the former, the positive responses ranged from only 1% for alcohol or substance abuse, up to 7.9% for depression, whereas for the latter the corresponding numbers rose to 14.5% for alcohol or substance abuse, and 18.7% for depression, respectively, a truly remarkable difference. This most likely predominantly represents solidarity with the service member along with fear of stigmatizing them: they don’t want to “label” the service member themselves, but more willingly attribute a diagnosis to a third party.

The results of this study indicate that web-based content has tremendous potential to impact knowledge and behavior. Future studies might seek to expand the range of web-based services provided; avatars could be employed to present different reactions service members with PTSD might have to various circumstances, facilitating role-play by military family members that could then foster more effective discussions and interventional efforts by family members after service members return from deployment. PTSD is common after deployment and is associated with marked morbidity and mortality. Fear of stigmatization leads to dramatically reduced utilization of healthcare services by returning military service members, and our study demonstrates that interventions targeted at their family members can persuade them to get the medical attention they need. Future studies should look at additional ways to harness the Internet to give family members the tools they need to help the military service members that return to them. While this approach may not directly reduce the high rate of symptoms observed in returning service members, it may limit adverse outcomes such as divorce and even mortality, so it would be worthwhile to incorporate hard outcomes in future studies.

3. Direct Evaluation of Service Members to Identify those at High Risk after Deployment: The Predictors Study

3.1 Background

At one time, group debriefing of individuals exposed to trauma was widely employed to try to prevent PTSD, because it seemed sensible. However, scientific evaluation subsequently found that debriefing conferred no benefit, and might even cause harm. Effective intervention to prevent PTSD and TBI must be predicated upon reliable early identification of those at highest risk, and then the intervention methods must be prospectively validated. Although PTSD and TBI have received considerable attention during the current conflicts in Iraq and Afghanistan, they still only afflict a minority of service members who deploy, so blind interventions are relatively impractical, as are efforts to try to screen individuals before deployment to identify those at greatest risk. Identification of independent predictors of PTSD and PCS upon return from deployment is far more practical and could realistically facilitate early intervention to prevent incident cases and disability, by identifying those at greatest risk and targeting
them with validated interventions. Unfortunately, effective methods of identification and early intervention for both PTSD and PCS currently represent significant research gaps. There are a variety of potential ways to try to sort out those service members at greatest risk for developing these complications of deployment to a warzone, and selection of any one of them might have some value in early identification; however, my belief that their combined assessment in a single prospective cohort study has far greater power to positively impact the health of SMs led to my undertaking of the “Predictors” study. The study design is highly innovative both in the sheer number of potentially high yield independent variables, as well as in the uniqueness of some of those variables, including assessment of psychophysiological responses to a Virtual Iraq/Afghanistan environment, advanced imaging techniques, and olfactory function. By assembling a wealth of expertise in a team of multidisciplinary researchers the predictors study has the potential to begin to identify the most promising baseline measures, to be followed in turn by the development of a risk index, and then in turn with a series of early intervention studies to prevent the chronic disability now inherent with TBI and PTSD. By necessity, confirmation of the utility of independent predictors must be a sequential process, and this study is the essential first step, assessing a broad range of measures to ascertain those that have the greatest promise to identify those at greatest risk for PTSD and PCS. This study has high military relevance because PTSD and PCS are frequent causes of disability and separation from military service. We anticipate that this study will ultimately improve functional status and retention rates for high risk SMs, reducing healthcare and disability expenses. Thus, this body of research should have high impact on both individual SMs—by extending careers and improving functional status—and the military by conserving the fighting strength via facilitation of early interventions to keep SMs in their units at maximal function.

3.2 Predictors Study Design

The predictors study features a comprehensive assessment of a cohort of SMs who do not meet criteria for PTSD, PCS or depression within 2 months of their return from Iraq of Afghanistan, with a serial follow-up at 3, 6, and 12 months later, to identify the baseline measures that are most strongly associated with subsequent neuropsychologic morbidity, leading to a more focused study incorporating only the most promising measures, in turn providing a basis for early intervention studies. In order to be included in the study, participants must have been deployed for at least 3 months to either Iraq of Afghanistan, and be within 2 months of their return at the time of the baseline assessment. They must have grossly intact hearing and vision, and must have had no more than 60 minutes’ loss of consciousness. I perform a medical history and physical exam on each participant, and have identified several with elevated blood pressure as well as one with an enlarged thyroid gland, for which I have advised medical follow-up; one participant also had a newly identified pregnancy that prevented her from getting scans, but no medical conditions that have been exclusionary for the overall study. Participants must not meet criteria for PTSD (PCL-M score < 50) or major depression (PHQ-9 score < 10), and there have been several who have been excluded because of each of these conditions. The specific elements included in the baseline assessment follow.
3.2.1 Psychophysiologic Measures

Psychophysiologic measures such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and skin conductance (SC) all have been shown to do moderately well at distinguishing between individuals with full-blown PTSD and controls [12-16], placing them among the most promising predictors of PTSD in those who have not yet developed significant symptoms after trauma. A metaanalysis of 100 studies [17]—many involving all or mostly combat veterans—found that HR, followed by SC, most effectively distinguished adults with PTSD from controls. Effect sizes were larger for standardized (e.g., a gunshot) and idiographic trauma (e.g., listening a script of their trauma read in the first person, present tense, while mentally reliving the experience) cues than for resting or startle measures. However, startle responses, measuring hyperarousal (a cardinal feature of PTSD), can also distinguish PTSD from controls, and is likely even more promising than just measuring baseline psychophysiologic measures. We also believe that some measures of fear acquisition and fear extinction validated at Emory University are especially promising to be able to discern combat veterans who are most likely to go on to develop PTSD after return from deployment [18,19]. These experiments use computer-screen based cues to herald a conditioned stimulus (short burst of loud white noise) and an unconditioned stimulus (powerful blast of air to the front of the throat) in a Pavlovian approach. During the initial, fear acquisition, phase of the study, a participant sees a combination of shapes and colors (danger cue) that are always paired with an imminent loud noise that is followed by the airblast, whereas a different pattern of shapes and colors (safety cue) is linked with the subsequent presentation of the loud noise with no ensuing airblast. At other times the participant also is exposed to the noise probe without the airblast in the absence of any visual cue. Upon presentation of each visual cue, the participant is asked to press a button denoting whether they anticipate danger, safety, or whether they are uncertain. The visual cues and stimuli are presented in three blocks, each of which presents the three possibilities (danger cue, safety cue, or no cue, each followed by the corresponding stimuli) four times each in random order. The fear extinction phase of the experiment presents the same visual cues, but in this phase there are no airblasts (e.g., no danger), so that the participant learns that there is no longer harm, as each of the visual cue possibilities is presented four times each in random order within each of 6 blocks.

A final novel psychophysiologic assessment incorporates 3 2-minute sequences of the highly realistic Virtual Iraq/Afghanistan environment that we have employed successfully to treat PTSD. The sequences are presented on a computer screen rather than completely immersing the participant in the virtual environment, but feature a range of visual and auditory stimuli including explosions and gunfire.

3.2.1.1 Preliminary Analysis of Psychophysiologic Findings: A Sample Case

A comparison of the baseline psychophysiologic assessment of two study participants from the U.S. Marine Corps provides an example of the potential power of such measures. Marine A is an Exploded Ordnance Disposal (EOD) technician who by the nature of his job was in the close vicinity of many explosions while deployed, was the driver of a vehicle that hit an IED, and is the veteran of 3 deployments to Iraq or Afghanistan. Marine B is also a veteran of 3 deployments, and had several psychologically traumatic experiences including holding a fellow Marine and close
friend while he died after a mortar attack. Marine A had a Patient Health Questionnaire (PHQ-9) depression screen score of zero and a Posttraumatic Stress Disorder Checklist, Military Version (PCL-M) score of 18 (possible scores range from 17 to 85, with 50 generally considered the best cut-off score for confirming a diagnosis of PTSD). Marine B had a PHQ-9 score of 5 (scores of 5 to 9 correlate best with minor or subthreshold depression, whereas a score of 4 or less is generally considered negative for significant depressive symptoms), and a PCL-M score of 5. On the gold standard Clinician-Administered PTSD Scale (CAPS, which is 17 pages long and takes an experienced administrator about an hour to complete with the patient), the results were even more divergent, with Marine A having a total score of 5, and Marine B a score of 42. While a score of 40 or more is often consistent with a diagnosis of PTSD, Marine B did not have sufficient impairment of function or a sufficient distribution of symptoms, to meet full diagnostic criteria, however, it does appear that Marine B is at much higher risk for developing PTSD in the coming months. Our follow-up is still in progress, but a comparison of the psychophysiologic responses for the two individuals is quite interesting. In the fear acquisition phase, Marine A was able to consistently discern whether danger or safety was imminent, whereas Marine B correctly identified danger but was uncertain, and even trending toward suspecting danger, when presented with the safety cue. Physiologically, Marine A displayed marked responses in heart rate, electromyography (EMG) and galvanic skin response (GSR, a measure of skin conductance or how much one is sweating) in response to danger cues but very little response to safety cues. Marine B had similar rises in HR with both the danger and safety cues, and actually had greater GSR and EMG responses to the safety cue. In the subsequent fear extinction phase, both Marines correctly identified that they could anticipate safety (noise alone, no airblast) regardless of what visual cue was displayed. However, Marine A displayed a more marked HR and GSR response to the danger cue than the safety cue similar to the pattern observed in fear acquisition, whereas Marine B again displayed almost as much of a HR response to the safety cue as to the danger cue, and again had an even more marked GSR and EMG response to the safety cues than to the danger cues. The observed pattern suggests that Marine B really could not let his guard down, and perhaps did not really trust the safety cue. This is perhaps not surprising if one thinks about the modern combat theater where one might be presented with a seemingly harmless civilian vehicle that is in fact bearing an IED—there is no room for letting one’s guard down, hypervigilance is necessary for survival. The response pattern during the fear extinction phase is even more striking, in that Marine B was able to consciously recognize that there is no threat of harm during this phase, yet he cannot help physiologically responding with an elevated heart rate, diaphoresis, and more muscle twitching; he seems to be expecting the other shoe to drop. This is analogous to anecdotes service members often report after returning from theater; for example, one sees a bag on the side of the highway and cognitively recognizes it is probably just harmless trash, but cannot help swerving across several lanes of traffic to keep one’s distance from it.

3.2.1.2 Preliminary Analysis of Psychophysiologic Findings: Comparison of Those with Subthreshold vs. Lower PCL-M Scores at Baseline

The above comparison of two Marines is compelling, but still anecdotal. While still in the process of both conducting baseline assessments on predictors study participants, and engaged in the follow-up assessments that are scheduled for 3, 6 and 12 months
after their initial evaluations, we did an interim comparison of those with PCL-M scores of 28 to 49 with those who had scores less than 28. The cut-off level of 28 was not random, but was chosen in part because some mental health professionals have suggested that a PCL-M score of 28 or more might be used as an initial, high sensitivity screen to ensure that the overwhelming majority of military service members with PTSD would be captured, with the requirement that a subsequent more specific assessment measure (e.g., the CAPS) could be employed to clarify whether there is in fact a true diagnosis. Thus, while we await the other measures we included in the study, this provides us with a peek at how successful a distinction psychophysiologic markers might make in discerning those at high risk for PTSD from the overall military population after deployment. We therefore divided our first 50 study participants and compared the 20 with PCL-M scores of 28 or more (A27), to the 30 with scores less than 28 (B28). To be able to learn even more from these comparisons, we reviewed both the fear acquisition and fear extinction phases after dividing responses into early, middle, and late periods. While the patterns elucidated are just preliminary and may change both as the number of participants increases and as we make the originally intended comparison of those who go on to develop PTSD versus those who do not, this nevertheless provides us with some provocative data to ponder.

A27 participants had higher heart rates in response to their earliest exposures to danger cues, suggesting a higher level of preconditioned response to danger; the B28 participants had lower HR responses initially but as they became more acquainted with the danger their HR response curve closely matched the A27 curve. Conversely, in response to safety cues, both groups had a similar initial response, but the A27 group had a greater HR response over time whereas the B28 group had a diminishing response over time, so that the curves diverged. This likely represents heightened fear that something bad is going to happen on the part of those with greater scores, whereas those with lower scores feel more confident about their safety with repeated reinforcement of the safety cues. For EMG, both groups demonstrated a similar response pattern to danger cues, but it was more marked for those the A27 participants. The B28 group had a progressive decrease in EMG response to safety cues over time, whereas the A27 group showed the same response to safety cues, albeit attenuated, as they did to danger cues. Overall, A27 participants had a greater HR, EMG, and GSR response to danger cues, and also had greater difficulty inhibiting their responses to safety cues. A27 participants had a greater HR response to danger cues than B28 participants throughout the fear extinction phase, as well as to safety cues during the initial segment of the extinction phase, but the differences disappeared by the middle of the extinction period, which may lead one to conclude that those with higher PCL-M scores had a heightened sensitivity to all cues initially but were eventually able to overcome some of the anxiety the experienced with safety cue in a timeframe where there was no danger. However, GSR demonstrated a more sustained elevation in responsiveness, which, if anything, became more pronounced as time went on, in both the fear acquisition and extinction phases. Perhaps this just means that HR is a more rapid response mechanism, whereas diaphoresis is somewhat more delayed. The EMG response primarily indicated a late response during the fear acquisition phase, and was similar to HR during the fear extinction phase, and would be expected to be a relatively rapid response. It is important not to make too much of these patterns at this point since it is only a review of the baseline patterns, and for only half the study population at this point, but it is nevertheless thought-provoking to start to look at the patterns elicited.
3.2.2 Neuroendocrine measures and biomarkers

Neuroendocrine measures have significant potential as predictors of PTSD. The hypothalamic-pituitary-adrenal (HPA) axis is altered in PTSD; for example, lower baseline cortisol levels are frequent [20-21]. In civilian emergency room patients, cortisol and catecholamine levels shortly after trauma correlate with subsequent PTSD [22], but I am not aware of similar data in combat veterans. We are checking for polymorphisms in genes encoding proteins for neurotransmitter functions such as the serotonin transporter (5HTT) [23-24], the dopamine transporter (DAT) [25], and catechol O-methyltransferase (COMT) [26] which have been linked to stress, PTSD and depression in some preliminary research. We are also checking a variety of measures that either may indicate direct neuronal damage, or a response to such damage, including neuron-specific enolase (NSE), S100 A and B, and myelin basic protein (MBP), along with other potential candidates including interleukin-6 (IL-6), interleukin-10 (IL-10), neurotrophins (brain deprived neurotrophic factor, and insulin like growth factor) and neuropeptides (neurotrophin-Y, galanin) [27-28]. We draw blood samples between the hours of 0800 and 0900 at the baseline and at the follow-up visits. We obtain additional samples immediately following the end of the acquisition phase of the fear-conditioning task and at the end of the second virtual reality exposure sequence. There has been little research published to date evaluating whether such measures predict the risk for PTSD or PCS, so we believe these represent an important element of our study.

3.2.3 Brain synchronization

Measurement of brain synchronization may also predict PCS or PTSD, since loss of connectivity and diffuse neuronal loss following TBI can impair effective stimulus-response coupling and other cognitive processes. Network failures are manifest by abnormalities of event-related or stimulus-dependent central nervous system (CNS) synchronization. CNS synchronization can be measured by Electroencephalography (EEGs) and event related potentials (ERPs). ERPs are EEG signals elicited by simple stimuli (in this case visual stimuli) and reaction times recorded in response to computer administered neuropsychological tests. Abnormalities in CNS synchronization have been documented in neuropsychiatric disorders including TBI [29] and PTSD [30-31]. While some studies have suggested that ERPs might have utility in identifying evidence of TBI, our study design should enable us to assess whether this holds true in individuals not currently manifesting significant symptoms of TBI, though we have not yet begun to analyze this data.

3.2.4 Vestibular and olfactory function

We are assessing both vestibular and olfactory function, which have not been previously studied to assess their prognostic value in veterans returning from a combat arena. We perform a clinical assessment of vestibular function that includes a careful ear and eye exam, assessment for nystagmus, a Rhomberg test, assessment of cerebellar function including finger-to-nose and heel-to-shin testing, and gait assessment including heel-to-toe walk, and walking on both heels and toes. To test olfactory function, we are using the University of Pennsylvania Smell Identification Test (UPSIT) [Semsonics, Inc, Haddon Heights, and NJ], which is considered the gold
standard in the United States. The UPSIT focuses on the comparative abilities of individuals to identify a number of odorants at the supra-threshold level. It is a standardized 40 stimulus microencapsulated “scratch and sniff” test. The UPSIT test categorizes individuals into 5 distinct levels of olfactory functioning: normosmics (normal), mildly, moderately, and severely hyposmic (impaired functioning), and anosmic (no sensation). The UPSIT is a 4-alternative, forced-choice microencapsulated odorant test. Physically, the UPSIT is comprised of four test booklets, each containing 10 pages. A strip embedded with a microencapsulated odorant is present on the bottom of each page, just below a four-alternative multiple-choice question. For a given item, the patient releases an odor by scratching the microencapsulated label with a pencil tip, smells the label, and indicates the odor quality from four alternatives. The subject’s total correct score out of the 40 items is determined. This score is then compared to scores in a normative database, providing an indication of the level of absolute smell function and a percentile rank for each age and gender group. Vestibular impairment has been documented with moderate to severe TBI [32-33], especially for blast injuries, though there was little data available with regard to mild TBI. Posttraumatic olfactory deficiency (PTOD) has been documented with closed craniocerebral trauma, with the severity of the head injury presaging the frequency and degree of olfactory loss [34-37]. We wondered whether the quantitative assessment of olfaction might predict not only PCS but PTSD as well, given the close proximity of the olfactory bulb to the hippocampus, anterior cingulate gyrus, and amygdala, which are important in PTSD. However, to date, our assessments of vestibular and olfactory function have been uniformly normal.

3.2.5 Imaging

Novel imaging techniques have profound potential to clearly identify PTSD and TBI before significant symptoms are manifest. Functional magnetic resonance imaging (fMRI) is a potent, novel method for objectively assessing the impact of trauma on the central nervous system. There are several variants of fMRI, but the most widely used, best studied method is known as BOLD (blood oxygen level dependent). Exposure to sensory stimuli results in neuronal activation in corresponding areas of the brain, which increases oxygen uptake in these areas. This results in a transient (3-6 seconds) decrease in blood oxygen levels in these areas, but there is a prompt response to increase blood flow to these areas, resulting in a more sustained increase in oxygenation which overwhelms the initial increase in extraction from these areas. T2-weighted images on fMRI show greater intensity in areas of increased oxygenation. Initial studies indicate that there are clear differences between those with and without PTSD on fMRI, upon exposure to various iterations of the Stroop test, among other stimuli: patients with PTSD exposed to various stimuli have previously been shown to have greater activation in the region of the amygdala, with lesser activation in the anterior cingulate gyrus of the frontal lobe, than controls [38-40]. In fact, colleagues of ours at NIH demonstrated the utility of the Affective Stroop in distinguishing PTSD from controls [41-42], and we more recently documented its ability to show improved brain function after treatment for PTSD. In the predictors study, we are conducting structural and functional MRI, using a 3T magnet, on all participants. The amygdala, hippocampus, and anterior cingulate gyrus represent the areas of greatest interest with regard to PTSD, corroborated by our prior work with this modality. We have begun some preliminary analyses using the same comparison,
those with PCL-M scores ≥ 28 vs. those below 28, and have found some evidence of significant differences between the two groups in the frontal lobe, hippocampus, and amygdala in response to various stimuli.

In addition to fMRI, we are also performing diffusion tensor imaging (DTI), a more sophisticated form of MRI that has particular promise for identifying subtle axonal damage associated with sequelae of mild TBI [43-44][46-47]; evidence that it can identify TBI in boxers before it is clinically manifest suggests it may have particular prognostic value [39] [42]. There is some evidence that DTI has both greater sensitivity and specificity than conventional MRI TBI [43-46] [46-47,49-50]. DTI relies on the fact that at the atomic level, Brownian motion is occurring within cells, with movement of water within cell bodies such as neurons usually occurring in all directions equally (isotropic); however, the axonal projections of neurons that constitute the white matter of the brain are essentially like long tubes or pipes, so the movement of them is more in one direction than any other, or asymmetric (anisotropic). DTI enables identification and quantification of the anisotropic flow that characterizes white matter, as well as when damage to it occurs, disrupting this anisotropy; a computer-generated representation of the data can show the anatomic integrity or lack thereof.

Conclusion

In this chapter we discuss two different ways of trying to improve the early identification of military service members at high risk for PTSD, depression, or PCS after return from deployment to a war zone. We demonstrated that a website developed specifically for military family members can significantly improve their understanding of PTSD. Use of the website can also spur them to take actions that they perceive as beneficial, including initiating discussions with the service members in their families about their post-deployment symptoms, and persuading them to seek medical attention. We are currently engaged in a study to directly and comprehensively evaluate service members through a variety of assessments including novel imaging techniques, genetics, neuroendocrine measures, psychophysiology, and electrical signals between cells. We report some preliminary evidence that psychophysiologic responses to a variety of stimuli appear particularly promising for being able to risk stratify service members after combat. Upon completion of the full study, we hope to be able to identify the strongest predictors of risk after deployment, which can in turn lead to studies of early intervention to mitigate risk.

References


Psychophysiological Indicators and Biofeedback Treatment of Stress Related Disorders: Our Experience

Dragica KOZARIC-KOVACIC and Andrea JAMBROSIC SAKOMAN

Abstract. Posttraumatic stress disorder (PTSD) and other stress related disorders are characterized by prominent psychophysiological symptoms, which are measured through changes mediated by the autonomous nervous system. Psychophysiological procedures in studies of acute and chronic trauma phase such as: baseline resting studies, startle reactivity studies, standardized trauma-related cues and idiographic-trauma cues have tried to gain insight into the neurobiology of the disorder. Psychophysiological parameters in PTSD are also considered as an additional method in diagnostics of PTSD. We will present results of previous studies as well as our research in search for psychophysiological indicators of PTSD. Our experience with applied psychophysiology (biofeedback) as an add-on therapy for psychiatric disorders will be discussed since it seems promising.

Keywords. Posttraumatic stress disorder, stress related disorders, psychophysiology, acute trauma, chronic trauma, psychophysiological studies, PTSD diagnostics, applied psychophysiology, add-on therapy

Introduction

Posttraumatic stress disorder (PTSD) is a prolonged reaction can develop after an extremely traumatic event that evokes an emotional response marked by intense fear, feelings of helplessness, or horror. Diagnostic criteria for PTSD include three symptom clusters: intrusive recollections (recurrent and intrusive distressing recollections of the event, recurrent distressing dreams of the event, acting or feeling as if the traumatic event were recurring, intense psychological distress at exposure to internal or external cues, and heightened physiological reactivity), avoidant/numbing symptoms (efforts to avoid thoughts, feelings, conversations, people, activities or places connected with the trauma, inability to recall an important aspect of the trauma, markedly diminished interest or participation in significant activities), and hyper-arousal symptoms (difficulties staying or falling asleep, hyper-vigilance, exaggerated startle response, difficulties concentrating) [1].

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Hyper-arousal symptoms, such as exaggerated startle responses and hyper-vigilance, are often reported by the patients and can be observed clinically but are very often difficult to objectify.

The prominence of psychophysiological symptoms in PTSD has been recognized long before this disorder was introduced to DSM-III (APA, 1980.). Those symptoms can be measured in the laboratory since they are mediated by the autonomic nervous system and its peripheral outputs. Diagnostic criteria for PTSD treat psychophysiology as a unitary construct. Laboratory measures can non-invasively and simultaneously record several biological processes such as electromyography (EMG), heart rate (HR), skin conductance (SC), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Exposure to intensely distressful stimuli triggers responses characterized by increases in all of the psychophysiological measures described above (heart rate, breathing, muscle tension, skin conductance).

Psychophysiological methods used with PTSD patients measure those peripheral changes in order to gain insight into the neurobiology of the disorder and are considered as possible additional methods in diagnostics of PTSD.

The neurobiology of fear has shown the amygdala to be involved in fear conditioning and in attributing emotional valence to stressful situations [2]. Many researchers have consistently reported that the amygdala plays a crucial role in the detection and response to threatening situation [3,4]. The amygdala is composed of different nuclei, which process input stimuli and subsequent fear responses [5]. Identifying neural pathways and types of neurons in the amygdala, which play a key role in the behavioral expression of fear, is a crucial component to understanding the neurobiology of PTSD [6].

The amygdala integrates external and interoceptive stimuli and modulates sensory, motor and autonomic processing of stressful stimuli [5-7]. Stressful stimuli activate the amygdala, which in turn triggers responses characterized by changes in all of the psychophysiological parameters.

Hyper-arousal symptoms are hallmarks of acute stress disorder (ASD) and PTSD and are primarily mediated by the sympathetic autonomic system. Those symptoms have been evaluated through the following psychophysiological procedures: baseline resting levels, external cues-auditory stressors, standardized traumatic stressors and idiographic traumatic cues.

I. Psychophysiological Procedures in PTSD Studies

1. Psychophysiological Baseline Studies

Studies using baseline, resting levels of psychophysiological recordings, have addressed the question of hyper-arousal in PTSD patients, that is, examining psychophysiological measures in the absence of trauma-related cues. Results of these studies are inconsistent.

There has been evidence of higher resting HR in ASD patients compared to controls [8].

Meta-analytic studies of basal cardiovascular activity done by Buckley and Kaloupek have pointed to higher resting HR and elevation in BP in PTSD patients, but not in individuals without trauma, thus pointing to positive correlation between diagnosis of PTSD and basal cardiovascular activity [9].
On the other hand, several studies have found associations between elevated resting HR in PTSD patients and reduced parasympathetic activity rather than elevated sympathetic activity [10,11].

A recent meta-analysis by Pole included 58 resting baseline studies. Results confirmed higher baseline arousal in PTSD patients, with higher resting HR ($r=0.18$) as the most reliable independent measure. Resting SC ($r=0.08$), SBP and DBP elevation were also related to PTSD [12].

Fewer baseline studies have examined the acute phase after trauma exposure. There have been reports on elevated baseline HR in the acute trauma phase [13-15]; however, other studies did not corroborate these findings [16].

### 1.2. Psychophysiological Studies of Startle Reactivity

Exaggerated startle response (Criterion D5, DSM-IV-TR) is one of the symptoms reported by the PTSD patients [17]. Startle stimuli used to trigger that response in the laboratory are loud tones with instantaneous onset. Acoustic startle reactivity is among the most common laboratory paradigms used in eliciting this response, with an individual’s response measured with EMG of the m. orbicularis oculi (eyeblink muscle contraction). It is characterized by a short latency of 20-100 ms [18], and slower response habituation in PTSD patients [19]. Autonomic responses can be measured peripherally using HR and SC responses [20], as well as the rate of habituation of these responses.

Results of startle studies included in one meta-analysis showed larger eye blink, increased HR and SC responses with slower SC habituation in PTSD patients [21].

A meta-analyses by Pole included 25 startle studies and found two measures to be most reliable predictors of PTSD in response to startling sounds: larger HR response ($r=0.23$) and slower habituation of SC response [12]. Measures also related to PTSD in these meta-analyses were the following: greater eye blink ($r=0.13$), and SC responses ($r=0.21$) to startling sounds [12].

A small number of studies have examined the acoustic startle response in the acute trauma phase. A study by Shalev and colleagues did not find significant differences in the acoustic startle response 1 week after the traumatic event [22], while another study showed elevated HR and initial SC startle response in ASD patients when compared to controls [16].

In a recent review of the literature, Bryant argues that the changing course of biological responses after trauma exposure, such as tonic arousal in the acute phase and increased startle and SC response that develop in the weeks following trauma are consistent with a fear-conditioning model of trauma response [23].

Studies of the exaggerated startle have not yet provided conclusive evidence whether this behavior is a vulnerability factor that precedes traumatic exposure [24] or an acquired trait that is a result of neuronal sensitization following trauma that develops along with PTSD [25].

### 1.3. Psychophysiological Studies Using Standardized Trauma-related Cues

Physiological reactivity to trauma reminders represents the core symptoms of PTSD (criterion B5, DSM-IV-TR). Those symptoms have been shown to be highly specific to individuals suffering from PTSD [26]. Psychophysiological studies of responsivity to trauma cues have been utilized as an objective tool in diagnosing PTSD, given that the
diagnosis of this disorder, as is the case in the majority of psychiatric disorders, relies mostly on patient self-report of symptoms and clinical observations. A meta-analysis of 17 studies that measured responses to standardized cues identified PTSD with a mean sensitivity of 77% and a mean specificity of 91% for HR, SC, EMG and BP [12].

Heightened psychophysiological responsiveness to trauma cues has been a consistent finding in a number of PTSD populations: combat veterans [27], victims of childhood sexual abuse [28], and in mixed trauma samples [29].

A study conducted with motor vehicle accident (MVA) survivors and assault survivors with and without PTSD showed group differences in HR responses to trauma-related pictures. Trauma survivors with acute PTSD (one month after trauma) showed greater HR responses to standardized visual trauma reminders than those without PTSD, HR responses were found to be a better predictor of PTSD than self-reported PTSD symptoms and depression [30]. HR reactivity has been the most reliable psychophysiological measure in a group of MVA survivors when audiotaped idiosyncratic accident descriptions were presented, inasmuch as PTSD patients had elevated psychophysiological responses compared to healthy controls and MVA survivors who did not develop PTSD [31,32].

A study by Rabe et al. undertaken in 2006 demonstrated trauma-specific exaggerated HR reactivity in PTSD when compared to MVA controls and non-MVA controls [33]. This parameter normalized with successful treatment. HR reactivity to standardized trauma-related cues predicted chronic PTSD and discriminated between individuals with and without PTSD [34]. These studies suggest that stimulus generalization may be an indicator of risk for chronic PTSD. Increased HR response has been considered characteristic of a PTSD subtype that shows over-generalized fear responses by some researchers [33,34].

Associative learning models of PTSD propose that fear responses become associated with stimuli present at the time during trauma exposure thus lending a theoretical basis for greater HR response to standardized trauma reminders in PTSD patients [35].

There are just a few studies of early physiological responses to standardized trauma cues with mixed results.

1.4. Psychophysiological Studies of Idiographic Trauma-related Cues

Idiographic trauma-related cues have been used in psychophysiological studies in order to individualize trauma reminders and gather results that are more reliable. The script-driven imagery procedure is the most commonly used laboratory paradigm; it consists of a narrative tailored to an individual’s traumatic experience. Such scripts are standardized for length and presented to the patient while recording psychophysiological responses. Psychophysiological data from idiographic trauma-related cue studies have also been examined for their potential as biological markers of PTSD. Larger responses on several psychophysiological measures have been a consistent finding for PTSD patients as opposed to non-PTSD controls in different studies.

A meta-analysis of 22 idiographic trauma-related stimulus studies found larger facial muscle EMG (r=0.21) and HR responses (r=0.22) to idiographic trauma-related cues as the most reliable index of PTSD, greater SC and DBP responses were reliable measures [12]. Idiographic trauma cue studies yielded the largest effect sizes across the broadest range of measures [12]. Pole identified PTSD in his meta-analysis with a
mean sensitivity of 65%, and mean specificity of 83% [12], while Orr and Roth found a sensitivity of 60%, and a specificity of 89% in identifying PTSD with the same laboratory paradigm [36]. This responsivity to idiographic trauma cues could be considered as a biomarker, and psychophysiology can be used as an add-on to existing diagnostic procedures.

There have been just a few such studies of the acute trauma phase. Trauma survivors with acute PTSD showed greater HR responses to trauma reminders than group without PTSD [37]. PTSD patients exhibited HR acceleration, while healthy controls and trauma survivors without ASD exhibited HR deceleration to individualized trauma-related pictures [37]. Greater HR responses to audiotaped individualized scripts predicted chronicity of PTSD in one study (Blanchard et al., 1996).

Results of those studies suggested early psychophysiological responses to be useful in identifying acute PTSD.

Psychophysiological studies that are available in the literature have several limitations that make it hard to generalize their findings. Some of the limitations include the following: they have been comprised of mostly male samples, war trauma, ethnic differences were not examined, and self-reported scales were not often applied.

2. Our Research

We have begun developing a psychophysiological laboratory at the Department of Psychiatry, Referral Centre for Stress Related Disorders of the Ministry of Health of the Republic of Croatia at University Hospital Dubrava in Zagreb, Croatia, for use in diagnostic and treatment procedures for psychiatric disorder (mainly stress related disorders), as well as for research studies. For research purposes we have been using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA), while for applied psychophysiology (biofeedback and neurofeedback) we have been using BioGraph Infinity Software (Thought Technology, Ltd., Montreal, Canada).

Psychophysiology research at our Department is a part of an ongoing project in which we are aiming to identify psychophysiological biomarkers of the acute trauma phase and their prediction of chronic trauma problems such as PTSD. We were also addressing dissociative symptoms in ASD, their psychophysiological profile, and possible predictive function of those symptoms for PTSD development. Although still ongoing, below we summarize our results to date.

2.1. Psychophysiology Research

The primary focus of our research to date has been on baseline and acoustic startle response studies.

In all of the studies we recorded electromyographic (EMG), electrodermal activity (EDA), electrocardiogram (ECG) activity, and respiration. EMG was used to record the magnitude of the eye blink muscle contraction (m. orbicularis oculi) during the startle response.

a) The results of our startle study in which we compared 45 Croatian war veterans suffering from PTSD to 33 healthy individuals found deficits in startle habituation in the PTSD group and replicated earlier findings of elevated basal HR in the same group. We found that baseline HR was elevated by
approximately 10 beats per minute in the PTSD patients compared to controls. However, we did not replicate the findings of exaggerated startle response in this study [38].

b) We conducted a prospective startle study in which we examined EMG responses in patients diagnosed with ASD after experiencing a traffic accident or violent attack, within one month after the traumatic event and 6 months later. The study included 16 individuals, 10 woman and 6 men. 50% of the participants met criteria for PTSD in the second assessment, after six months. Results showed that individuals who developed PTSD had significantly higher startle magnitude compared to those who did not develop PTSD. Only those that improved showed significant startle habituation over the 7 startle probes, and this group showed significant startle habituation six months after the initial trauma. We concluded that heightened startle magnitude in the immediate aftermath of trauma might be a good predictor of PTSD, while a lack of startle habituation appears to be a more stable marker of PTSD, which persists for six months after trauma exposure [39].

c) A startle study that included patients with ASD resulting from a traffic accident or interpersonal assault within the first month after trauma and 6 months after trauma showed attenuated startle habituation in ASD patients who were victims of interpersonal assault. SC levels during the startle phase increased for these ASD patients, more than for patients who survived traffic-related traumas. Individuals that had ASD due to interpersonal assault were more similar in psychophysiological parameters to PTSD patients [40].

d) We compared basal psychophysiology and startle reflexes in ASD patients (16 male and 13 female participants) and healthy controls (19 male and 14 female participants) in the first month following the traumatic event. Patients with ASD resulting from civilian trauma, traffic accident or interpersonal assault, were included in the study. Results showed an increase in SC in ASD patients following traffic accident compared to healthy controls. This result is consistent with increased activity of the sympathetic nervous system. We did not find exaggerated startle response in this sample [41].

e) A psychophysiological prospective study conducted as a part of a PhD thesis (Jambrosic) aimed to contribute to the identification of parameters of psychophysiological arousal in the acute and chronic trauma, and to describe psychophysiological parameters of hyper-arousal in the acute phase that are predictive of PTSD development [42].

f) We used a well-validated fear-conditioning paradigm to compare fear-potentiated startle responses in patients with ASD in the immediate aftermath of trauma (less than 30 days) and those with chronic PTSD (10 or more years since trauma). In this paradigm, one pair of stimuli (the danger signal) is paired with an aversive airblast to the larynx, while a second pair of stimuli (the safety signal) is never paired with the airblast. We found that both groups showed comparable levels of fear-potentiated startle to the danger signal, and unlike the non-traumatized controls, both groups showed deficits in inhibition of fear-potentiated startle in the presence of the safety signal. The results of this study suggest that fear inhibition may be a vulnerability factor that is evident in the immediate aftermath of trauma exposure and persists in those who develop chronic PTSD [43].
2.2. **Applied Psychophysiology**

Biofeedback (BFB) and neurofeedback (NFB) as methods of applied psychotherapy are techniques that enable individuals to learn how to control their physiology with the goal of improving physical and mental health. The goal of biofeedback is to reduce sympathetic nervous system (SNS) arousal and is used in disorders that are associated with heightened SNS activity.

In psychiatry BFB is most often used in treatment of stress related disorders, addictions, depressive disorder, attention deficit and hyperactivity disorder (ADHD), psychiatric disturbances following traumatic brain injury, and anxious disorders. Other indications are chronic pain, tension headaches, migrenous headaches, and hypertension, among others.

Research has shown that biofeedback interventions are efficacious in treating a variety of medical conditions. Among studies using patients with PTSD diagnoses, biofeedback has been beneficial when symptoms of numbing, avoidance, and hyper-arousal were present.

In BFB treatment, we have used surface electromyography (sEMG) when treating tension headache, chronic pain, and somatized anxiety. Heart rate, respiration rate, skin surface temperature, skin conductance and heart rate variability were variables that we used in treating anxiety disorders, such as PTSD, generalized anxiety disorder, and panic disorder. We have also used it as a psychophysiological psychotherapy model, when trying to help patients determine thoughts or behaviors that contribute to the physiological symptoms they are experiencing. This application of BFB includes stress management, and is considered the most successful in treating stress related disorders.

Neurofeedback (NFB) treatment has been used at our Department with the aim of alleviating symptoms of depressive disorder, attention disorder resulting from TBI, anxious disorders (PTSD, panic disorder, generalized anxiety disorder, social phobia). It requires the trainee to be active, regularly in attendance and to practice between sessions.

Alleviation of the symptoms is achieved by training individuals in techniques to define the primary problem and to correct or alleviate it through physiology.

BFB sessions last 30-45 minutes, are held in weekly sessions, for a total of 10-15 sessions. NFB treatment usually takes 20-30 sessions; one session takes 45 minutes, and is administered twice weekly.

We have been using applied psychophysiology as add-on therapy in patients who have been resistant to previous treatment (pharmacotherapy, individual and group psychotherapy, anxiety management, and psycho-education), those who did not achieve good control or alleviation of hyper-arousal symptoms with the treatment regime they had been receiving, or with psychotherapy.

Individuals with secondary gain were not considered for treatment. Other exclusion criteria are, as cited in the literature, dementia, suicidality, schizophrenia, delirium, and depersonalization. Assessment was done before and after the treatment, and it included symptom scales [44-48] and a psychiatric interview.

A case study of BFB and NFB treatment of two individuals who developed psychiatric disorders after TBI and were resistant to previous treatment were promising [49]. After treatment was completed we considered applied psychophysiology for psychiatric disorders following TBI in persons resistant to the standard treatment protocol. We also found useful BFB and NFB treatment as add-on therapy in PTSD patients with chronic pain syndromes, primarily in reduction of anxiety symptoms [50].
In summary, in our opinion methods of applied psychophysiology are a promising new tool in psychiatric settings and treatment of psychiatric disorders, but need further evaluation.

References


D. Kozaric-Kovacic and A. Jambrosic Sakoman / Psychophysiological Indicators


Multimodal Paradigm for Mental Readiness Training and PTSD Prevention

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Abstract. Multimodal paradigm for cognitive-emotional elicitation, estimation and regulation may strengthen military training and enhance selection process. It includes multiple sessions involving mission-relevant audio-visual stimulation and simultaneous measurement of the trainee’s multimodal physiological, facial and vocal response. The initial audio-visual adaptive stimulation screening sequence contains personalized mission-relevant semantically and emotionally congruent static pictures and sounds, based on the initial interview with the soldier conducted by military psychologists. After each stimulus as well as the entire sequence, the soldier provides subjective emotional ratings in terms of valence, arousal and discrete emotions. These subjective ratings and recorded multimodal response (physiology, voice, and facial expressions) represent initial information regarding the soldier’s appraisal of mission-relevant stimuli. Subsequent sessions use dynamic stressful video clips captured in real missions, with soldier’s entire multimodal response measurements. To maximize training relevance, video clips are personalized and can be mixed with instructions of the commander and potentially other unit members. Additionally, mission-relevant audio-visual interactive tasks are delivered separately and in conjunction with stressful video clips, to strengthen the soldier’s cognitive-emotional capabilities. Offline analysis of the soldier’s multimodal response can be additionally enhanced by fMRI to the presented pictures, sounds, video clips, and interactive tasks, to reveal changes that occur as a consequence of training. Parameters of the soldier’s cognitive-emotional state estimators are tuned continuously in real-time based on physiology, voice, and facial expressions. Aggregate information from these cognitive-emotional state estimators may assist instructors during real-time decision-making when striving to present the most appropriate stimuli for the trainee’s current multimodal response. Such stimuli generation based on expert knowledge and experience in cognitive-behavioral stress inoculation training is implemented in our closed-loop audio-visual adaptive stimulation system.

Keywords. Mental readiness training, PTSD prevention, emotion regulation, cognitive-emotional capabilities, audio-visual stimulation, multimodal response, physiology, voice, facial expressions, fMRI.

Introduction

It is recognized that highly stressful emotional situations in military operations may negatively affect soldiers’ performance, lead to erroneous decisions and actions, as well as to later psychological injuries, like posttraumatic stress disorder (PTSD) [1]. For

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psychological disorders like PTSD that have already occurred as a result of traumatic mission-related experiences, considerable research has been devoted to their treatment [2]. In addition to various pharmacological and psychotherapeutic methods, virtual reality assisted exposure therapy has also been applied more recently (e.g. see review in [3]).

Various literature points to an adverse impact of stress on task performance, which may have relevance for a military setting. Seminal work by Yerkes and Dodson in the beginning of the 20th century [4] resulted in the often-cited curve linking arousal and performance that depends on task difficulty, which shows that high levels of stress adversely affect performance of difficult tasks. Strong mission-related stress and emotions certainly affect the responses in the central and peripheral nervous system related to the person’s arousal, so consequently should impair performance of difficult highly cognitive mission-related tasks. From the neurobiological standpoint, [5] studies have shown that stress impairs the prefrontal cortex structure and function, and the prefrontal cortex is regarded as the part of the brain responsible for complex cognitive functions [6], like planning, working memory, rule-based decision-making etc. Recognizing that training for task performance is related to, but also different from, training for task performance under high stress, training protocols have been investigated to find optimal combinations of task-related skills training with stressor exposure, in order to obtain high performance in stressful situations [7][8][9].

Thus, besides treatment of existing psychological disorders, it is also valuable to consider training approaches that may facilitate operational performance in highly stressful environments and return from deployment without serious psychological consequences. Mental readiness training (MRT) has been proposed [1] as a form of stress inoculation training [10][11], i.e. cognitive-behavioral approach, which is focused on training with mission-relevant stressors to help the soldiers develop the needed mental capabilities. Borrowing the terminology from resilience research [12], mental capabilities that are of particular interest in this paper are related to “stress resistance”, i.e. ability to maintain task performance under highly stressful conditions, and “stress recovery”, i.e. ability to regain the normal functioning after the exposure to such stressful conditions. In this context, we are developing support tools and methods for multimodal cognitive-emotional elicitation, estimation and regulation, which may complement existing military training along the lines of the MRT approach, in order to facilitate soldiers’ stress resistance and recovery, and consequently to also contribute to PTSD prevention.

1. Multimodal Cognitive-Emotional Elicitation

Cognitive-emotional elicitation processes should use personalized fusion of multimodal stimuli to achieve a powerful and focused impact on soldiers in the MRT approach. Multimodality refers to different types of stimuli, which may be categorized according to their diverse properties. Audio and visual elicitations are the most common stimuli but other sensory modalities like haptic, olfactory and vestibular are also applicable in the multimodal elicitation process. However, compared to combined audio-visual stimulations, they are far less commonplace in practice, require specialized hardware and do not have as standardized stimuli databases. Furthermore, modality categories with different levels of interactivity, artificiality, dynamics, delivery modes and
multimedia types are possible and can be combined together to form a complex multimodal emotion elicitation sequence. Such stimulation would target several senses at once, for example sight, hearing, touch and smell, and could be used for an integrative cognitive and emotional training of the soldier’s personal stress-coping abilities. Real-life video clips augmenting virtual computer generated environments with a high degree of immersion will be more intensive in stimulation than individual pictures or sounds [13]. Further enhancing multimodality with concurrent stimulation using several senses should result in even stronger personal appraisal and consequently better MRT and PTSD prevention.

Of particular interest are interactive stimulations, which demand active participation of the soldier during a cognitive-emotional elicitation. Resting state or passive stimulations do not require any voluntary response from the soldier. Passive participation elicits central and peripheral nervous system responses related to processing of stimuli, which includes various associations triggered by stimuli, contextual understanding of stimuli, as well as unspecific neural activity that depends on participant’s thought-switching. Participant’s thought switching is a difficult variable to control during passive elicitation, but as the stimuli intensity and relevance increase for the participant, it is reasonable to hypothesize that unspecific thought-switching is decreased.

In contrast to passive stimulations, in interactive tasks the soldier must perform certain volitional actions, which may range from just opening or closing eyes, verbalizing, answering questions, communicating with the instructor, or watching certain geometrical shapes, emotion-inducing pictures with or without personalized significance. In more complex interactive stimulation paradigms the soldier has to solve problems intended for evaluation of his executive functioning in a stressful environment. In a choice reaction time test, the solider must focus on a given stimulus while inhibiting attention to stimuli flanking it. This test, also called “flanker task”, measures the soldier’s inhibitory control level [14]. Another test of this type is the dimensional change card sort (DCCS) [15], which evaluates personal cognitive flexibility. In DCCS the soldier must point to a certain shape on the screen according to its description, which he simultaneously sees and hears. The trick is to intentionally display same shapes with different properties whose discrimination requires certain cognitive performance. DCCS can also be applied to emotion elicitation by using picture databases with universal facial expressions like NimStim [16]. These sequences may be further enhanced with pictures of acquaintances, loved ones or comrades in arms, either dead or living. Also, a suitable narrative, which enhances the effect of the pictures, can be read by the instructor and played along the visual stimuli, thereby, taking full advantage of multimodal cognitive-emotional elicitation paradigm.

Active participation elicits central and peripheral nervous system responses not only related to the processing of stimuli, but also to voluntary execution of motor programs. Interactive tests look to separate responses related to stimuli processing versus responses related to task execution. Complex interactive tests (like flanker tasks, DCCS, or cognitive games), may elicit not only cognitive, but also emotional responses (e.g. frustration because the person cannot perform task successfully).

All these strategies are successfully implemented with specialized intelligent computer systems for adaptive stimuli generation and emotion elicitation. Such systems contain many ready-to-be-used, commercial-of-the-shelf (COTS) components. Complex components in such systems are stimuli databases and intelligent tools for
database search and multimodal stimuli sequence generation. These tools must be custom built for individual user’s needs and include state-of-the art technologies in such areas as knowledge representation, image retrieval and artificial intelligence. The most involving component are stimuli databases which are either generic as a vast storage of different stimuli modes – visual, auditory, haptic, etc. – or must be strictly specialized, containing a much smaller number of stimuli but directed at a specific occupation, situation, locality or even a person undergoing the stress training. Tools for multimodal cognitive-emotional elicitation are frequently based on a several networked computer servers and multiple workstations. A typical system would be made up of an instructor workstation with at least two monitors, trainee visualization subsystem (e.g. HMD), and three servers for stimuli database, supervision and stimuli generation tools and graphics generation, respectively.

Cognitive-emotional elicitation tools enable the supervisors, (instructors, psychologists) to perform intuitive retrieval of a variety of audio-visual stimuli from semantically and emotionally annotated stimuli databases. By maximizing the stimuli relevance for each trainee, through the use of appropriate questionnaires and interviews, the stimuli can then be matched to the trainee’s potential stressful experiences in the upcoming deployment. This can include the stressful situations encountered in the past. Examples of such questionnaire may be Life Events Checklist [17], or any other standard or custom-made questionnaire regarding stressful encounters in life. Due to different experiences of trainees, “semantic and emotional gap” exists among them when viewing and interpreting the same stimuli. Therefore, initial information gathering is important for facilitating the selection of personalized stimuli that correspond with dominant neural semantic and emotional associations of a particular trainee.

2. Multimodal Cognitive-Emotional Estimation

Multimodal cognitive-emotional estimation is related to the simultaneous multimodal monitoring of the trainee’s responses, like autonomic physiology and motor expression related to voice and facial features, while the trainee is presented with the audio-visual stimuli [18][19][20]. If Scherer’s appraisal theory [21][22] is adopted as emotion-theoretic framework, cognitive appraisal of events drives interactions of various emotion-related components: bodily symptoms, motor expression, action tendencies, and subjective feelings. In order to simultaneously capture the components of this multimodal cognitive-emotional response, which is related to bodily autonomic physiology, and vocal and facial motor expression - physiological sensors, microphones, and cameras are applied. Various features are calculated from these response signals and analyzed in real time by appropriate algorithms, including estimation of the trainee’s cognitive-emotional states [23][19]. Multimodal response monitoring, as well as cognitive-emotional estimation from each of the three modalities and their fusion, provides the instructor with continuous augmented insight into the trainee’s state during training.
2.1. Estimation Based on Physiological Signals

The use of physiology as a means of measuring emotion and stress has several advantages. Since physiological signals, like skin conductance, electrocardiogram (ECG), heart rate, respiration rate etc., are dominantly related to the autonomic nervous system activity, these signals are harder to conceal and consciously manipulate than predominantly motor, vocal and facial expressions. Information about the trainee’s cognitive-emotional states can be continuously gathered from physiology, as long as the trainee is connected with the appropriate sensors. Moreover, physiological sensors are becoming less and less disruptive as their size is decreasing. Unobtrusive, small, wireless physiological sensors may be an ideal solution for real-time emotional state monitoring [24][25][26].

The main difficulty in cognitive-emotional state estimation based on physiology, lies in the fact that it is a very hard task to uniquely map physiological patterns onto specific cognitive-emotional states. A multitude of variables such as time, context, space, culture, and personal characteristics may explain why physiological patterns widely differ from user to user and from situation to situation [27]. Therefore cognitive-emotional estimation based on physiological signals needs to be learned gradually for each trainee after a particular MRT session is completed (offline learning), and the estimator should also adapt in the ongoing MRT session to the newly collected data (within-session adaptation).

The first step in the offline learning procedure is raw physiological signal processing, which includes preprocessing, characteristic waveform detection (like QRS complex detection or detection of skin conductance responses) and additional physiological signal extraction (like heart rate from ECG, respiration rate from respiration signal, etc.).

Physiological features computation is the second step in which a wide range of physiological features is calculated from preprocessed signals in various analysis domains, like time/frequency, entropy, geometric analysis, subband spectra, multiscale entropy, etc. Typical physiological features are statistical measures such as mean, standard deviation, minimum, maximum or mean of first difference of each signal, heart rate variability measures [28], skin conductance response measures [29] etc.

Feature reduction represents the third step, in which only features that are the most relevant for differentiating various cognitive-emotional states are retained, while other computed features are discarded. Reducing the dimension of the feature space has two advantages, lowering the computational costs and the removing of noisy information to improve estimation accuracy. Reduction of physiological features is conducted using the Sequential Floating Forward Selection (SFFS) [30] algorithm. As a criterion function of SFFS that needs to be maximized in order to determine the best feature set, an estimation accuracy obtained using leave-one-session-out cross-validation [31] is used.

Supervised learning of the cognitive-emotional estimator is the last step, in which the estimators’ parameters are learned from the data obtained by pairing of selected physiological features with known cognitive-emotional state of the trainee. This cognitive-emotional state can be obtained by the trainee’s subjective ratings of stress, discrete emotions, or valence and arousal, emotional annotations of the presented stimuli, and/or by performance measures that may index task difficulty, trainee’s attention to the task, level of trainee’s technical proficiency, etc.
The output of the off-line learning procedure is the learned cognitive-emotional estimator, which has relevant selected physiological features as inputs and computes functions that transform this input into the cognitive-emotional state of the trainee. Such functions can be obtained by using, for example, an artificial neural network [32], support vector machine [33], REPTree, [34] etc. This learned estimator can be used in the next MRT session to estimate the cognitive-emotional state of the trainee on the basis of measured physiology.

In addition to offline learning, the estimator is also capable of adapting itself to the newly collected data within each session. This process of within-session adaptation can be triggered during the session whenever new information is provided regarding the trainee’s cognitive-emotional state, because the estimator can immediately associate this information with the current values of physiological features. Due to ongoing estimation, within-session adaptation of the estimator has limited time available for execution of the necessary learning algorithms.

2.2. Estimation Based on Voice

Implementation of a voice feature modality in a multimodal cognitive-emotional state estimation process can certainly provide a significant contribution to this field. Speech can be sorted out as a great potential, being the most non-invasive recording sensor that gives the clue of the trainee's cognitive-emotional state. The main goal of cognitive-emotional estimation from voice is to develop a system that can serve as an assistant to the supervisors (instructors, psychologists) during MRT. The great advantage of such a system is that it can also provide cognitive-emotional information from the trainee based on some vocal features that are rather hard to observe by an average listener. The idea is to iteratively adapt system parameters after each training session in order to converge and to provide robustness of estimation. Also, system will adapt parameters according to each trainee individually and store responses. Thus, supervisors will be able to monitor the progress of a trainee, as well as individual vocal responses of a particular trainee to a stimulus.

Cognitive-emotional states can be estimated via acoustic and linguistic features of the trainee’s voice. Relevant acoustic features that contain emotional information can be calculated from non-verbal cues in an utterance, including prosodic parameters like the vocal cords oscillation period (pitch frequency and contour), energy and power of the voice (in decibels), zero-cross rate and the voice spectrum distribution [35][36][37][38][39]. Additionally, emotionally relevant linguistic features are obtained from verbal cues, in the form of keywords [40], phrases [41] or descriptors on a semantic level in a trainee’s vocal response [42]. Fusion of these two complementary feature sets can provide integral information for estimation based on voice and, therefore, potentially lead to higher estimation accuracy than each individual feature set [41][40][43][44].

Cognitive-emotional state estimation using acoustic features of the speech can be done in several ways. Given the feature set, each cognitive-emotional state can be modeled by an appropriate statistical model. The Gaussian mixture models (GMM) [45] and Hidden Markov models (HMM) [46] are the most popular methods. GMM model captures only the static probability distribution of feature vectors for each emotional state. Only one feature vector is computed and the most probable model is selected given the observation. With HMM model, the time dynamics can also be
included in the cognitive-emotional model (i.e. changes across the trainee’s vocal expression during the MRT session). Recognition is achieved by evaluating the probability of a time series of observed feature vectors, given the set of designed HMM models, one for each cognitive-emotional state. Each vector is calculated from a subsequence of vocal expression extracted with a time window of an appropriate duration and time shift. For the linguistic features, an n-gram language model for each cognitive-emotional state can be built with a vocabulary consisting of specific keywords and phrases for this specific cognitive-emotional state. As a model input, linguistic features are extracted from word chains, (tokens). Calculating the statistical probability of keywords and phrases performs cognitive-emotional state estimation. Estimation can be done on three levels: lexical, syntactic and semantic.

2.3. Estimation Based on Facial Expressions

Facial expressions can be considered as aspects of both an emotional response to certain stimuli and of social communication. Facial expressions are shaped through muscular activity, which is driven by complex neural control that includes both autonomous and voluntary components. The process of facial expression recognition involves linking visual representation of the face, reflecting a generation of knowledge about the category of emotion that it belongs to. According to neurobiological findings from various experiments i.e. electroencephalography, magnetoencephalography and functional magnetic resonance imaging, the simplicity of facial expression recognition process can be easily castoff. Recognizing facial emotions involves a large scale of diverse psychological processes, which involve activity of different brain structures (mainly in occipital and temporal lobes) [47].

Facial expressions are a rich source of information in the process of understanding emotions, which can be represented as a complex psycho-physiological and mental state that consists of various multimodal responses (physiological, vocal and acoustic, facial, etc.). Based on the similarity of facial responses, induced by group of stimuli with similar emotional content, they can be divided into different disjoint categories (discrete emotional states). The categorization process is of paramount importance in a social communication environment, due to the high informational complexity and rapid behavioral response to facial emotions.

Based on visual appearance, face emotions can be represented by a set of geometric properties (spatial features), which describe both position, and movement direction of main anatomic structures of the face. In the domain of computer vision, efficiency of emotion estimation observing facial expressions relies on the possibilities for generalization of social relevant attributes that are not influenced by various demographic aspects. There are many examples that contribute to the sufficiency of spatial-based face features for recognition of basic (discrete) emotions [48][49][50][51][52]. In the publication, authored by P. Ekman and W. Friesen [53], a technique for the measurement of facial movement has been proposed. They introduced a system to taxonomize human facial expressions, better known as Facial Action Coding System (FACS). FACS encodes various movements of individual facial muscles, which are called Action Units (AU). Action Units are a standardized form of describing visual movements of particular anatomical face regions i.e. Inner Brow Raiser, Cheek Raiser, Lip Corner Puller, etc. The presence of certain AU can be detected by observing the spatial characteristic of certain morphological structure of the
face expression with regard to the corresponding spatial characteristic in the *neutral face*. Neutral face is a special representation of spatial properties of main anatomical regions of the face where the mouth is closed, the gaze is directed perpendicular to the screen plane, eyes are open and the eyelids are tangent to the iris [48].

There are 46 main AUs that are used for coding movements of facial muscles. P. Ekman and W. Friesen revealed demographic and cultural independence in facial expressions of six basic emotions: happiness, sadness, surprise, fear, anger and disgust [54]. In relation to this knowledge, they also defined a set of AUs that describe spatial characteristic of face regions for these basic emotions. For example, happiness is related to simultaneous occurrence of AU 6, Cheek Raiser, and AU 12, Lip Corner Puller, while sadness to co-occurrence of AU 1, Inner Brow Raiser, AU 5, Upper Lid Raiser, and AU 15, Lip Corner Depressor.

Using different computer vision methods, it is possible to locate and extrapolate the face with its spatial characteristic (features) of main anatomical regions from the given video or image data, e.g. by using Active Shape Models [55]. Automated emotion recognition from facial expressions can be conducted by several algorithms for pattern recognition, like support vector machines, artificial neural networks etc. Based on extrapolated facial features, the estimation process first codes them with a corresponding AU. Second, the estimation process is searching for discrete emotions whose AU description best matches the AU representation of computed facial features.

### 2.4. Estimation Based on Multimodal Fusion

While each modality of the soldier’s recorded multimodal response provides useful data for estimating the soldier’s cognitive-emotional state, it can be expected that integration of all modalities provide the most comprehensive basis for such estimation. When estimating cognitive-emotional states for mental readiness assessments over an integrated feature set from physiology, voice and facial video, measures can range from correlations of individual features, i.e. linear regressions, to non-linear regressions computed with machine learning methods like artificial neural networks, support vector machines, regression trees etc.

Altogether, multimodal fusion can be performed on multiple levels. One level of analysis is related to short time frames that carry information regarding the current and recent soldier’s state, which may be mostly related to the changes of presented stimulations within the current session. Another level of analysis is related to longer-term changes, comparing the soldier’s data between sessions by looking back weeks, months or even years, depending on how much prior data is available. Such approaches may, for example, reveal differences related to the progress of training, such as habituations to initially highly arousing stimuli, or differences related to the potential traumatic encounters in recent missions, like heightened physiological reactivity to previously non-arousing stimuli.

### 3. Multimodal Cognitive-Emotional Regulation

Having the appropriate tools and methods for mission-related elicitation and estimation of cognitive-emotional states of soldiers, they can be applied as adjunct to the military skills training in order to improve soldiers’ mental readiness and potentially contribute
to prevention of combat stress-related disorders. These tools and methods need to support the soldiers, their instructors and psychologists in strengthening the soldiers’ cognitive-emotional capabilities for two reasons: (a) to minimize potential negative impacts of strong emotional states during military missions on the soldiers’ performance of their mission-related tasks (i.e. to improve stress resistance); (b) to preserve the soldiers’ psychological well-being, so they may continue to lead normal lives after return from missions (i.e. to improve stress recovery).

Established and tested cognitive-behavioral frameworks like stress inoculation training [10][11][56], stress exposure training [57][58] have been used as foundation for Thompson and McCreary’s proposal [1] of MRT approach. MRT is aligned with these cognitive-behavioral approaches, but the focus has now shifted from lectures concerning stress to message and technique delivery that is directly integrated into more intense training situations with operational relevance.

It should be noted that common military training focused on military skills development by itself provides important knowledge and experience that facilitates operational effectiveness. Consequently, such training also contributes to the decreasing of adverse psychological sequelae of mission stressors, because it is to be expected that competent well-trained soldiers will be able to handle stressful mission situations better than untrained ones. For example, Thompson and McCreary [1] clearly emphasize that military lectures, briefings, demonstrations and drills improve soldiers’ technical skills, build strength, endurance, discipline, and teamwork, which improves confidence of soldiers and thereby contributes to their resilience. Transfer of expert knowledge from instructors to the trainees, overlearning of technical skills and internalization of standard operating procedures in numerous drills are all very important for the soldiers’ ability to withstand mission stressors.

However, such implicit building of resilience through common military training is regarded as insufficient for certain individuals, who may have difficulty in implicitly developing such psychological skills. The consequences can include slowed down acquisition of technical skills and higher stress vulnerability, both of which can compromise the soldiers’ operational effectiveness [1]. Therefore, in addition to the declarative and non-declarative learning of technical skills and standard operating procedures, declarative and non-declarative learning of cognitive-emotional self-regulation skills are indicated, in line with principles of stress inoculation training, stress exposure training, mental readiness training, as well as broader framework of emotion regulation [59].

In other words, soldier effectiveness and safety in the mission depends on many variables, including well-functioning military equipment, mastery of technical skills and procedures as a consequence of rigorous military training, well-planned mission, mental readiness etc. Mental readiness together with technical skill proficiency may help in maintaining operational performance and minimizing casualties even in unexpected stressful situations, such as when equipment fails, or when unplanned, unpredictable, and unfavorable events takes place.

At the level of brain regions, effectiveness of self-regulation skills learned while being exposed to mission-relevant stressors, may depend on prefrontal cortex and amygdala, which are important for interactions between cognition and emotion [6], as well as on their mutual interactions and interactions with other regions involved in bottom-up and top-down emotion generation [60][61]. In stressful situations that demand highly cognitive abilities, the inhibition of the amygdala activity by the
orbitofrontal cortex and ventromedial prefrontal cortex (OFC/vmPFC) [62] may play an important role in the successful performance of stressful tasks. Based on contextual information provided by the hippocampus, the OFC/vmPFC may be able to perform a selective context-dependent amygdala inhibition [63]. Given that psychotherapy may produce changes in the brain visible via brain imaging [64], the hypothesis here is that inhibitory connections from the OFC/vmPFC to the amygdala may be strengthened during the stressful training, by practicing the skills that are an integral part of stress inoculation training and various emotion regulation approaches.

Tools and methods for multimodal cognitive-emotional elicitation and estimation may be used within mental readiness training in combination with the aforementioned cognitive-behavioral approaches to “enhance … the baseline psychological resiliency of military personnel” ([1], p. 54). Furthermore, additional tools specifically related to cognitive-emotional regulation are at the disposal of the instructors and military psychologists for improving mental readiness of soldiers. These tools may assist with selection of emotion eliciting audio-visual stimuli of appropriate semantics and emotional intensity, based on integration of all available information regarding the soldier, including current and past multimodal responses, initial interview and questionnaires regarding encountered stressors etc., as such comprehensive decision-making may become challenging.

During multiple sessions, delivery of audio-visual stimuli evolves with the progress of the trainee, as well as with the growing supervisors’ understanding of what the best stimulation strategies might look like. An initial session, for example, may include delivery of semantically and emotionally congruent pairs of static pictures and sounds, using standardized databases like International Affective Picture System (IAPS) and International Affective Digitized Sounds (IADS), or some custom-made database. The supervisors may update stimulation strategy for all later sessions that use real-life video clips and interactive tasks, after analyzing the data collected during earlier sessions. For example, the supervisors may find strong physiological reactions across sessions to stimuli of certain semantics, and decide to create a specific predetermined scenario that focuses on this content. At a particular point during the subsequent session, such scenario can be selected by the supervisors and delivered to the trainee. Alternatively, the supervisors may specify the keywords denoting the desired semantics for the next session, and type the keywords during the session for interactive delivery of desired stimuli. Besides referring to the stimuli semantics when defining the stimulation strategy for the next session, the strategy can be specified in terms of emotional properties of stimuli, like valence-arousal or discrete emotions, because the stimuli database contains both semantically and emotionally annotated stimuli.

Changes of strategy between sessions by the supervisors, as well as delivery of individual stimuli within a particular session may be represented as a state machine or a set of rules, which encode parts of expert knowledge and experience of the supervisors. In this sense, such an expert system could assist the supervisors in selecting appropriate stimuli based on the soldier’s multimodal responses, past encountered stressors, impending mission-related stressors, and specific training goals and objectives of a particular session. Via an appropriate message exchange, various modes of collaboration between the supervisor and this expert system can be supported [20], corresponding with the taxonomy of levels of automation proposed by Sheridan and Verplank [65].
4. Longitudinal Evaluation of the Proposed Multimodal Paradigm

The tools and methods described in this paper can be used longitudinally in various soldier training and testing settings. One setting includes laboratory conditions, where cognitive-emotional elicitation with our tools may include audio-visual stimuli like mission-related static pictures and sounds, real-life video clips and/or general interactive tasks related to spatial planning, time-critical decision-making etc. During elicitation, our tools for multimodal cognitive-emotional estimation can record and analyze in real-time the soldier’s multimodal responses and display them to the supervisors. Based on their extensive experience, supervisors can select appropriate stimuli/tasks that best match the integrated multimodal responses of the soldier, and in this work our closed-loop stimuli delivery tools for multimodal cognitive-emotional regulation may support them.

Another setting includes drills of specific military skills and procedures using simulators or other substitutes for the real in-field training and testing. In this setting, audio-visual stimuli from the simulator are used as cognitive-emotional elicitors, while our cognitive-emotional estimation tools can continuously monitor relevant aspects of the changes in the cognitive-emotional state of the soldier. The supervisors can have options to adjust the intensity of training, i.e. choose simulated scenarios of varying difficulties, in order to match the soldier’s progress in task performance and integrated multimodal response. Our tools for multimodal cognitive-emotional regulation can again assist the supervisors in this task.

Final setting is the in-field training and testing of skills and procedures. Here, cognitive-emotional elicitation is the consequence of encountering real stimuli in the field, rather than computer-generated audio-visual stimuli, interactive tasks or simulated environments. Therefore, only very compact versions of our tools for cognitive-emotional estimation might be applicable in this setting, for continuous monitoring of the soldier’s response.

The procedure for applying our multimodal paradigm in analysis, training and testing of soldiers’ mental readiness in the laboratory setting consists of: (a) multiple sessions involving delivery of mission-related audio-visual stimuli and/or interactive tasks, with simultaneous multimodal measurements of the trainee’s autonomic physiology, voice and facial expressions, as well as cognitive-emotional regulation support; (b) two fMRI measurement sessions with selected mission-related audio-visual stimuli and/or interactive tasks, before and after training. In this way, it is possible to analyze autonomic physiological, motor, and central nervous system response of trainees when exposed to relevant stimuli, and their evolution with the progress of training. Similar procedure could be used in the simulator setting, in which fMRI measurement sessions may include the recorded videos of the virtual practice scenarios of varying difficulties. This approach is proposed as potential adjunct to the common training practices (Figure 1).
Preliminary results obtained with fMRI monitoring on a few volunteers indicate that there are differences in the central nervous system processing of stressful real-life combat video clips between professional mission-ready soldiers a week before their deployment to Afghanistan and novices who have not started training [66]. This is encouraging for more extensive and longitudinal monitoring of trainees during the training to find more conclusively how professional military training modulates the neural processing of relevant combat stimuli, and multimodal responses in autonomic physiology, voice and facial expressions. Furthermore, brain research on fMRI patterns related to intensity of general psychological stress, e.g. induced via mental arithmetic test [67], as well as brain correlates of stress-related psychopathology, like decreased hippocampal volume in PTSD [68], can all be informative for future research and development of mental readiness training programs and metrics. In any case, collaboration between military instructors, psychologists, psychiatrists, neuroscientists and engineers would be important for combining various cognitive-behavioral approaches with tools for multimodal elicitation, estimation and regulation, in order to enhance the mental readiness of soldiers and contribute to their stress resistance and stress recovery.

5. Conclusion

The paper has described our approach regarding development of tools and methods for multimodal cognitive-emotional elicitation, estimation and regulation, in the context of mental readiness training and PTSD prevention. Cognitive-emotional elicitation is related to generation of personalized mission-relevant audio-visual stimuli and tasks, estimation involves real-time acquisition, processing and fusion of autonomic physiology, voice and facial expressions that reflect cognitive-emotional states of trainees, while regulation includes closed-loop stimuli delivery based on the trainees’ multimodal responses. It has been discussed how the outlined concepts and tools can support the qualified supervisors in monitoring, training and testing of soldiers for the purposes of mental readiness training and PTSD prevention, which requires close collaboration between various disciplines.
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References


Extreme Political Attitudes and Emotionally Based Strategic Communications

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Abstract. Group based dominant emotional maps characterized by long lasting negatively valenced emotions, such as fear, anger, hatred or humiliation may elicit strong extreme political attitudes, actions and behaviors, as well as massive posttraumatic stress disorders. The impact of these dominant negatively valenced emotions on political attitudes, actions and group behavior can be referred as toxic power of negatively valenced emotions. Persistent negatively valenced group based dominant emotions may be also used as quantitative statistical measure and the most relevant early warning indicator of potential terrorism and violence among respected group members. The toxic power of extreme political attitudes, actions and behavior might be reduced by Emotionally Based Strategic Communications (EBSC) as a communication method for transforming negative dominant emotional maps into more positive ones. EBSC is conceptualized as the positively valenced stimulation of a negatively emotionally affected group by an appropriate communications strategy, in order to influence extreme political behavior of a targeted group. We argue for significant potential of EBSC to prevent the arousal of intense negative emotions within human collectives and groups, as well as mitigate the toxic power of negatively valenced emotions. Prevention and reduction of negative emotions may ease social and security tensions in politically polarized, culturally fragmented, or economically stratified social settings, and prevent political terrorism by facilitating harmonization of diversified communities. The extreme political attitudes, and related dominant negatively valenced emotions have their neural representation in specific changes on biochemical and molecular levels of related limbic and prefrontal cortical structures of affected brains. Societal enrichment based on positively valenced EBSC might have positive social impact eliciting various positive neuronal responses and changes in the brains of affected people, ranging from different biochemical to neural structural changes like neurogenesis, synaptic plasticity, dendritic arborization, increase of synapse-to-neuron ratios, axonal growth, neurotransmitter changes etc. We regard EBSC “soft power” as important contribution to prevention of extremist action tendencies and radicalized behaviors in afflicted societies. EBSC policy can be also viewed as a large-scale strategy of emotion regulation that might decrease destructive power of extreme political behavior and terrorism.

Keywords. Extreme political attitudes, radicalized behaviors, terrorism, dominant, emotional maps, strategic communications, associative and reinforcement learning, amygdala, prefrontal cortex.

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Introduction

We are proposing Emotionally Based Strategic Communications (EBSC) as a soft power for restoring political stability, security and prosperity in turbulent societies [1-3]. We strongly believe that the proposed emotional transformation based on the concept of dominant emotional maps may assist targeted groups or even entire societies to overcome their challenging political, social and security problems. Dominant emotional map illustrates potential of particular social groups to cope with its own social and security challenges. A well-designed EBSC strategy in the form of adequate public campaigning can induce vitally important positive emotions facilitating positive emotional transformation of the entire group. Conveying EBSC messages to the particular emotional space in order to induce its own positive emotional change may help us to take the majority of a targeted population away from the individuals who insist on extreme political attitudes, actions and behaviors. The hearts and minds of the masses must be won to prevent them to resonate with all of those radical entrepreneurs who instigate and organize terror.

The target of EBSC, is usually a socially and culturally homogeneous group, i.e. “the group which may function as a part of the self” ([4], p. 303) for its members, and to whom a message containing a group-relevant, emotionally charged content, that should be sent by all available communication media, such as leaflets, radio, television, internet, social networks etc. An important precondition for the start and cascade of positive emotional changes, as well as group based mental transformation, is networking of individuals who may act as agents of positive change and who enable spreading and diffusion of EBSC messages within and across entire groups eliciting in group positive emotions and feelings.

Emotionally Based Strategic Communications can be defined as a comprehensive and coherent set of activities, conducted across strategic, operational and tactical communication space, to promote and sustain a peaceful approach to the security challenges, influencing perceptions, attitudes, beliefs and behavior of a targeted audience by using emotions more explicitly. Influencing people without touching their emotions is almost impossible, either in individual psychotherapy or in strategic communications. Strategic communications, interpreted within a larger social and cultural environment, extended and innovated by an appropriately embedded emotionally based strategy, may play a more important role in conflict management, making traditional strategic communications more influential and effective. Taking into consideration a larger social and cultural environment within which strategic communications take place, the concept of Emotionally Based Strategic Communications (EBSC) is based on specifically designed emotional stimulation of peoples “emotional brains” [5], as an enhancement of the traditional concept of strategic communications.

1. Transformation of Dominant Emotional Maps

Emotionally Based Strategic Communications have been conceptualized as a mechanism for transformation of negative dominant emotional maps into more positive ones (Figure 1). The negative dominant emotional map can be characterized by negative discrete emotions, such as fear, anger, humiliation etc., or by their
corresponding valence/arousal values in a dimensional representation of emotions [6], and with the associated radical behavioral signatures. As we have already emphasized, the ultimate goal of EBSC is to facilitate and to change the emotions of a critical mass of individuals within the targeted group, so that the negatively valenced dominant emotional map of the group begins to converge, through a series of tipping points, to the map characterized by more positive dominant emotional map.

Figure 1. Emotionally Based Strategic Communications transform the initial negative dominant emotional map of a targeted group to the more positive dominant emotional map.

The transformation of a dominant emotional map by Emotionally Based Strategic Communications is based on the controllable trajectory of Center of gravity (CoG(t)) of a dominant emotional map which represents an average of all valence/arousal values of individuals in the targeted group:
The bottom panel in Figure 1 illustrates two of the infinite number of possible trajectories during the transformational process from the initial dominant emotional map to the more positive dominant emotional map. However, if EBSC is inappropriately conducted, such transformation does not need to converge towards the more positive dominant emotional map.

A successful transformation of a negatively dominant emotional map, which is root of extreme political attitudes and behavior, depends on the overall transformational potential and efforts of the entire society. We need to emphasize that EBSC are certainly not a panacea to all societal problems and that its chances of success are meager if the efforts of its implementation are not simultaneously combined with real economic, political and security improvements and other institution-building measures. Only then, strategic emotional management embedded in EBSC may contribute to the success of the entire transformational processes. But, from a psychological viewpoint, many economic, political, security and institution-building results and achievements are not perceived as positive and extremely useful and valuable in the hearts and minds of the targeted group, without facilitative efforts of EBSC. In other words, EBSC may be regarded as a necessary, but not sufficient precondition to a full societal recovery. Emotional management in the form of EBSC as soft power is essential for stabilization of fragmented and confronted groups and societies.

EBSC transformation can be defined as an extension of Cognitive Behavioral Therapy (CBT) [7], cognitive appraisal theory [8], and emotion regulation theory [9], toward top-down group based emotional regulation [10]. These processes and efforts might be conscious or unconscious, controllable or stochastic, and may have more or less effects on the ground. EBSC as group based emotion regulation strategy is based on processes of cognitive change focused on transformation of negatively valenced dominant emotions of a targeted group into more positive dominant emotions. In particular, EBSC is directed towards reappraisal of the ongoing negative emotional context of real life events and environment through processes of cognitive change. These cognitive reappraisal processes supported by EBSC may reduce a strong impact of negatively valenced, high arousal emotions on moods and sentiments of a targeted population and corresponding dominant emotional maps. The reappraisal of negative real-life stimuli and events should be mixed and embedded in the meaningful context of positive societal change related to the building of a new transportation and communication infrastructure; new schools, hospitals and highways, higher employment rate, more social security etc. EBSC is an innovative and creative technique of emotional change based on cognitive reappraisal, and should be successful in reducing dominant group based negative emotions. This is reason why we believe that EBSC is a really new approach towards large-scale strategies of emotion regulation, which might transform the destructive power of dominant emotional maps in fragmented and conflicting societies’ into a more constructive one.
However, we would like to note that a synchronous change of dominant emotions of wide segments of the population may provide a driving force or leverage for more all-encompassing societal changes. The synchronous change of individuals’ emotions by EBSC at a micro-level may lead to sweeping changes at the macro-level. Changing emotions of individual subjects changes their mutual relationships, which provides a social foundation for changing entire societies. In particular, the change of dominant emotional maps implies a change of intrinsic extreme political attitudes, action and behavior of large numbers of in-group individuals providing a new basis for a positive coherent collective transformation at the societal macro-level.

2. Neural Background of Extreme Political Attitudes and Behaviors

Extreme political attitudes and behaviors may elicit various cognitive and emotional changes in the affected brains ranging from changes in their brain biochemical parameters to a decrease in a number of neurons, particularly in hippocampal structures, and may result in severe anatomical and physiological changes with serious long-term consequences. A complex set of cognitive-emotional processes is important for analysis of extreme political attitudes and behaviors that is associated with: the medial PFC (mPFC), the anterior cingulate cortex (ACC), the temporoparietal junction (TPJ), the superior temporal sulcus and the temporal poles. While the mPFC has a special role in political and social cognitive processes, amygdala activities are crucial in shaping responses to socially threatening images and life-threatening situations [11]. These findings suggest that extreme political attitudes may strongly impact amygdala and the PFC neural networks, providing an explanation for the lack of flexibility and adaptability in rigid extreme political attitudes, conflicts and terrorism [12]. The degree to which a political statement is regarded as radical or moderate is associated with activation in the anteroventral striatum and posterior cingulate cortex/precuneus (PCC/PC). The degree of individualism of political beliefs is connected with activation in the mPFC and TPJ, and the degree of conservatism with activation in the dorsolateral PFC (dLPC) [13]. Social psychologists and cognitive neuroscientists have investigated the psychological and neural mechanisms of inter-group hostility, and have found that only the PC activity is correlated strongly with both explicit and implicit behavioral measures of negative attitudes toward the outer groups [14]. As the PC is located in the medial parietal cortex, this evidence seems to indicate that, in addition to the amygdala and PFC, the parietal cortex may have an important role in the formation and maintenance of extreme political attitudes.

It is well known that the amygdala plays a vital role in many highly emotional processes and that emotional variables such as valence and arousal are mainly encoded in the amygdale. Cognitive variables that describe cognitive processes such as attention, evaluation, rule-based decision-making, rule-based problem-solving, rule-based actions, goal-directed behavior, i.e. executive functions, working memory etc., are mainly encoded in PFC, while ACC and OFC are more involved in the valuation of actions and stimuli i.e. valence assessment [15-17]. It is also well known that the amygdala interconnections with the PFC mediate cognitive, emotional, and behavioral responses. The amygdala has a prominent role in fear conditioning and aversive processing, but the amygdala also plays important role in appetitive processing [18] what is a crucially important neural background of emotion regulation and
implementation of our proposed *neurally wired* Emotionally Based Strategic Communications. The amygdala and its interconnections with the prefrontal cortex (PFC) underline many aspects of the interactions between emotion and cognition [19-22]. The amygdala is essential for many of the visceral and behavioral expressions of emotion, while the PFC (especially its medial and orbital regions) is mainly responsible for many of the cognitive aspects of emotional responses and emotion regulation. These bidirectional connections between the amygdala and the PFC influenced by brain stem neuromodulation circuitry form the basis of complex interactions between cognition, emotion and motor responses.

The output from the amygdala is directed towards a wide range of different structures, including the PFC, the striatum, sensory cortex, the hippocampus, the perirhinal cortex, the entorhinal cortex, the basal forebrain, and to subcortical structures responsible for aspects of physiological responses related to emotion, such as autonomic responses, hormonal responses, and startle [23]. The PFC extrinsic connections through dorsolateral areas which receive input from sensory areas [24], or through orbitofrontal areas which receive inputs from advanced stages of sensory processing from every modality, including gustatory and olfactory [25-27], and makes the PFC a site of multimodal convergence of information regarding our external environment. In addition, the PFC intrinsic connections and received inputs could inform it about our internal mental state variables, such as motivation and emotions. Orbital and medial PFC is closely connected with limbic structures such as the amygdala, and also has direct and indirect connections with the hippocampus and rhinal cortices [26,28-29,30-31]. Medial and part of orbital PFC has connections to the hypothalamus and other subcortical targets that could mediate autonomic responses [32]. Neuromodulatory input to the PFC from dopaminergic, serotonergic, noradrenergic, and cholinergic systems could also convey information about internal state [33]. Finally, outputs from the PFC, especially from dorsolateral PFC, are directed to motor systems, consistent with the notion that the PFC may form, represent, and/or transmit motor plans [34] [35]. Altogether, the PFC receives inputs that provide information about many external and internal variables, including those related to emotions and to cognitive plans, providing a potential anatomical substrate for the representation of complex mental states. It means that the emotional regulation depend critically on the cognitive variables and vice versa cognitive variables depend on emotional regulation based on tightly coupled dynamic interactions of PFC-amygdala neural circuitry (Figure 2). As already mentioned, while these two regions interact with each other, they also interact with various sensory systems, which enable a human to observe external environment, as well as with long-term memory systems containing knowledge and experiences collected during a lifetime. When PFC and amygdala receive appropriate external or internal inputs, multiple feedforward and feedback connections lead to dynamic changes in the brain and body as a result of PFC-amygdala outputs toward hypothalamus, neuromodulatory systems, and other regions in the brain stem.

According to the given description it is obvious that the overall activity of the brain can be represented as multiple-input multiple-output, hierarchically organized, nonlinear and stochastic time variant, distributed massive parallel computing system that simultaneously receives and processes millions of data streams passing through a series of complex dynamic multidimensional and multimodal mental states and responses. These responses are a reflection of interactions of each individual brain with
its own current political, social and economic environment and personal situation as well.

Figure 2. PFC–amygdala interactions and the most important I/O projections showing simultaneous feedforward and feedback signal propagation, synthesized from considerations regarding interconnectivity of various brain structures encountered in the following works: [18,23,36-40]. Abbreviations: ACC – anterior cingulate cortex, OFC – orbitofrontal cortex, LA – lateral nucleus of the amygdala, B – basal nucleus of the amygdala, ITC – intercalated cell masses, CE – central nucleus of the amygdala, LC – locus coeruleus, VTA – ventral tegmental area, SN – substantia nigra, RN – raphe nuclei, NBM – nucleus basalis of Meynert, LH – lateral hypothalamus, PVN – paraventricular nucleus of the hypothalamus, NE – norepinephrine, DA – dopamine, 5-HT – serotonin, ACh – acetylcholine, ANS – autonomic nervous system, CRH – corticotropin-releasing hormone.

Neurophysiological recordings revealed that the amygdala, as well as PFC, contains some neurons that respond more strongly when a Conditional Stimuli (CS) is paired with a rewarding Unconditional Stimuli (US+) [18]. These positive value-coding neurons i.e. conditioned rewarding neural network tend to increase their firing rate for such type of positive-associative conditioning (US+,CS), while the other neurons are more sensitive when the same CS is paired with a US aversive stimulus i.e. (US-,CS).
These negative value-coding neurons or punishment-conditioned neurons tend to decrease their firing rate for such type of stimuli. These neurons, therefore, could participate in valence-specific emotional coding processes, while arousal i.e. intensity coding neurons which occur in response to intense emotional stimuli of both valences, modulate their responses to both rewards and punishment. It means that these neural networks represent neural background of our valuation system and associative conditioned learning processes based on the Hebbian “fire together-wire together” rule. The amygdala and OFC neurons in cooperation with the brain stem encode valence and arousal variables, as well as our valuation system i.e. reward and punish mechanism which is a precondition for reinforcement learning [41-42]. These interactions between amygdala and the PFC encodes a variety of additional processes critically important for our adaptive behavior in uncertain environments, such as: associative supervised learning based on I/O model (AL), reinforcement unsupervised learning without I/O model (RL), dopamine-based learning i.e. dopaminergic modulation which is responsible for AL and RL learning, Hebbian association learning etc.

Neuroscience researchers strive to better understand the critical periods of brain evolution and development and suggest that extreme political attitudes and actions, stress, aggression, and violent behavior may strongly affect the brain developmental process. Hostile destructiveness is not present at the moment of birth; it is a consequence of experiencing excessive displeasure in social environment over lifetime. This type of aggression is influenced by the relationships children have within their social environments provided to them [43]. The old debate on the relative contribution of nature versus nurture to the construction and maintenance of brain architecture has led to the widely accepted consensus that genes and environment work in concert in shaping neural circuits and behavior. Fundamental contributions to the development of the nature–nurture debate came from the experiments by Rosenzweig and colleagues, who introduced environmental and social enrichment as an experimental protocol, specifically devoted to investigate the influence of the environment on brain development and behavior, showing that the morphology, chemistry and physiology of the brain can be remarkably altered by modifying the quality and intensity of environmental stimulation. Since then, many studies have shown that social and environmental enrichment elicits in the brain changes ranging from the molecular to the anatomical and functional level [44-45].

3. Application of Associative and Reinforcement Learning in Emotionally Based Strategic Communications

Social learning emerges from our personal experiences of reward or punishment, but also from dominant behavior in our social environment. It is mainly based on reward-punishment paradigms of learning and its mechanism of neural implementation, which drives our behavior. The social algorithms and information acquired using the processes of reward-based learning are key variables for our adaptation in the complex and uncertain social environment. Two neighboring divisions of the anterior cingulate cortex are central for learning about social valuation and social relations and determining our behavior.
In general, social emotional regulation is related to the development of our abilities to adapt our individual emotional response to our social environment and to the most prevalent group behavior. The basic ways in which this can occur are related to the associative and reinforcement based learning and emotional adaptation based on switching between a variety of augmented mental states representing different social contexts or situations.

Associative Learning mechanism may change the representation of the existing dominant emotional maps, and their emotional pairing and meanings. Indeed, based on cognitive reappraisal and associative learning we can forget or overwrite previously stored association contents. Moreover, previously associated stimuli with a particular reinforcement, which elicits specific emotional response, by experiencing the CS stimulus in the absence of the US, can induce extinction. Extinction, as a learning process, whereby previously acquired responses are inhibited, is the basis of our proposed EBSC policy design, and transformation of negatively dominant emotional maps towards a more positive one. In the case of fearing extinction, scientists currently believe that original CS-US associations pairing continue to be stored in the brain, so that they are not forgotten or overwritten, but newly developed inhibitory mechanisms suppress the fear response restoration [46].

Basically, associative learning as a form of behavior modification involves the association or conditioning of two or more stimuli, or between a stimulus and response, which happened together, and takes place only when a conditioned stimulus is followed by an unconditioned stimulus. This is really a fundamental component of conditioning, since a response to a stimulus would not really be learned if the brain does not get the point that the stimulus input and response output are supposed to occur together. This does not have to be conscious learning, but the temporal and spatial neuronal association must be made for the learning to occur. Delay conditioning is more effective than trace conditioning [47].

In a simple model, we can assume that associative learning is based on appropriate synaptic learning rules, which modify synaptic connections from neurons representing the conditioned stimulus (CS) to some of the neurons representing the unconditioned stimulus (US). In this type of classical associative learning i.e. conditioning a previously neutral stimulus is repeatedly presented together with a reflex eliciting stimuli until eventually the neutral stimulus will elicit a response on its own. The typical paradigm for classical conditioning involves repeatedly pairing an unconditioned stimulus with another previously neutral stimulus. Following conditioning, the response occurs both to the unconditioned stimulus and to the other, unrelated neutral stimulus (CS). The response to the conditioned stimulus is termed a Conditioned Response - CR. This biological and molecular mechanism of Associative Learning can be written in the following form vector-matrix form:

\[
US(t) = \begin{bmatrix}
us_1(t) \\
us_2(t) \\
\vdots \\
us_n(t)
\end{bmatrix}, \quad US^+(t) = \begin{bmatrix}
us_1^+(t) \\
us_2^+(t) \\
\vdots \\
us_n^+(t)
\end{bmatrix}, \quad US^-(t) = \begin{bmatrix}
us_1^-(t) \\
us_2^-(t) \\
\vdots \\
us_n^-(t)
\end{bmatrix},
\]

(2)
Where $US(t)$ is a vector of unconditioned stimuli, and $us_i(t)$ is $i$-th component of unconditioned stimuli on axon/dendrite $i$, $i = 1, 2, ..., n$; $US^-(t)$ is a vector of negative i.e. unpleasant unconditioned stimuli, and $us_i^-(t)$ is $i$-th negative component of unconditioned stimuli on axon/dendrite $i$, $i = 1, 2, ..., n$; $US^+(t)$ is a vector of positive i.e. pleasant unconditioned stimuli, and $us_i^+(t)$ is $i$-th positive component of unconditioned stimuli on axon/dendrite $i$, $i = 1, 2, ..., n$.

$$CS(t) = \begin{bmatrix} c_{s1}(t) \\ c_{s2}(t) \\ \vdots \\ c_{sn}(t) \end{bmatrix}, \quad (3)$$

- Which is a vector of conditioned neutral stimuli, where $cs_j(t)$ is $j$-th component of unconditioned stimuli on axon $j$, $j = 1, 2, ..., m$.

$$CR(t) = \begin{bmatrix} cr_1(t) \\ cr_2(t) \\ \vdots \\ cr_n(t) \end{bmatrix}, \quad CR^+(t) = \begin{bmatrix} cr_1^+(t) \\ cr_2^+(t) \\ \vdots \\ cr_n^+(t) \end{bmatrix}, \quad CR^-(t) = \begin{bmatrix} cr_1^-(t) \\ cr_2^-(t) \\ \vdots \\ cr_n^-(t) \end{bmatrix}, \quad (4)$$

Where $CR(t)$ is a vector of conditioned responses, and $cr_i(t)$ is $i$-th component of conditioned response on axon $i$, $i = 1, 2, ..., n$; $CR^+(t)$ is a vector of positive i.e. pleasant conditioned responses, and $cr_i^+(t)$ is $i$-th positive component of conditioned response on axon $i$, $i = 1, 2, ..., n$; $CR^-(t)$ is a vector of negative i.e. unpleasant conditioned responses, and $cr_i^-(t)$ is $i$-th negative component of conditioned response on axon $i$, $i = 1, 2, ..., n$.

If additional variables are defined as:

$$h_i(t) = \text{dendritic activation, } i = 1, 2, ..., n$$

$$w_{ij}(t) = \text{synaptic weight matrix } (i, j), i = 1, 2, ..., n, j = 1, 2, ..., m, \quad (5)$$

Then, Hebbian learning enhanced by neuromodulators changes the synaptic weights on amygdala neurons depending on the intensities and temporal correlation of unconditioned and conditioned stimuli and neuromodulator secretion:

$$\frac{dw_{ij}}{dt} = f_i^\prime \left( us_i(t), cs_j(t), cr_i(t), corr(us_i(t), cs_j(t)), \text{ixicorr}(us_i(t), cs_j(t)), \text{DA}(t), \text{NE}(t), \text{5HT}(t) \right)\right)$$

$$i = 1, 2, ..., n, j = 1, 2, ..., m, \quad (6)$$

Where,
is a hypothetical measure of temporal overlap between unconditioned and conditioned stimuli, as correlation of signals on corresponding axons \(i\) and \(j\) in the neural computation timespan \([t−\tau, t]\),

\[
\text{corr}(us_i(t), cs_j(t)) = \int_{t-\tau}^{t} us_i(t')cs_j(t')dt',
\]

\(7\)

The above is a hypothetical measure of temporal precedence of conditioned stimulus onset with regard to unconditioned stimulus, as an integral part of cross-correlation function of corresponding signals, using time lags from 0 to \(d\) in neural computation.

In Associative Learning processes temporal relationship between unconditioned and conditioned stimuli needs to respect the stimuli delivery protocol for delay and trace conditioning. In delay conditioning, unconditioned stimulus overlaps with conditioned stimulus and occurs after conditioned stimulus has started, while in trace conditioning it occurs after the conditioned stimulus ends, either immediately or after some time elapses. Synaptic weight changes can be strengthened by repetitive presentations of unconditioned and conditioned stimuli.

Conditioned response (CR) that is dependent on synaptic weights and intensities of unconditioned and conditioned stimuli can be written by:

\[
CR(t) = f_2(h_i(t)) = f_2(\sum_j \alpha_{ij}us_i(t)cs_j(t)) = \text{for simplicity } \\
= \sum_j \alpha_{ij}us_i(t)cs_j(t), i = 1, 2, ..., m
\]

\(9\)

\[
\begin{bmatrix}
CR_1 \\
CR_2 \\
\vdots \\
CR_m \\
\end{bmatrix} = 
\begin{bmatrix}
us_1 & 0 & \cdots & 0 \\
0 & us_2 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & us_n \\
\end{bmatrix} \begin{bmatrix}
w_{11} & w_{12} & \cdots & w_{1m} \\
w_{21} & w_{22} & \cdots & w_{2m} \\
\vdots & \vdots & \ddots & \vdots \\
w_{n1} & w_{n2} & \cdots & w_{nm} \\
\end{bmatrix} \\
\begin{bmatrix}
us_1 & \cdots & \cdots & \cdots \\
\cdots & \cdots & \cdots & \cdots \\
\cdots & \cdots & \cdots & \cdots \\
\cdots & \cdots & \cdots & \cdots \\
\end{bmatrix}
\]

\(10\)

\[
CR(t) = US(t)W(t)CS(t)
\]

\(11\)

The prefrontal (PF) cortex has a remarkable ability to form and rearrange arbitrary associations rapidly. Many of our complex, learned behaviors depend on arbitrary stimulus–response associations as high-level cognitive processes and brain neural plasticity, which can change and modify a result of our experience. The newest imaging technique can track these neuronal networking processes and changes what might be a promising venue for evaluation of EBSC real impact and influence.

Different stimulation strategies and different learning mechanisms lead towards different emotional regulation policies, producing different synaptic reinforcement algorithms and interconnections within the specific dynamic neural networks. The
cognitive regulation of emotion, may, cause a change in the associated emotional variables i.e. valence and arousal. Different social situations can demand different emotional responses to similar sensory stimuli, and knowledge of the social situation, i.e. essentially a context variable can thereby constrain the possible emotional responses.

Therefore, the intention of EBSC approach is to use Associative Learning to facilitate targeted modification of the emotions, attitudes and behaviors of the observed group regarding the current political, economic and social situation in the country towards the desired, optimal mental states which are not characterized by extreme political attitudes. Goal function of EBSC is to transform CoG of the targeted group from the initial, dominantly negative and high-arousing value to the dominantly positive and low-arousing value. In fact, best EBSC could be formulated as a solution of optimal control problem, for which the corresponding CoG minimizes index of performance in the form of cumulative distance with respect to some hypothetical preferred CoG over the period of time $[t_0, t_0 + T]$

$$\int_{t_0}^{t_0 + T} \|CoG(t) - CoG^*\| dt \rightarrow \min,$$  \hspace{1cm} (12)

Where $CoG(t)$ is defined by equation (1). From equation (12), it is quite evident that its minimum depends on the valence and arousal values of each individual in the targeted group.

However, as CoG* is a hypothetical construct, a more realistic approach to designing appropriate EBSC strategy may be based on comparing CoG locally, between two successive moments of measurement, and evaluating how much CoG has improved since the previous measurement with regard to the EBSC goal. In such approach, EBSC attempts to maximize cumulative improvements over the period of time $[t_0, t_0 + T]$

$$\int_{t_0}^{t_0 + T} \text{improvement}(CoG(t), CoG(t_{\text{previous}})) dt \rightarrow \max,$$ \hspace{1cm} (13)

where $t_{\text{previous}}$ denotes a previous time at which CoG was measured, which may be, for example, 6 months or 1 year ago. Local improvement of $CoG(t)$, in terms of valence and arousal, may be related to incremental change of each subcomponent in the right direction:

$$Valence_{TG}(t) - Valence_{TG}(t_{\text{previous}}) > 0,$$

$$Arousal_{TG}(t) - Arousal_{TG}(t_{\text{previous}}) < 0, t, t_{\text{previous}} \in [t_0, t_0 + T].$$ \hspace{1cm} (14)

EBSC attempts to induce associative learning in the targeted group by using the repertoire of carefully selected positive unconditioned and conditioned stimuli (US* and CS) over time:
In response, the targeted group transitions from one to another mental state, but it is uncertain how these transitions will actually unfold, and whether a decreasing trend of extreme political attitudes and behaviors will appear over time. Existing tools for modeling dynamic decision-making under uncertainty, like agent-environment framework of Markov Decision Processes and Reinforcement Learning in partially observable environments [48], may, therefore, be applicable to EBSC approach. EBSC strategy has a specific goal related to achieving appropriate transformation of dominant emotional maps of the targeted group, where available actions at each time, \( EBSC(t) \), consist of sequences of (US+, CS) pairs. These actions influence the overall mental state of the targeted group, but this state can be measured only intermittently in some limited way, and it is uncertain how an action will affect this state before it is actually taken. The reason of uncertainty is that \( Valence_{TG}(t) \) and \( Arousal_{TG}(t) \) of targeted group are functions not only of valences and arousals of all unconditioned and conditioned stimuli delivered by EBSC, but also a function of numerous other variables (institution-building, economic, security, political measures etc.):

\[
Valence_{TG}(t) = Valence_{TG}(t_{previous}) + f_1(Valence_{EBSC}(t) + \ldots) \\
Arousal_{TG}(t) = Arousal_{TG}(t_{previous}) + f_4(Arousal_{EBSC}(t) + \ldots) \\
\]

Where:

\[
Valence_{EBSC}(t) = \frac{1}{k(t)} \sum_{j=1}^{k(t)} Valence_{EBSC}(US^j, CS^j) \\
Arousal_{EBSC}(t) = \frac{1}{k(t)} \sum_{j=1}^{k(t)} Arousal_{EBSC}(US^j, CS^j) .
\]

Based on the measurements, the new state of the targeted group is evaluated in terms of improvement toward the EBSC goal relative to the previous state. In Reinforcement Learning terminology, this means that the reward associated with state transition is computed. Measured state and computed reward are used to update the knowledge regarding how the actions affect the targeted group, based on which the appropriate (US+, CS) pairs are selected in the next step.

It is important to notice that the measured state of the targeted group can include more information than valence and arousal, such as press-clipping keyword statistics, frequency of extreme behaviors etc. This constellation of variables that represents observable aspects of the targeted group state may require multiple frame times of measurement, like the shortest possible 1-day frame time, as well as 1-week, 1-month, 3-months, 6-months, 1-year frame times and so on. For example, local key features of the state that can be measured with shorter frame times, may include press-clipping
keyword statistics, while other, more global, key features like the number of extreme behaviors that occur in the targeted group, or $CoG(t)$ require observation over the longer period of time. After each short-term, mid-term, and long-term measurement appropriate reward is computed and used to update knowledge how the EBSC strategy should unfold in the next short-term, mid-term and long-term interval of time. Therefore, EBSC strategy actually includes multiple control loops, simultaneously operating at multiple timescales.

Presented approach is essentially based on multimodal stimulation, estimation and emotion regulation. In this context, intensity of elicitation by multimodal stimuli is defined by:

$$E(US^{+/−}(t)) = f_3 \begin{bmatrix} E(US^{+/−}_{visual}(t)) \\ E(US^{+/−}_{narrative}(t)) \\ E(US^{+/−}_{linguistic/ acoustic}(t)) \\ E(US^{+/−}_{olfactory}(t)) \end{bmatrix}$$ (18)

Where $E(US^{+/−}(t))$ is energy of multimodal unconditioned pleasant/unpleasant stimuli, which depends on each particular sensory modality (visual, narrative, linguistic/acoustic, olfactory) and their congruence.

Multimodal and multi-frame estimation is based on acquisition of multiple features, like: aggregated statistics of keywords on a level of decomposed subgroups in multiple frame times, frequency of extreme political statements, actions and behaviors, including the trajectory of group-based dominant emotional map center of gravity ($CoG$).

Multimodal emotion regulation is based on EBSC Associative Learning and Reinforcement Learning protocols in multiple frame times and in each subgroup of the targeted group.

4. EBSC policy design: Case study: Afghanistan

EBSC is conceptualized as the positively valenced stimulation of a negatively emotionally affected group by an appropriate communications strategy in order to influence extreme political behavior of targeted groups. EBSC as well as CBT are based on the fact that the emotionally charged messages and communications have much stronger impact on formation of our associative memory due to specific receptors and neurotransmitters. Both techniques are based on stimulation of individual’s emotional brain by semantically and emotionally annotated multimedia stimuli in various forms, like real-life video clips, static pictures, sounds, stories, and synthetic images and clips. When we design stimuli, we must take into account culture, history, and traditions of the intended audiences. Understanding specific psychosocial mental complexes, socio-cultural and socio-political structures, as well as their mutual interdependence, is crucial for designing effective EBSC messages directed to specific audiences. Particularly interesting in this respect are different socio-cultural features of a targeted group which are shaped by its members’ behavior, and which at the same
time shape this behavior through cognitive processes resulting in distinct socio-cultural and political conflict patterns (e.g. [49-50]).

Each EBSC-generated message should be designed with the intent of transforming the initial dominant emotional map towards more desirable emotional state. Productive EBSC messages must resonate among targeted audiences and ignite a form of “transformational feedback” [51] that moves the targeted group closer to the desirable dominant emotional map. Such EBSC may provide more desirable behavior, i.e. conditioned response (CR) of targeted group in a form of acceptable political attitudes and actions characterized by cooperative peace gestures, willingness for peace talk, compromise, mediation, etc.

An example of EBSC message and mechanism of Associative Learning that may take place in Afghanistan is illustrated by Figure 3. Using delay conditioning paradigm, conditioned stimuli CS\textsubscript{1} can be associated with negative-unpleasant unconditioned stimuli US\textsuperscript{-}, leading to subsequent negative conditioned response CR\textsuperscript{-} even in the case when CS\textsubscript{1} is encountered alone. Likewise, association of CS\textsubscript{2} with positive-pleasant unconditioned stimulus US\textsuperscript{+} leads to subsequent positive conditioned response CR\textsuperscript{+} when encountering CS\textsubscript{2} alone.

Each US is generally a multimodal stimulus that may include pictures, sounds, video materials, appropriate narratives and keywords. For example, US\textsuperscript{+} stimulus

![Image](image_url)

**Figure 3.** EBSC Associative Learning in Afghanistan. Abbreviations: PFC – prefrontal cortex, OFC – orbitofrontal cortex, vmPFC – ventromedial prefrontal cortex, ParC – parietal cortex, TmpC – temporal cortex, TPJ – temporoparietal junction, Ht – hypothalamus, BS – brain stem, BF – basal forebrain.

Each US is generally a multimodal stimulus that may include pictures, sounds, video materials, appropriate narratives and keywords. For example, US\textsuperscript{+} stimulus
shown in Figure 3 is a video material, coupled with the following narrative: “The internationally-funded projects of Kabul main square reconstruction create jobs for Afghan people and help them to speed up Afghanistan economic growth by improving infrastructure for business and trade, creating a brighter future for Afghan children…” Highly positive valence and arousal that such stimulus might elicit in the local population can be associated with CS$_2$ stimulus via the delay conditioning paradigm. EBSC pairing of unconditioned and conditioned stimuli creates conditioned responses, which promote positive cognitive change toward the content of CS$_2$, positive reappraisals, emotion regulation, tolerance, and reduction of extreme political attitudes, behaviors, and terrorism.

In order to choose a highly responsive emotional stimulus, we need all kinds of relevant databases which contain information and knowledge about targeted group’s social psychology, history, local cultural context, language/symbol systems, behavioral codes, power relations, motivations, intentions, and most pressing personal needs of the group’s members and leaders, including potential agents of positive change.

Cognitive and emotional brains of targeted group members process delivered EBSC messages, placing them into a particular historical, cultural, and political context and evaluating their meanings and emotional properties. The integration of emotional properties and narrative content must be designed with flexibility in mind in order to emphasize right issues in right time, strongly and effectively, with full confidence and credibility. The best and most successful combinations of emotional properties and narrative content are those that embrace ideas and emotions and that quickly gain resonance with the targeted group [52]. Creative fusion is a way of a variety of available media resources in generation of multidimensional stimuli that may induce resonance with the targeted audience and enhance the effectiveness of EBSC.

Emotionally Based Strategic Communications present a soft approach to the hearts and minds of the local population, which may help them to minimize reluctance, resistance and coerciveness towards international economic and military assistance. Based on EBSC and the neuroplasticity of individual neural networks, emotional maps of many individuals may be aggregated into new dominant emotional maps becoming new social and political power for a successful societal transformation. Such clusters of emotionally positive, aggregated individuals and the corresponding mental maps based on common goals, objectives, interests, and values may comprise leading emotional power of change towards a new, healthier socio-cultural environment. Therefore, EBSC may definitely bring real added value to Afghanistan as a new “soft power”, important for reaching more desirable mental states, and at the same time minimizing limited international financial and military resources.

5. Conclusions

We have proposed the application of Emotionally Based Strategic Communications (EBSC) as a potential leverage in ongoing efforts to maintain political stability and security in social settings threatened by extreme political attitudes and intense radicalization. Emotionally Based Strategic Communications have been conceptualized as a means of transforming negative dominant emotional maps of targeted groups into more positive ones. Prevention and reduction of negative emotions may ease social tensions in politically polarized, culturally fragmented, or economically stratified social
settings, thereby facilitating harmonization of diversified communities. Proposed EBSC policy design aiming to decrease the destructive power of extreme political attitudes can be regarded as a “large-scale [strategy] of emotion regulation” ([10], p. 98).

Identifying dominant emotions of targeted groups and reversing them wherever they are negative and taking advantage of them wherever they are positive is the main goal of EBSC. A well-designed EBSC approach in the form of adequate public campaigning can induce vitally important positive emotional enrichment facilitating a genuine positive outlook of targeted groups on their future.

However, we would like to note that a synchronous change of dominant emotions of wider population may provide a “driving force” or “leverage” for more all-encompassing societal changes. The synchronous change of individuals’ emotions by EBSC at a micro-level may lead to sweeping changes at the macro-level. Changing emotions of individual subjects changes their mutual relationships, which provides a social foundation for changing entire social collectivities. In particular, the change of dominant emotions implies a change in action tendencies of large numbers of individuals providing a basis for a coherent collective action at the societal macro-level.

Based on EBSC and the neuroplasticity of individual neural networks, emotional maps of many individuals may be aggregated into new dominant social emotional maps. Such aggregated clusters of emotionally positive people may provide a base for collective action of diverse individuals, who do not necessarily share common goals, objectives, interests, or values, and may be a remarkable soft emotional power of change towards a new, healthier socio-cultural environment. Therefore, we regard EBSC as compatible with and capable of contributing to a distinct soft power approach to security policy.

We need to emphasize that EBSC are certainly not a panacea to all societal problems and that its chances of success are meager if the efforts at its implementation are not simultaneously combined with economic, political, security, institution building and other measures at the societal level. Only then, strategic emotional management embedded in EBSC may contribute to the success of transformational processes. But, from a psychological viewpoint, results and achievements of economic, political, security and institution-building policies are often not, without the facilitative effects of EBSC, perceived as valuable in the hearts and minds of affected individuals and groups. In other words, EBSC may be regarded as a necessary, but not a sufficient precondition to any comprehensive policy implementation.

References


Section 3

Stress Inoculation Training
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Our Experiences in the Use of VR Technology in Therapy and Prevention of Combat Related Stress Disorders in the Polish Army

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Abstract. This paper is a report on 5-year partnership between the Department of Psychiatry and Combat Stress (DP&CS) of the Military Institute of Medicine in Warsaw with the Virtual Reality Medical Center (VRMC) of San Diego, USA in implementation of VR technology in the area of protection of mental health of Polish Military Contingent’s (PMC) soldiers and veterans who participated in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). The partnership was initiated by the VRMC that transferred free of charge to the DP&CS computer hardware along with dedicated software and provided training to the personnel in the field of the Graded-Exposure, Virtual-Reality-Facilitated, Biofeedback-Guided Treatment for Combat-PTSD. Initially this method was applied to all patients with combat related stress disorders, hospitalised in our clinic. Later on it was limited to PTSD and the VR therapy was based on a therapeutic link and patient’s trust to the therapist. Control of arousal by a proper breathing pattern restored to those patients a sense of control over their emotions and facilitated deepened psychotherapeutic work. A strong point of the VR therapy was a possibility of grading the difficulty level of the VR exposed scenes. An excessively technical nature of this method was a source of reserve of the therapists towards this approach. Because of this the VR therapy should be used for treatment of PTSD patients only as additional and supporting one. Good results in PTSD treatment were obtained by a combination of the VR therapy with behavioural training.

Another area of cooperation between the DP&CS and the VRMC was an implementation of a short-term, collective VR Computer-Assisted Stress Inoculation Training for soldiers preparing for a deployment to Afghanistan. The results obtained indicate a short-term effectiveness of the training as a method of tension reduction. However, in the long-term perspective these results are ambiguous and they suggest a need of further research.

The latest chapter of research on application of VR technologies in activities of the DP&CS is utilisation of exposure to virtual war stressors to assess changes in the central nervous system, observed by means of PET-imaging, used as a predator of resistance to battlefield stress in special forces’ soldiers. This research is in progress.

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Introduction

Five years ago a partnership was established between the Virtual Reality Medical Center (VRMC), San Diego, United States of America and the Department of Psychiatry and Combat Stress (DP&CS) of the Military Institute of Medicine (MIM), Warsaw, Poland, in the field of Virtual Reality Technology application for treatment of combat stress-related disorders. I believe that a NATO conference on this subject is the right forum to present a report on an outcome of this cooperation.

At the beginning I’d like to present the unusual circumstances of establishing this partnership. In the first decade of the 21st century, Polish Armed Forces were undergoing a reduction in the total number of troops, a gradual replacement of conscript soldiers with contractual ones, as well as liquidation of military hospitals and outpatient clinics that became excessive in that situation. Concurrently, the involvement of Polish Military Contingents (PMC) in international operations conducted in Iraq (OIF) and Afghanistan (OEF) was growing. One of the results of this involvement was an increase in the numbers of mental disorder diagnoses connected to combat stress in veterans of those operations.

Polish military medical services were not prepared to treat those disorders because they were only incidentally occurring in UN missions that our armed forces participated in since 1953. Thus, when the Department of Psychiatry and Combat Stress (DP&CS) was established in 2005, its personnel started to look for contacts with centres in the allied forces that had had experience in that area.

On the 5th anniversary of the 9/11 attack on the New York’s World Trade Center - due to help provided by Office of Defence Cooperation of the US Embassy in Warsaw, headed by Dr. Richard Olesinski - a few-day long workshop was arranged to take place in Warsaw, named “Countering the Psychology of Terrorism and Combat Stress”, and conducted by the Defence Institute for Medical Operations (DIMO). Unfortunately, budget cuts that affected the Office prevented a continuation of this partnership.

By a fortunate coincidence, an American psychiatrist of Polish origin, Cmdr. Stanley Raczek, MD from San Diego, re-established his contacts with our Department. Back in early nineties Cmdr. Raczek rendered considerable services to bringing American and Polish psychiatrists (both military and civilian ones) closer to each other. In 1997 he was granted the highest award of the Polish Association Physicists - the Gloria Maedicinae medal - for that. Continuing his initiatives from the nineties he indicated our clinic to the President of the VRMC, Mark Wiederhold, MD, as a credible partner for cooperation. This suggestion was accepted and today I have the honour to report on this 5-year long and very fruitful partnership. I would be happy if the VRMC’s opinion on this cooperation is similar to ours.

I. VR-Assisted Combat PTSD Therapy in the DP&CS

After an exchange of letters of intent between the VRMC and MIM, on June 19, 2007 the VRMC’s Professors Brenda K. Wiederhold PhD and James Spira PhD arrived in Warsaw, bringing with them equipment for VR therapy in the form of 3 laptops with
software and accessories, with a total value of USD 15,000; this equipment was transferred free of charge to our clinic.

Within 4 days, they delivered VR Therapy lectures and hands-on training for a group of 20 DP&CS employees; all participants obtained certificates. In addition to the scientific programme, the meeting was used to present the history of Polish military psychiatry, functioning of our clinic as well as Warsaw culture and monuments to the VRMC’s representatives as this was their first visit to our city.

Before Brenda’s and James’ visit, their publication on the usage of VR in the therapy of PTSD was translated and a skeptical editorial comment on the possibilities of using this technology in the clinical practice in Poland was added [1].

Contrary to these forecasts, having prepared, according to the VRMC’s recommendations [2,3], an air-conditioned room for VR therapy, we have begun its use in our clinical practice. This was the responsibility of two psychologists who were conducting examinations as well as both individual and group psychotherapy for veterans hospitalised in the clinic. Initially the veterans represented approx. 20% of the 30-bed day-and night psychiatric ward and then this share has increased to 40%. So far 250 patients have been treated by the clinic; some of them underwent several treatments. The total number of hospitalisations has exceeded 350. Combat related stress disorder (PTSD) was diagnosed in 38.9% of the hospitalised veterans. Other diagnoses were adjustment disorders 26.9%, neurotic and somatoform disorders 19.6%, personality disorders 1.4%, alcohol-related disorders 3.3%, mental disorders of an organic origin 3.3%, psychotic disorders 4.7% and no disorders 1.9%.

A large workload of the psychologists resulting from their current duties made it difficult to introduce the VR therapy as a routine element of the treatment provided by our clinic. On the other hand, the Polish system of financing military medical units, based on a contract with the National Health Fund that did not take into account differences between civilian and military PTSD in terms of comorbid combat traumas, prevented hiring additional personnel because of negative financial consequences for the clinic. Later on we managed to overcome this deadlock by hiring a part-time psychologist working on her doctor’s thesis, who was interested in the VR therapy.

Patients were qualified for the VR therapy basing on a clinical interview, psychological tests as well as psychiatric and psychological observation during hospitalisation. The following psychology questionnaires were utilized: Minnesota Multiphasic Personality Inventory (MMPI-2), The Impact of Event Scale–Revised (IES-R), Combat Exposure Scale (CES), Watson’s Post-Traumatic Stress Disorder Interview (PTSD-I), Clinician-Administered PTSD Scale (CAPS). The basic condition for qualification for the VR therapy was a direct connection between patient’s PTSD and a traumatic combat experience.

Basing on the above-mentioned criteria, 20 patients with PTSD diagnosis were qualified for VR therapy. Four of them gave up after the first session, explaining they were not interested in the VR technique. Another 6 patients withdrew from the therapy before its completion, as a date of their discharge from the clinic was close. The remaining 10 patients successfully completed the treatment.

1.1. Examples of the soldiers with diagnose of PTSD treated with support of VR

The first four out of five examples of the VR therapy illustrate attitudes of the patients towards this form of treatment and an assessment of the therapy results in the initial period of its implementation in our clinic.
1.1.1. Warrant Officer M. W., 36 (age)/ 14 (service), 2xOIF 12 months, 2 hospitalisations. 129 days, Dg. F43.1
Initially, his attitude towards VR therapy was distrustful. He was comparing it to an „electric chair” and „lie detector”. His behaviour during the session was impulsive. He would rapidly take the sensors off and ask: - „Can we finish now?” Between the sessions he was anxious and was complaining about intensification of PTSD symptoms. After many exercises finally an effective method of relaxation by focusing on an object in the room was found. Near the end of the therapy he became much calmer and more patient. Using a 1-10 scale, he assigned „4” to the VR therapy. He said it had allowed him to learn how to control „his physiology”. He assessed that the weak point of that approach were images and sounds of the virtual scenarios, „differing from real conditions of the missions”.

1.1.2. Warrant Officer A.T., 40/22, 2xOIF 15 months, 1 hosp., 67 days, Dg. F43.1
In the beginning he was in a high state of physiological arousal, especially when he was talking about a traumatic event at the he was showing a high level of motivation to undergo the therapy and was patiently performing all procedures. He was claiming he did care very much about recovering and return to his normal life. He did not stop the therapy despite a sudden death of his sister. During the sessions he did not comment on their technical aspects but in the end he confessed he had expected something special, advanced, „revolutionary” while it turned out these are standard laptops with software resembling kid’s computer games. Despite of this he assessed that the VR therapy, combined with other forms of therapy used by the Clinic (especially so called „tape”), turned out to be very effective in his case.

1.1.3. Warrant Officer D.G., 38/19, 2xOIF 12 months, 2 hosp., 64 days, Dg. F43.1
Initially the contact was difficult. He reluctantly accepted the proposed relaxation method. Being briefed about the therapy he was interrupting, became distracted and run away into digressions on his deployment. Entered into the VR environment he responded with a high physiological arousal. After the session he needed a long discussion on his traumatic experience from the deployment. Only then he was able to focus on relaxation. During the next sessions he was demonstrating impatience because of lack of quick therapeutic effects. He used to say that although the VR looked like a computer game, he felt anxious wearing the goggles. He was often comparing the VR to situations from his deployment. As time passed he mastered relaxation and concentration of attention on breathing and objects from his vicinity. Satisfaction of the patient with results of the therapy was correlated with the computer data.

1.1.4. Platoon Sergeant S.M., 35/14, OIF&OEF 12 months, 3 hosp., 203 days, F43.1 ∙F43.2
He entered the VR therapy readily. He said: - If this is invented by the Americans then it means this is good and will help me. Entered into the VR environment he responded with a high physiological arousal. Between the sessions he was complaining about an increase in sleep problems and somatic disorders. Despite this he maintained his willingness to continue the therapy. During five sessions and the next ones he asked to
switch the computers off and he sat silently for even up to 10 minutes. He was finishing the sessions calmed down. He was also calmer between the sessions. The impression was that his emotional, sometimes „theatrical” behaviour during the sessions resulted from his constant personality-related predispositions, with only a slight contribution from a remote traumatic event. After the 8th session the therapy was stopped due to current family problems of the patient.

Now I would like to shortly present a case study of the Iraqi veteran, which illustrates the our clinic’s attitude toward VR therapy of disorders connected to combat stress.

1.1.5. Private 1st class D.G., 29/3, OIF 8 month, 3 hosp., 276 days, Dg. F43.1

He has narrowly escaped death three times. The first time was when during a change of guard he unintentionally shot by his colleague from his personal weapon. The projectile penetrated the victim’s helmet, slid along its internal shell curvature and left the shell causing only a scratch on the scalp skin. Another trauma was experienced by the soldier a month after the first incident. As a guard of honour he was “shot” in the same rear head area with a cap of a cream tube, inadvertently stepped on by a colleague. This incident caused a strong reaction to stress. The third event occurred a couple of days later, during a rocket attack on the Diwaniyah base. Just before the attack the soldier was heading for the laundry but he returned from the laundry building as he forgot to take some of his dirty washing. Right at that time a large-calibre projectile hit the laundry building, destroying it completely and killing an American civilian employee. After this incident the soldier was evacuated to the DP&CS with diagnosis of ASD.

During the first 4 month hospitalisation a satisfactory stabilisation of the mental condition was achieved due to classical psychotherapeutic actions provided both in a group and individually. The psychotherapeutic treatment was accompanied by medication. However, the patient did not agree to undergo a therapy using VR. Despite a balanced mental condition of the patient found at the checkout, his fear of a contact with weapon was so intense that he was found unfit for further professional military service.

The second hospitalization that took place 3 months after the first one was caused by a spontaneous recurrence of PTSD symptoms. During this second hospitalization it was decided that the patient would undergo a treatment using VR and, concurrently, in vivo training. Participation of the patient in this form of therapy was “forced” by the therapeutically team by telling him this would be the basic condition for his mental condition estimation, qualifying the patient for discharge from the hospital. The patient could hardly wait for the discharge as he had been already bored by the forms of therapy used so far and his lengthening stay in the ward.

Exposure Therapy Using Virtual Reality was being used according to standards of VRMC. Prior to the VR therapy three sessions were provided to refresh the attention concentration training by means of a method that was used with the patient during the first hospitalization. The patient was getting impatient and disenchanted quickly. However, continuous monitoring of his results recorded on the computer screen was helping him to persevere. VR stimulation was used from session 4. Altogether 22 VR sessions were provided. The frequency was two sessions a week and each session took 30 – 45 minutes. The patient saw the whole session data records on the screen that provided him with feedback on his own capabilities of effecting the measured results by, e.g. breathing control. This was so important to him that with time he believed he’s able to control what’s happening to him.
Exposure _in vivo_ was planned as a three sessions of participation of the patient in shooting training with live ammunition. During the first session the patient was supposed to be an observer of the shooting. Despite a mental preparation of the patient by means of the VR sessions, on the day of the trip to the shooting range he was experiencing a big anxiety. Having returned to the clinic the patient went to bed and slept nearly all afternoon. In the evening he was complaining about pain of his legs muscles, buttocks and back similar to those experienced after an extensive physical effort. During the second in-vivo exposure session the patient was supposed to participate passively in all activities with shooting training but without firing on his own. At that time the patient experienced the same feelings like during the first exercise; however, he figured out himself that these symptoms abated already during the exercise and the afternoon sleepiness was smaller alike the muscle pain.

During the third session the patient was to participate fully in the firing. With, as he described himself, full mobilisation and full control of his own fear, he did the firing but none of his 20 shots hit the target. However, he was glad about his achievement. After this session he asked about participation in one more exercise like that. Another trip to the shooting range turned out to be a complete success. The patient, without any fear, performed all the steps and fired 20 shots hitting all the targets.

After a discharge from the Clinic, he continued service as a driver in a logistic unit. He got married and became a father. After approx. 7 months of feeling well, he became “more nervous”. Problems with sleeping and twitches occurred again. The occurrences of these symptoms were preceded by: a traffic accident in which he participated as a passenger of a military vehicle, detection of cancer in his mother and a sudden death of his father. A spontaneous return to the Clinic in an early phase of the disorder recurrence and initiation of the treatment gave positive results. After less than 20 days the patient was discharged in a significantly better condition. This example demonstrates positive effects of psychoeducation. The ability to self-diagnose prodromal stress disorder symptoms allows for an early initiation of the treatment that prevents development of full-blown PTSD.

1. The presented case study of treatment of a full-symptom PTSD syndrome of significant intensity in an Iraqi mission veteran has shown effectiveness of the therapy using VR in combination with _in vivo_ desensitization training.
2. The method of combining the VR and in-vivo in PTSD therapy seems especially efficient in cases resistant to other forms of psychotherapy and medication.
3. For young people experiencing severe PTSD symptoms for whom no satisfactorily effects of treatment by means of classical methods have been achieved and who are afraid of VR therapy it is justified to motivate them for this method of treatment within a directive approach.

### 2. Stress Inoculation Training

Virtual Reality can be easily used both in prevention and therapy of mental disorders. The review of literature shows that one of the effective forms of prevention is Stress Inoculation Training (SIT) – a flexible, individually tailored, multifaceted form of cognitive-behavioral therapy. It is aimed at reduction of tension and preparation of the participants for coping with difficult situations by a gradual and controlled exposure to an anxiety-triggering stimulus. SIT can be enhanced by VR as it makes the training more enjoyable and interesting especially for young people that are used to computer games,
internet and virtual worlds so such stimuli as virtual scenarios are engaging for them. VR is also realistic and immersive so the training is effective. Moreover it can be easily fitted to one’s characteristic which is important when gaining stress resistance. Another advantage of adding VR to standard SIT is the fact that real time assessment of physiological parameters allows to precisely evaluate the level of stress and anxiety during training exercises. [4-7]

Taking this into account we decided to use VR computer assisted SIT for Polish soldiers preparing for their mission in Afghanistan as a form of prevention. More details on this topic and the description of the experiment can be found in other articles [8,9,10].

This form of training was effective in the short-term reduction of anxiety levels, however taking into account all results obtained it cannot be declared that it was effective in the long-term. We observed a decrease in anxiety level independent of SIT. Taking this into account there is a need for further studies. [11]

3. Other Applications of VR Technology in Clinical Practice of DP&CS

3.1. Assessment of suitability of exposure to VR battlefield stressors in diagnostics of somatisation disorder

44-year old career soldier, a veteran of six deployments outside of Poland. During his latest deployment to Afghanistan he developed some lesions on his hands and feet in the form of skin cracks and exfoliation. Having returned to Poland he was hospitalised twice in the Department of Dermatology. The diagnosis revealed contact dermatitis. The applied symptomatic treatment resulted in only temporary improvement followed by a recurrence of the symptoms. After a psychiatric consultation a possibility of a psychogenic basis of the lesions was identified. The patient was admitted to the DP&CS, where the examination shown a comorbidity of PTSD symptoms and the lesions. In order to verify the effect of stressors on worsening of the lesions the patient underwent a VR experiment.

The patient was entered into the VR Battlefield Fallujah scenario. After approx. 30 seconds hyperventilation was observed in the patient. After 1 minute he began scratching his feet intensively. After one more minute he began scratching his hands, neck and ears, then he took the goggle off and finished the experiment in the 3rd minute. Because of his high arousal level the patient was relaxed. He did not need any pharmacologic intervention. The exposure to VR stressors was administered again after 2 days. During this second exposure the patient withstood the whole planned session (10 min.) and he did not stop the experiment. During intensification of the stressors the patient began feeling itching of his hands and feet. After completion of the test his physiological parameters were at a standard level; the only deviation was increased dermatographism that remained for 2 hours. Patient was discharged on day 53 of treatment with diagnosis of somatisation disorders in the course of PTSD. [12]

3.2. Effect of in vitro and in vivo exposure to combat stressors on PET brain image

The goal of the project was examination of combat stress effect on both the central and peripheral nervous system. Fifteen soldiers qualified for deployment within the PMC ISAF Afghanistan underwent twice a PET examination. The examination covered
brain structures, thyroid and adrenals. The second examination was preceded by a VR simulation, using combat operations scenario in Iraq and Afghanistan. During the whole VR exposure parameters of the vegetative system arousal were measured. The PET examination showed the presence of active brown adipose tissue in six soldiers. During exposure to VR stressors and increase of the body temperature, recorded by means of a transducer placed on a finger occurred in these soldiers. In the nine remaining cases where no brown adipose tissue presence was observed, the exposure to VR stressors gave the typical reaction of temperature drop as measured with the finger-mounted transducer. Our examination indicates that the presence of brown adipose tissue in organism changes the response to stressors. Is it therefore a factor predisposing to occurrence of PTSD? Or just the opposite – does the presence of brown adipose tissue either prevent the occurrence of PTSD or soothe their course? Control psychological and neuroimaging examinations are scheduled after return of the soldiers from deployment. [13]

3.3. VR stimulation influence on PET brain imaging

We have examined a group of 24 soldiers, who were qualified for deployment within the 10th rotation of PMC ISAF in Afghanistan. Five of them (21%) disagreed to participate in the research. The other nineteen (79%) were hospitalized in the DP&CS for 48 hours. On the first day 14 of them (74%) underwent a basal PET examination. Next day, using VR equipment, we conducted a study consisting of three parts. First, for 10 minutes, we measured basic parameters of life: the heart rate (HR), blood pressure (BP), skin conduction (SC), peripheral temperature (PT) on the index finger and tidal volume. Then for 5-10 minutes we introduced a soldier into the VR environment using the Battlefield Falujah scenario. During this stimulation we also measured the life parameters. We noticed that all 14 soldiers (100%) experienced autonomic arousal manifested by an increase in the HR, average of 3%, BP: systolic average of 8%, diastolic average of 7.5%, and SC average of 90 %. Then for 5 minutes they were recovering using diaphragm breathing techniques. After stimulation we conducted another PET examination. We noticed that PET results were correct. No memory traces in the subjects’ central nervous system were observed. As a result of our research we are not convinced that using the VR environment as a stress inoculation makes any sense. As we proved 10 minutes VR stimulation does not leave any memory traces in human’s brain that can be measured using PET. It shows that we have to focus on improving the stimulation techniques and find out how intensity and frequency of stressors affects the formation of memory traces in the central nervous system. [14]

4. Presentations of the DP&CS Experiences in VR Therapy and SIT at Scientific Conferences and Publications

Introduction of the VR therapy that so far had not been used in Polish psychiatry was met with the medical community’s curiosity. We have presented our still modest experience in this area alone or together with the VRMC at both domestic [15-17] and international scientific conferences [18-19] but also in various publications [20-23]. The DP&CS VR-enhanced PTSD therapy was reported by major media outlets [24].

Our clinic, in cooperation with by the Military Institute of Medicine and the Polish Scientific Publishing House, has contributed to publishing a Polish translation of the
5. Conclusions

An improvement and recession of PTSD symptoms have been observed in patients who had completed the VR therapy. However, the therapeutical success should be attributed to a comprehensive therapy applied to the patients which takes into account the multi-dimensional structure of trauma. VR should be used together with other methods (the behavioural, therapy, individual and group psychotherapy). VR has turned out to be an effective treatment tool. However, in order to make this therapy successful some additional conditions such as therapeutical relationship with patient, therapist’s belief in the therapeutical usefulness of VR, treatment time fitted to the aim of therapy and proper technical conditions for VR therapy should be met. It is also important to take patient’s motivation to treatment into account before starting any kind of therapy.

As it is a case in therapy, VR should be also treated as an adjunct to Stress Inoculation Training. The equivocal results of the experiment show that there is a need for further studies and deeper analysis to find out why the training was an effective method only in the short term. Basing on our experience, we can say that for successful training there should be a careful selection of participants and prior to training evaluation of their predispositions. Equally important is their positive attitude toward SIT as they should be ready to train their new skills on their own and only periodically meet with their trainer in a control meeting.

The weak point of the VR therapy is, on one hand, an insufficient fidelity of software available in Poland. Often the setting is poor in details and what is missing are additional stimuli, e.g. olfactory ones. Traumatic memories may be triggered by various factors. On the other hand a low awareness and acceptance of psychotherapy in the military community may be also an anti-therapeutical factor for combat stress.

To sum it up, the 5-year partnership between the DP&CS and the VRMC has turned out to be very fruitful. It has brought us closer to the mainstream of research on traumatic stress and opened prospects of scientific development.

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VR Stress Inoculation Training Results for Polish ISAF Soldiers – A Study of 4 Cases

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Abstract. The aim of this study was to evaluate the results of VR Stress Inoculation Training (SIT) for 4 soldiers preparing for their first mission in Afghanistan (ISAF) and to assess if their temperamental structure was related to successful training.

Method. For 5 days, 4 soldiers took part in 10 SIT sessions, in accordance with the Virtual Reality Medical Center, San Diego methodology (Training of Physiological Control Exposure to Virtual Stressor while Maintaining Physiological Control). The initial and final arousal/relaxation in response to VR exposition were assessed using Heart Rate Variability: Very Low Frequency (VLF) and Low Frequency (LF) Ratio as an indicator of relaxation/arousal. The temperament traits and structure were assessed using the Formal Characteristics of Behavior – Temperament Inventory (FCB-TI).

Results. The analysis of VLF and LF Ratio graphs showed that 3 soldiers succeeded in reducing their arousal during final session. Two of them achieved better results in relaxation during final exposition, when compared to the initial session. Three of them could effectively reduce the arousal after the exposition as the effect of training. We found their temperament structure more harmonized than the soldier’s who has achieved weaker results in training.

Conclusions. Due to the preliminary nature of our findings, replication is necessary on a larger group.

Keywords. Stress Inoculation Training (SIT), temperamental structure, military psychiatry, ISAF Afghanistan

Introduction

Serving in conditions featuring a combat exposure may lead to stress-related disorders [1, 2]. One of the methods of mitigating the risk of occurrence of these disorders is Stress Inoculation Training (SIT) [3].

It has been found out that cognitive-behavioural techniques combined with VR exposure (Virtual Reality Exposure Therapy), that are effective in PTSD treatment, can be also applied for SIT to improve better performance in stressful situations and...
prevent consequences of exposure to stress. [4 - 11]. A review of the existing research in application of Virtual Reality Stress Inoculation Training (VR SIT) shows usefulness of this approach [12 - 14].

The study described is a part of the Stress Inoculation Training in the Polish ISAF Soldiers project being implemented by authors of this paper and presented in a more detailed way in other publications [15, 16].

This study had the following goals:

- Assessment of VR SIT effectiveness in soldiers preparing for deployment within the Polish Military Contingent in Afghanistan.
- Checking whether there is a dependency between temperament structure in the participants and the training results.

The VR SIT method applied has been developed by Virtual Reality Medical Center (San Diego) [6]. It is designed to improve an ability to reduce arousal in a combat stress situation. Physiological parameters allow for checking effectiveness of arousal reduction.

It was demonstrated that temperament traits affect an individual’s resistance to stress, i.e. they determine efficiency of actions and a magnitude of emotional consequences in situations of a specific stimulating value. Depending on temperament people develop various patterns of behaviour [17, 18]. Because of this we wanted to check whether there may be a relationship between temperament structure and effective use of the VR SIT method by the participants.

1. Material and Method

1.1. Participants

Four soldiers qualified for a deployment within the Polish Military Contingent to Afghanistan (the 8th rotation) were participating in the experiment. They came forward voluntarily from among 60-strong group of soldiers participating in the preparatory training.

The participants were male of a similar age (27, 28, 28 and 30 years), with secondary education (2 persons) and vocational education (2 persons). All they were in the rank of private, in contractual service and they were in service from 3 to 7 years. Two of them were married and had children while two others were childless bachelors. None of them had been previously deployed outside of Poland.

1.2. Procedure

All participants of SIT, having agreed for participation, were informed about conditions and goal of the training. Having filled a personal data questionnaire and the one for measurement of temperament traits and structure (the Formal Characteristics of Behavior - Temperament Inventory, FCB-TI) the participants took part in VR SIT while their physiological indicators were monitored.

The Behavioral Avoidance Test (BAT), consisting in measurement of physiological parameters: Heart Rate Variability, Respiration, Finger Temperature and Skin Conductance/Resistance, was conducted both in the beginning and in the end of the training. Both the initial and the final measurement were performed during 5-minute „baseline” and „recovery” sessions, separated by a 3-minute VR session exposing to stimuli related to participation in a military convoy.
The Heart Rate Variability: Very Low Frequency (VLF) and Low Frequency (LF) were used to compare changes of arousal state in the participants. A drop in arousal was found out when LF value exceeded that of VLF.

Obtained values of physiological indicators were analysed in relation to temperament traits that depend on inborn neurobiological mechanisms. Also the STAI Inventory, Coping Inventory for Stressful Situations (CISS), Revised NEO Personality Inventory (NEO-PI-R) questionnaires that measure anxiety level, stress-coping styles and personality traits were used in the research. This analysis was focused on temperament structure that undergoes changes in time to the slightest extent and plays an important role in adaptation of an individual to requirements of the environment.

1.3. Equipment

Three portable computers with software supporting virtual reality, allowing for simultaneous monitoring of physiological indicators, were used for the training. The following programmes were used: Afghan Kabul, Iraq Convoy, Main PTSD, Convoy PTSD, Enchanted Forest. They were made available by the Virtual Reality Medical Center, San Diego.

The first computer, via goggles and headset, was enabling an exposure in virtual environment where the participant was moving by means of a joystick.

Another computer was used by the trainer to control VR exposure parameters.

Third computer, through connected sensors, was monitoring physiological parameters (respiration, heart rate, skin conductance, finger temperature) and was controlling a feedback system.

1.4. The Formal Characteristics of Behavior - Temperament Inventory (FCB-TI)

The FCB-TI questionnaire used for diagnosing the basic primarily biologically determined dimensions of personality called temperament [19, 20] was used in the study. Temperament traits occur at two levels.

The first is the energetic level of behaviour, i.e. mechanisms that are responsible for energy gathering and relief. Energetic traits of temperament are examined by means of the FCB-TI to [19]:

- Emotional Reactivity (ER) – a tendency to react intensively to stimuli expressed in a high emotional sensitivity and low resilience.
- Endurance (EN) – ability to react adequately to strong stimulation and ability to manage in situations of a long-lasting activity.
- Activity (AC) – a tendency to undertake a strongly stimulating behaviour or to seek an external stimulation.
- Sensory Sensitivity (SS) – an ability to react to weak sensory stimuli.

The next level are temporal characteristics of behaviour that determine the course of reaction in time [19]. They are:

- Briskness (BR) – a tendency to react quickly, to maintain a high tempo of actions and changing the behaviour easily in response to a change in conditions of the surroundings.
- Perseverance (PE) – a tendency to continue and to repeat the reaction after the cessation of original stimulus that triggered it.
What is important for functioning of an individual is not only the level of particular traits but their balancing. Control effectiveness is connected with equilibrium between stimulation input and its relief. In addition to this there should be also a balance between possibility of stimulation processing and looking for or avoiding it. Depending on a balance of temperament traits a temperament structure can be classified as harmonised or non-harmonised.

In order to determine a balance of temperament traits in the soldiers-participants relationships between the crucial energetic and temporal traits were checked: Activity and Endurance, Activity and Emotional Reactivity, and between Briskness and Perseverance.

1.5. Training

The training we used consisted of 10 sessions, two sessions a day, one in the morning and another in the afternoon. Each session was run by a psychologist-trainer who was working directly with the participant, and a psychologist-assistant who monitored recording measurement of physiological indicators.

The first session included measurement and recording of BAT profile. The initial measurement of the baseline physiological indicators lasted for 5 minutes and took place before the exposition. Next the parameters were measured during exposition in the VR programme (3 minutes). The last measurement - relax after exposition (recovery) took 5 minutes after the exposition.

Having created the BAT profile the participants were undergoing training in diaphragmatic respiration using a physiological feedback and elements of education. In the end the participants were encouraged to train diaphragmatic respiration between sessions of the training. Session two included training in arousal reduction in conditions of an imaginary exposure to stress, with physiological feedback. Session three again consisted of the following sequences: baseline – VR exposure – recovery. An animated environment without combat stimuli was used for the exposure. The next six training sessions (from 4th to 9th) were also conducted according to the baseline - VR exposure - recovery pattern. In the next sessions programmes for exposure to a combat environment were used, with a growing possibility of exposure to stress; during these sessions the participants were learning how to reduce their arousal.

A comparative record of the BAT profile was created during the last session, in the same form as during the first session. Also effects of the training were summed up. During each session the participants were assessing the subjective stress level (from 0 to 100) by means of the Subjective Units of Distress Scale (SUDS) for baseline, exposure and recovery.

2. Results

2.1. LF and VLF Indicators

Values of the LF and VLF from the first and the last sessions were compared in order to assess both the initial and final arousal status in the participants.

Graphs of the Participant 1’s results show a significant reduction of the arousal in the final baseline and recovery comparing to session 1 (value of the LF indicator exceed that of the VLF one). No improvement was found out in the final exposure comparing it to the initial one. However, a surprising fact of a reduction of arousal in
the exposure within the initial session. A comparison of the graphs is shown in Figure 1.

Graphs of the Participant 2’s results show a reduction of the arousal in all three parts of the final session comparing to the initial one. A drop in arousal is visible in the baseline, exposure and recovery. Figure 2 shows a comparison of the graphs.

Graphs of the Participant 3’s results present a significant reduction in arousal in the final session only within the baseline, i.e. prior to exposure to stressors. In the other sessions the participant was not able to relax. Despite that it can be noted that the arousal in the final recovery is lower than the recovery within the first session. A comparison of the graphs is shown in Figure 3.

Graphs of the Participant 4’s results show a significant reduction of the arousal in the baseline, exposure and recovery of the final session comparing to the initial session that brings about a conclusion on an improvement of skills in terms of arousal reduction. The graphs are compared in Figure 4.

A comparison of the indicator values from the first and the last session allows for finding out a clear improvement in the arousal reduction skills in three out of four participants (Participants 1, 2 and 4).

2.2. Subjective Stress Assessment

The SUDS analysis in the 0-100 scale, conducted by the participants, indicates their large difficulties in an adequate assessment of the arousal state. Both in the beginning and during the training the participants assessed stress intensity inconsistently with values of their physiological parameters.

Within the last session, during the exposure, Participant 2 and Participant 4 assessed they were aroused while the measurement of their physiological parameters indicated a relaxation state. Participant 2 assessed SUDS as 40 and Participant 4 as 50. Similarly, Participant 1 and Participant 3 assessed that they were completely or almost completely relaxed in moments when arousal occurred. Participant 1 assessed SUDS as 0 and Participant 3 as 5. In the same time the participants who overestimated their arousal (Participant 2 and Participant 4) were able to relax in a more effective way.

2.3. Temperament Structure

Results of examination by means of the FCB-TI questionnaire indicate a differentiation of temperamental structures in the participants. The individual results were interpreted by comparing the results of the scales that measure both energetic and temporal temperament dimensions (AC - EN, AC - ER, BR - PE), re-coding the PE and ER scales and assuming the confidence level of 95% (stanines difference result +/- 3 stanines). Table 1 presents the results for individual scales, after re-coding of PE and RE.

<table>
<thead>
<tr>
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<th>Emotional Reactivity</th>
<th>Endurance</th>
<th>Activity</th>
<th>Sensory Sensitivity</th>
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<td>Participant 1</td>
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<td>Participant 2</td>
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<td>4</td>
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<tr>
<td>Participant 3</td>
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<tr>
<td>Participant 4</td>
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</table>
Figure 1. Comparison of the graphs from sessions 1 and 10 for Participant 1.
Gray line – LF; black line – VLF; dotted line – HR.
Figure 2. Comparison of the graphs from sessions 1 and 10 for Participant 2.
Gray line – LF; black line – VLF; dotted line – HR.
Figure 3. Comparison of the graphs from sessions 1 and 10 for Participant 3.  
Gray line – LF; black line – VLF; dotted line – HR.
Figure 4. Comparison of the graphs from sessions 1 and 10 for Participant 4. Gray line – LF; black line – VLF; dotted line – HR.
In terms of energetic behaviour traits in Participant 1, the result in the Emotional Reactivity and the result in the Activity scale are balanced. The value obtained in the Endurance scale is close to the result in the Activity scale and thus it may be concluded that the level of stimulation seeking is harmonised with stimulation processing. At the level of the temporal behaviour patterns, the results in the Briskness and Perseverance scales are balanced. The arrangement of the Participant 1’s temperament traits is closest to a harmonized structure featuring large stimulation processing capabilities.

In case of Participant 2, the results for energetic properties indicate balancing of Endurance and Activity as well as Emotional Reactivity and Activity. At the level of temporal temperament traits Perseverance and Briskness are balanced.

In Participant 3, in terms of energetic characteristics, Reactivity and Activity are balanced. However, there is no balancing of Activity and Endurance because abilities of this participant in terms of stimulation processing are larger than the level of stimulation seeking. At the level of the temporal behaviour patterns, the results in the Briskness and Perseverance scales are balanced.

Participant 4 features the most balanced temperament structure. Both his energetic and temporal temperament traits are balanced. The results show a set of traits that indicates a harmonised structure showing large stimulation processing capabilities.

Analysis of the results obtained by means of the FCB-TI questionnaire leads to a conclusion that the temperament structure of Participants 1, 2 and 4 is more balanced than that of Participant 3.

In addition to this it was observed that Participants 1, 2 and 4 had achieved high results in the Sensory Sensitivity scale.

2.4. Balancing of Temperament Traits and Training Effectiveness

Basing on an analysis of the LF and VLF indicators’ graphs an improvement of results in terms of arousal reduction in Participant 1, 2 and 4 was observed. It was also observed that temperament traits of these participants were more balanced than in Participant 3 who achieved the worst results in arousal reducing. Participants who achieved better training results feature also a high level of Sensory Sensitivity.

Discussion

The VR SIT method turned out to be effective in gaining the arousal reducing skills in the participants-soldiers. Three out of four of them were achieving definitely better results in the last session comparing with the beginning of the training.

Basing on the data collected it was found out that the participants featuring a more balanced temperament structure had achieved better training results. Therefore it may be preliminarily concluded that the temperamental background may facilitate gaining arousal reducing skills by the VR SIT training.

The occurrence of high results in the Sensory Sensitivity scale in participants who learnt how to reduce their arousal in a more effective manner is an interesting fact. Results of research on temperament indicate that this trait may have another adaptive meaning than the other temperament characteristics. It is classified as a trait from the interface of temperament and abilities and it may have a different physiological background than the other traits [18, 21]. This trait is specified as an indicator of
organism’s effectiveness in the area of stimulation and the nervous system arousal state control that seems to be consistent with the results achieved by the participants.

According to the study results [8, 14] learning of new skills in a situation where a stressor occurred resulted in better coping with application of these skills in a new environment. The study results presented allow for supposing that also learning of arousal reducing skills in the VR SIT situation, when the participants were exposed to stressors, will allow them for a better stress control during military operations.

However, the results obtained require verification by examination deferred in time (check of training effectiveness both in a real stress situation and afterwards). Because of a preliminary nature of the examination and the small number of participants there is a need to conduct the examination on a larger group.

References


The Influence of Pre-Deployment VR Computer-Assisted Stress Inoculation Training on the Anxiety Level in the Polish ISAF Soldiers

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Abstract. The aim of this study was to evaluate the influence of Stress Inoculation Training (SIT) on the anxiety level measured by State-Trait Anxiety Inventory (STAI) both as temporary/emotional state anxiety (X1) and stable personality trait anxiety (X2) in soldiers preparing for their mission in Afghanistan (ISAF).

Method. 118 soldiers were randomly selected from the contingent that consisted of 1500 soldiers and split into two, equinumerable groups - experimental (E) and control (C). Both groups listened to a lecture on the nature of stress, its symptoms and coping with stress. They also filled in the following inventories: STAI, PCL-M, BDI-2, CISS, NEO-PI-R, FCB-TI and TAS. Soldiers from the E group - split into four subgroups - took part during the next 5 days in 10 SIT sessions according to the methodology of Virtual Reality Medical Centre, San Diego. At the same time soldiers from the C group did not take part in SIT and continued with their scheduled training in their military area. After completing the SIT both groups filled in STAI. After the end of their deployment in Afghanistan the soldiers filled in STAI, PCL-M and took part in a structured interview.

Results. The statistical analysis of STAI results shows that: 1) Before SIT, there were no statistically significant differences in STAI and other tests results in both E and C groups. 2) After SIT, both X1 and X2 values in E group were significantly lower (p=0.04). 3) In the C group which did not take part in SIT, there were no statistically significant differences in X1 value after 5 days; however, there was a statistically significant decrease in X2 value (p=0.01). 4) After deployment, both X1 and X2 values in the E and C group were significantly lower than before SIT (p<0.05) 5) After deployment, X2 values in the E and C group were significantly lower comparing to values measured after SIT (p<0.01) 6) There were no statistically significant differences in X1 values after deployment compared to values measured before SIT in the E and C group 7) There were no statistically significant differences in X1 and X2 values between the E and C group before, after the experiment and after deployment.

Conclusions. Given the equivocal results of the experiment there is a need for a further study or a deeper analysis.

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Introduction

Since 2003 r., approximately 35,000 soldiers and civilian employees of Polish Armed Forces have participated in Operation Iraq Freedom and Operation Enduring Freedom (Afghanistan); some of them had several tours of duty. Fifty-nine soldiers lost their lives in these operations and approximately 400 were wounded including some 200 in combat actions. Because of stress-related mental disorders approximately 50 soldiers were sent back to Poland before the scheduled end of their deployment; that represents 0.014 % of manpower. However, it is estimated that symptoms of post-traumatic stress disorder occur in some 5-10% of veterans of Polish Military Contingents (PMCs). Because of that approximately 300 veterans have been hospitalised in psychiatric wards including roughly every tenth of them several times.

All Polish soldiers undergo routine medical and psychological examinations prior to their deployment. Prior to depart for deployment they also attend lectures and practical exercises to learn how to cope with war stress. Psychologists provide this training for the military units that form the contingent. In addition to this, psychologists and psychiatrists of the Department of Psychiatry and Combat Stress (DP&CS) of the Military Institute of Medicine (MIOM), in Warsaw, participate in the last phase of preparations for deployment.

Trying to adjust the forms of pre-deployment training to the needs of soldiers during deployment, Stress Inoculation Training (SIT) was experimentally incorporated into the preparatory programme, which was conducted by experts from the DP&CS. This incorporation was inspired by publications showing effectiveness of this method of developing skills in coping with war stressors [2-3]. The VR Computer-Assisted SIT methodology, developed by the Virtual Reality Medical Center San Diego (VRMC), Virtual Reality Medical Center, San Diego (Training of Physiological Control and Exposure to Virtual Stressor while Maintaining Physiological Control) was used (MIOM signed an agreement on a long-term scientific partnership with the VRMC in 2008). The project was executed in autumn of 2010 in the Polish 10th Armoured Cavalry Brigade based in Swietoszow that provided approximately 2,000 soldiers to the approximately 2,600-strong International Security Assistance Force (ISAF) deployed to Afghanistan in the period of October, 2010 – April, 2011.

As equipment allowing for individual SIT training was available, in agreement with the authors of the methodology a modification was applied enabling participation of an additional group of 14 soldiers in the training sessions. By means of multi-media projection they were exposed to the same virtual stressors from Iraq and Afghanistan to which the soldier being trained was actively exposed and they were observing visualisation of his physiological reactions. Together with him they were performing instructions on breathing control and relaxation, given by the psychologist who was conducting the training.

The experiment was designed to obtain answers to the following questions:
1. What was the level of anxiety in participants of SIT before the training?
2. What changes in anxiety level occurred in participants of the training immediately after completion of SIT?
3. What was the anxiety level in veterans of ISAF’s PMC 19 months after SIT and 12 months after return to Poland?
4. What was the veterans’ opinion on the usefulness of SIT during deployment?

The effects of the experiment were assessed using a statistical analysis of anxiety level measurements of SIT participants and soldiers of the control group who did not participate in the training, as well as being based on interviews conducted with the individuals.

1. Material and Method

1.1. Participants

118 soldiers were selected randomly from the 1500-strong contingent that took part in the research. The age of the participant ranged from 21 to 44 years. There were 112 males and 6 females who had been in service from 8 months to 19 years and 3 months. Ninety-five soldiers have not been deployed before to missions outside of Poland, 16 had been deployed once, 5 twice and one female soldier had been deployed three times. The soldiers were split into two equinumerable groups: experimental (E) and control group (C).

After their return to Poland, 19 months after the training and one year after completion of the deployment, the soldiers were examined again. The examination covered 84 persons – 80 males and 4 females, 23 to 46 year old, 45 from the experimental group and 39 from the control group.

All participants passed a deployment-qualification examination by the Military Medical Commission.

1.2. Procedure

First, the soldiers from both the experimental and control group listened to a 90-minute lecture on stress symptoms and way of coping with stress (Introduction to Operational Stress Control). Having listened to the lecture, both groups filled in test forms of the State-Trait Anxiety Inventory - STAI, PTSD Checklist - Military Version, PCL-M, Beck Depression Inventory - BDI-2, Coping Inventory for Stressful Situations - CISS, Formal Characteristics of Behavior-Temperament Inventory - FCB-TI, NEO-Personality Inventory-Revised - NEO-PI-R and Tellegen Absorption Scale - TAS. Additionally the members of the experimental group filled in the Immersive Tendencies Questionnaire - ITQ. Soldiers from the experimental group, divided into 15-strong subgroups were participating for five successive days in 10 SIT sessions according to the methodology of the Virtual Reality Medical Center of San Diego (Training of Physiological Control and Exposure to Virtual Stressor while Maintaining Physiological Control). In each of the experimental subgroups, one person was actively participating in the training, i.e. the active participant’s physiological indicators were monitored and he/she was able to affect the virtual reality while the others were observing the actions of the participant that were being projected by a beamer. Whilst the experimental group was participating in the training, soldiers from the control group were attending routine training activities in the barracks area. On the last day of the experiment, the E and C groups filled in the STAI test form and the experimental group also filled in the Immersion Scale (IS), the Simulator Sickness Questionnaire (SSQ) and the Presence Questionnaire Revised (PQR). After completion of the
deployment to Afghanistan and return to Poland – 19 months after the stress inoculation training – the soldiers underwent the questionnaire tests again, filling in the STAI and PCL-M forms, and responding to questions of a standardised interview.

All participants were given information on goals of the examination.

1.3. Training

The stress inoculation training, underwent by the participants, was a training in which the trainees were acquiring skills by gradual use of virtual reality. This reality allowed for simultaneous immersion in the stress experience and controlled by the increasing of the number of threatening stimuli. The soldiers participated in 10 sessions, two sessions a day (in the morning and in the afternoon) for 5 days in a row. Each session had its structure and a specified course.

During the first session, the Behavioural-Avoidance Test (BAT) was conducted by writing a profile of a single selected person. The first measurement of the baseline physiological indicators, conducted prior to the exposure, took 5 minutes. Next, the physiological indicators were measured during their exposure within the Iraq Convoy programme for the next 3 minutes. During the first exposure, the subject was staying in the virtual reality in a vehicle and could only look around. Other participants were observing his actions on the beamer’s screen. The last measurement of that session concerned a recovery after exposure and lasted for 5 minutes. The BAT profile created was discussed in detail with all participants of the training (the results were displayed on the beamer’s screen); explanations of the meaning of the obtained data were also explained and presented. At the end of the session, all participants underwent deep breathing training and the active participant also obtained precise measurements of his physiological indicators during the training. Also at the end of the sessions, the participants were encouraged to train in deep breathing between the sessions. They were given a CD with recorded instructions for personal training to facilitate that task.

The second session was focused on the training of tension reduction during imagination exposure to stress. The active participant also obtained feedback on his physiological parameters. Other participants could observe these indicators on the beamer’s screen. This session also covered psychoeducation concerning control of thoughts and emotions.

The third session was similar to the first one. First, the initial baseline measurement was conducted and then virtual reality exposure was applied, using the Enchanted Forest software (scenario without military stimuli), in which the active participant could move while the other participants were observing his actions on the beamer’s screen. The exposure time was 20 minutes.

The next six sessions had a similar structure, i.e. baseline measurement – VR exposure – recovery, and the only variable was use of military-type scenarios featuring an increasing intensity of stressors.

The last session was designed for re-measurement of the BAT profile and discussion on the entire training.

During all session the active participant was asked about his subjectively felt stress level in a scale from 1 to 100.
1.4. Equipment

Three computers, software enabling audio-video presentation and sensors allowing for measurement of physiological parameters were used for the training.

The first computer provided a virtual reality exposure via VR goggles, headset and a joystick, allowing the participant for moving and performing actions in the virtual world.

Another computer was used for supporting the software for monitoring of physiological parameters and the feedback system. Devices for measurement of physiological indicators: breathing, heart rate, skin conductivity and finger temperature were connected to that computer.

Both computers were connected with a projector allowing the other participants to watch both the virtual reality and variations in physiological parameters of the active participant. Sounds were reproduced in parallel through the headset for the active participant and through loudspeakers for the other participants of the training.

By means of the third computer, the trainer was operating the control panel and menu that provided a possibility of introducing visual and audio stimuli to the active participant.

The active participant was seated on a rotary chair enabling for movements reflected in the virtual reality. By means of the joystick he was able to control his figure in the virtual environment by selecting both direction of movement and turning in the vehicle or shooting, depending on scenario selected.

The hardware used in the tests consisted of two Dell Inspiron M1710 computers with Intel Core 2CPV 2GHz processors, 2G RAM and the nVIDIA GeForce Go 7900 GS graphic card (supporting the VR images and sounds). The Dell Inspiron MXC 061 computer with the Intel Core 2CPV 1.99 GHz processor and 2G RAM was used for measurement of physiological parameters. The following software was used to support the virtual reality: Afghan Kabul, Iraq Convoy, Main PTSD, Convoy PTSD and Enchanted Forest. This software was made available by the Virtual Reality Medical Center from San Diego.

1.5. State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory, STAI was used in the research. This is a tool designed for examination of anxiety understood as a transitional and situation-dependent state of an individual and anxiety understood as a relatively permanent personality feature. STAI has two subscales. The first subscale (X-1) is used for the measuring of the state anxiety while the other scale (X-2) – is for the trait anxiety.

Anxiety as a trait is defined as a permanent, acquired behavioural characteristics that makes a given person perceive objectively harmless situation as harmful ones and responds to them with an increase of agitation and a state of anxiety that is incommensurable to the objective situation. Individuals of a high level of trait anxiety—comparing to those of a low level of this feature not necessarily will respond permanently with a high level of anxiety; they would rather respond with anxiety in threatening situations. The relation between the level of state anxiety and that of trait anxiety depends on characteristics of the threat and it is lower in a physical threat situation.

On the other hand the state anxiety is a subjective feeling of tension and fear that results in activation or arousal of the nervous system [4].
2. Results

A statistical analysis was conducted in order to find out whether the training sessions have a statistically significant effect on the variables: the state and trait in STAI questionnaire examination.

The analysis started with a comparison of the experimental group and the control group before the training, after completion of the training and after the return from deployment. The results are presented in Table 1.

<table>
<thead>
<tr>
<th>STAI Results</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Z</th>
<th>U</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-State</td>
<td>3215</td>
<td>2890</td>
<td>0.31</td>
<td>1459</td>
<td>0.76</td>
</tr>
<tr>
<td>Anxiety-Trait</td>
<td>3361.5</td>
<td>3193.5</td>
<td>0.47</td>
<td>1540</td>
<td>0.64</td>
</tr>
<tr>
<td>After Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-State</td>
<td>2717.5</td>
<td>2742.5</td>
<td>-0.08</td>
<td>1339.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Anxiety-Trait</td>
<td>2802.5</td>
<td>2553.5</td>
<td>1.33</td>
<td>1122.5</td>
<td>0.18</td>
</tr>
<tr>
<td>After Return from Deployment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-State</td>
<td>1881</td>
<td>1689</td>
<td>-0.28</td>
<td>846</td>
<td>0.78</td>
</tr>
<tr>
<td>Anxiety-Trait</td>
<td>2026</td>
<td>1544</td>
<td>1.01</td>
<td>764</td>
<td>0.31</td>
</tr>
</tbody>
</table>

In terms of the state and trait, there were no statistically significant differences between both groups before the training that show that the participants selected for the control group represented a set suitable for comparisons with the experimental group. At the same time, the results of the statistical analysis allow for assuming that there were no statistically significant differences in the experimental group in relation to the control group for the state and trait variables after completion of the training. This outcome may result from conditions in which the test was conducted (e.g. conditions of service independent of the experiment). Similar to this, no statistically significant differences between the experimental and control group were found after returning to Poland from the deployment; this might result from both the time from the training and time of completion of the deployment.

Additionally, a statistical analysis, using the Wilcoxon matched-pairs-rank test, was conducted to check whether the training provided, had an impact on the experimental group. Statistically significant differences before, and after the training were observed at the significance level \( p = 0.04 \) for the state and trait variables \( (p = 0.04) \). After the training a declining trend was observed for both variables. These results are shown in Table 2.
Table 2. Differences in intensity of anxiety as the state and trait in the experimental group before and after completion of the training.

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety-State</td>
<td>46</td>
<td>352</td>
<td>2.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Before and After Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-Trait</td>
<td>45</td>
<td>336</td>
<td>2.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Before and After Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Another statistical analysis was conducted to check whether the learning and memorising time or process, and effect of “everyday” life had impacted the control group. Again, the Wilcoxon matched-pairs-rank test was used for this purpose (Table 3).

Table 3. Differences in intensity of anxiety as the state and trait in the control group before and after completion of the training.

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety-State</td>
<td>44</td>
<td>361</td>
<td>1.56</td>
<td>0.12</td>
</tr>
<tr>
<td>Before and After Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-Trait</td>
<td>46</td>
<td>303</td>
<td>2.59</td>
<td>0.01</td>
</tr>
<tr>
<td>Before and After Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It was found out that there was no statistically significant difference for the state variable (p=0.12) while there was a statistically significant difference at the significance level p = 0.01 for the trait variable, where a declining trend at the level of 5% was observed.

Additionally, a statistical analysis was conducted to check whether there is a significant difference between the STAI test results prior to deployment (both before and after the training) and the results from after the deployment. Once more the Wilcoxon matched-pairs-rank test was used for this purpose.

The statistical analysis, without splitting into groups, showed that there was a statistically significant difference for all variables of the STAI test. A drop in each variable of the test after return from the deployment is visible. These results are presented in Table 4.
Table 4. Differences in intensity of anxiety as the state and trait before the training, after completion of the training and after return from the deployment (Wilcoxon matched-pairs-rank test).

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety-State Before and After Return from Deployment</td>
<td>73</td>
<td>619</td>
<td>4.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Anxiety-Trait Before and After Return from Deployment</td>
<td>76</td>
<td>43</td>
<td>7.35</td>
<td>0.00</td>
</tr>
<tr>
<td>Anxiety-State after Training and Return from Deployment</td>
<td>67</td>
<td>734.5</td>
<td>2.53</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety-Trait after Training and Return from Deployment</td>
<td>69</td>
<td>162.5</td>
<td>6.25</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Statistically significant differences for individual variables of the test with the corresponding significance levels shown in table 5 were observed in the experimental group. The only exceptions are the results of the STAI anxiety state after the training in relation to anxiety state measured after return from the deployment: no statistically significant differences between the variables were found. A reduction in values of all variables occurred after return from the deployment. Again the Wilcoxon matched-pairs-rank test was used for the analysis (Table 5).

Table 5. Differences in intensity of anxiety as the state and trait in the experimental group before the training, after completion of the training and after return from the deployment (Wilcoxon matched-pairs-rank test).

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety-State before Training and after Return from Deployment</td>
<td>40</td>
<td>205</td>
<td>2.75</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety-Trait before Training and after Return from Deployment</td>
<td>41</td>
<td>0</td>
<td>5.58</td>
<td>0.00</td>
</tr>
</tbody>
</table>
A similar analysis for the control group shows that there are some statistically significant differences for individual variables of the test with corresponding significance levels, shown in the table below. The only exception are results of the STAI anxiety state after the training in relation to anxiety state measured after the return from the deployment: like the experimental group, there is no statistically significant difference. Similarly, the experimental group saw a reduction in values of all variables that occurred after return from the deployment. The results are shown in Table 6.

### Table 6. Differences in intensity of anxiety as the state and trait in the control group before the training, after completion of the training and after return from the deployment (Wilcoxon matched-pairs-rank test).

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety-State before Training and after Return from Deployment</td>
<td>33</td>
<td>118</td>
<td>2.90</td>
<td>0.00</td>
</tr>
<tr>
<td>Anxiety-Trait before Training and after Return from Deployment</td>
<td>35</td>
<td>20</td>
<td>4.83</td>
<td>0.00</td>
</tr>
<tr>
<td>Anxiety-State after Training and after Return from Deployment</td>
<td>29</td>
<td>134.5</td>
<td>1.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Anxiety-Trait after Training and after Return from Deployment</td>
<td>34</td>
<td>53</td>
<td>4.18</td>
<td>0.00</td>
</tr>
</tbody>
</table>

After their return from Afghanistan the SIT participants were asked whether they had been using at the deployment the skills learnt during the training. Every tenth of them responded that he “was controlling the breathing and that it was helpful in difficult
situations.” Also, every tenth person responded “at lower stress levels, the breathing control helped slightly but at higher levels, it was difficult to focus on breathing”. Eight out of ten responded that they had not remembered much from the training and they were using their own, previously learnt, ways of coping with stress.

3. Discussion

Basing on the results obtained, it may be stated that the VR SIT approach was a short-term effective approach to anxiety reduction in the soldiers examined. A gradual, repeatable, controlled exposure to anxiety-triggering stimuli allowed the participants to learn the skills in arousal reduction. During the SIT training sessions, enhanced by virtual reality, the participants were experiencing stressful situations similar to those who they may encounter during a real deployment. The arousal level in the participants after the training was lower than before the training, which confirms the assumed hypothesis that SITS is an effective method of learning about anxiety reducing techniques.

However, based on the results obtained, it cannot be unambiguously declared that the VR SIT method turned out to be long-term effective approach in anxiety reduction in the soldiers examined. Due to the fact that a reduction in anxiety-state value was observed in both groups of soldiers examined after their return from the deployment, a hypothesis can be put forward that this value reduction resulted from other factors than participation in the stress inoculation training e.g. the fact of a safe return home from the deployment.

In addition, the fact that there was an observed drop in the anxiety-trait value level, both in the experimental group and the control group after the training and after return home from the deployment, seem to be puzzling. According to Spielberger’s theoretical assumptions, this is a relatively constant personality feature and as such, it should not change easily. During the same time, research on the Spanish version of the STAI questionnaire had shown that the questionnaire measures negatively affect intensity rather than anxiety-trait [5]. Such a broad understanding allows for putting forward the next hypotheses on an impact and role of psychoeducation in the form of the lecture that was delivered to both the control group and the experimental one which may explain the reduction of the anxiety-trait right after the training. Also, the safe return home from the deployment could be responsible for the reduction in the intensity of negative effects and for reduction of the anxiety-trait level after returning from the deployment. In this case, there is also a question about effect of time that elapsed both from the examination itself and from the return from the deployment as well as the effect of other variables on the results of the experiment.

Comparing the results of the study presented with those of similar studies in which participants of SIT were more frequently confirming usefulness of the learnt skill of anxiety control in combat situations, one should keep in mind the constraints under which the experiment was conducted. Lack of technical possibilities for individual training and a limited training time did not allow for creating the belief of the superiority of the method for coping with stress offered to them over their own techniques.

The conclusions presented above have a nature of hypotheses that need verification in further research.
References


Personality and Stress-Coping Factors in VR Computer-Assisted Stress Inoculation Training of Polish ISAF Soldiers

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Abstract. The main goal of this study was to evaluate the impact of personality, temperament and stress coping factors in Stress Inoculation Training (SIT) in soldiers preparing for their first deployment to Afghanistan (ISAF).

Method. 120 soldiers were randomly selected from the contingent that consisted of 2000 soldiers and split into two groups of 60 people each - the experimental (E) and control (C) ones. Soldiers from the E group - split into subgroups of 15 - took part during the next 5 days in ten SIT sessions according to the methodology of the Virtual Reality Medical Center, San Diego (Training of Physiological Control Exposure to Virtual Stressor while Maintaining Physiological Control). Both groups filled in inventories such as: Coping Inventory for Stressful Situations (CISS), Revised NEO Personality Inventory (NEO PI-R), and The Formal Characteristics of Behaviour – Temperament Inventory (FCB-TI). Both before and after the training they filled in the STAI inventory. Having returned from the deployment the soldiers filled STAI once again as well as the PCL-M inventory.

Results. The statistical analysis results show: 1) Before SIT, in E group there was a negative correlation between X1 value in STAI and briskness, sensory threshold and endurance and positive correlation between X1 value in STAI and emotional reactivity; 2) After SIT In the E group there was a correlation between X1 value in STAI and emotional reactivity; 3) After deployment In the E group there was a correlation between X1 value and emotional reactivity as well as between X2 values and the emotions-based, avoidance style and conscientiousness.

Conclusions. Results could be taken into account when analyzing individual susceptibility to SIT.

Keywords. Stress Inoculation Training (SIT), coping stress, personality, CISS, NEO – PI-R, FCB-TI, military psychiatry, ISAF Afghanistan

Introduction

The goal of the study was an attempt to determine effects of factors related to personality, temperament and a style of coping with stressful situations on
susceptibility to Inoculation Training that was conducted in 2010 among Polish soldiers preparing for deployment to Afghanistan within Rotation 8th. Stress Inoculation Training (SIT) is a type of training used to prepare individuals for stressful situations, to help diminish the potential for negative psychological reactions [1-2]. SIT is intended both to create more effective troops and to help prevent or reduce rates of PTSD in returning troops.

The virtual reality (VR) technique is widely used in this training. VR can enhance the effect of SIT by providing vivid and customizable stimuli. Numerous studies show effectiveness of the SIT VR in terms of preventing post-traumatic stress results [3]. This method, developed by Virtual Reality Medical Center (San Diego), combines an exposure in virtual environment with elements of education and techniques of physiological stress control with simultaneous use of monitoring and physiological feedback. Exposure to stressor is monitored, gradual and repeatable, and due to this a gradual desensitisation is possible. The training provided was aimed at improvement of the skill of arousal reduction by soldiers in order to better cope with stress during service within the Polish Military Contingent.

The problem of individual predispositions’ effect, connected with the possessed personality or temperament structure, on coping with stress and resistance to stress outcome is widely discussed in the literature on the subject [4]. In our study we wanted to check what set of individual traits connected with personality, temperament or a style of coping in stressful situations could be combined with an effective utilisation of the SIT VR method.

1. Materials and Method

1.1. The Formal Characteristics of Behaviour - Temperament Inventory (FCB-TI)

The FCB-TI questionnaire, used for diagnosis of the basic, primarily biologically determined personality domains, named temperament [5], was used in the study. Temperamental traits are examined at two levels.

- The first is the energetic level of behaviour, i.e. mechanisms that are responsible for energy gathering and relief. Energetic traits of temperament are examined by means of the FCB-TI to [16]:
  - Emotional Reactivity (RE) – a tendency to react intensively to stimuli expressed in a high emotional sensitivity and low endurance.
  - Endurance (WT) – ability to react adequately to strong stimulation and ability to manage in situations of a long-lasting activity.
  - Activity (AK) – a tendency to undertake a strongly stimulating behaviour or to seek an external stimulation.
  - Sensory Threshold (WS) – an ability to react to weak sensory stimuli.

- The next levels are temporal characteristics of behaviour that determine the course of reaction in time [16]. They are:
• Briskeness (ŻW) – a tendency to react quickly, to maintain a high tempo of actions and changing the behaviour easily in response to a change in conditions of the surroundings.
• Perseverance (PE) – a tendency to continue and to repeat the reaction after the cessation of original stimulus that triggered it.

1.2 Coping Inventory in Stressful Situations (CISS) Questionnaire

Also the CISS questionnaire, designed to determine patterns of behaviour of an individual in stressing situations was used in the study. This questionnaire consists of 48 simple statements referring to various behaviour patterns used by people in stressful situations. The questionnaire specifies three basic styles of behaviour in situation of this kind [6]:

• Task-oriented style (SSZ) - a style of coping with stress consisting in undertaking tasks. Those who achieve high results in this scale are prone in stressful situations to undertake efforts aimed at solving the problem by cognitive transformations or attempts to alter the situation. The main emphasis is on the task or problem-solving planning.

• Emotions-oriented style (SSE) - a style characteristic for those who in stressful situations show a tendency to focus on themselves and on their emotional experiences, such as anger, feeling guilty, and tension. Such persons also have a tendency towards wishful thinking and fantasizing. These actions are aimed at a reduction of emotional tension related to a stressful situation. However, sometimes they may experience an increase of stress, resulting in an increase of tension, or depression.

• Avoidance-oriented style (SSU) - a style of coping with stress characteristic for those who in stressful situations show a tendency to avoid thinking, experiencing and being affected by this situation. This style may take two forms: engaging in substitute situations (ACZ), e.g. watching TV, stuffing himself with food, thinking about pleasant things, sleeping, or looking for social contacts (PKT).

1.3 NEO – PI – R Questionnaire

The NEO – PI – R personality inventory, designed for diagnosing basic domains of personality in accordance with the 5-factor personality, developed by P.T. Costa Jr. and R.R McCrae [7] was used in the study. According to this theory, the five basic domains of personality [7] are:

• Neuroticism (N) – the domain allowing for the distinguishing of adjusted, emotionally stable people from unadjusted and emotionally unstable ones. High results achieved in this domain are connected with a tendency towards negative emotions, such as anxiety, sadness, and embarrassment, which makes adjustment difficult. They are connected with nervousness, a low feeling of safety and a poor control of impulses.
• Extraversion (E) – the domain that determines engagement in interpersonal contacts and an energy level.

• Openness to Experience (O) – the domain that determines curiosity about an individual’s external and internal world.

• Agreeableness (U) – the domain that determines behavioural patterns in interpersonal relations, connected with altruism, friendliness and readiness for cooperation on one hand, and combativeness and rivalling tendencies on the other.

• Conscientiousness (S) – the domain that determines the level of self-control, integrity and perseverance in pursuing goals.

1.4 State – Trait Anxiety Inventory (STAI)

The State – Trait Anxiety Inventory (STAI) was used in the study. This questionnaire is a tool designed to examine anxiety understood as a transitory and situation-dependent state of an individual and anxiety understood as a relatively constant personality trait. STAI consists of two sub-scales, out of which one (X-1) is used for measurement of state anxiety while the other (X-2) - trait anxiety [8].

State-anxiety is connected with a subjective feeling of tension and fear resulting in an arousal of the nervous system while trait-anxiety is defined as a constant behavioural predisposition that makes a given person perceive objectively harmless situations as harmful ones and responds to them with incommensurable increase of tension and anxiety.

1.5 PTSD Checklist- Military (PCL-M)

The PTSD Checklist – military (PCL-M) was used in the research. The PCL is a self-report measure of the 17 DSM-IV symptoms of PTSD. The PCL has a variety of purposes, including: screening individuals for PTSD, diagnosing PTSD and monitoring symptom change during and after treatment [9].

2. Results

2.1 Anxiety Level

Values of STAI results are compared before the training, after the training and after return from deployment in order to check whether the training provided affected the anxiety level. The Mann - Whitney U-Test was used. The statistical analysis has not shown any significant difference between the experimental and control group. The results are presented in Table 1.
Table 1. Pre-deployment and post-deployment comparison of STAI results in the experimental and control group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>Sum of</th>
<th>Sum of</th>
<th>U</th>
<th>Z</th>
<th>P</th>
<th>Z</th>
<th>P</th>
<th>N</th>
<th>N</th>
<th>Signif</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI X-1 State [pre-train.]</td>
<td>3215.000</td>
<td>2890.000</td>
<td>1459.0</td>
<td>0.30508</td>
<td>0.760300</td>
<td>0.30552</td>
<td>0.759969</td>
<td>57</td>
<td>53</td>
<td>0.761227</td>
<td></td>
</tr>
<tr>
<td>STAI STEN X-1 [pre-train.]</td>
<td>3210.500</td>
<td>2894.500</td>
<td>1463.5</td>
<td>0.27816</td>
<td>0.780884</td>
<td>0.283325</td>
<td>0.776928</td>
<td>57</td>
<td>53</td>
<td>0.779454</td>
<td></td>
</tr>
<tr>
<td>STAI X-2 Trait [pre-train.]</td>
<td>3361.500</td>
<td>3193.500</td>
<td>1540.5</td>
<td>0.47320</td>
<td>0.63606</td>
<td>0.474204</td>
<td>0.635355</td>
<td>57</td>
<td>57</td>
<td>0.635289</td>
<td></td>
</tr>
<tr>
<td>STAI STEN X-2 [pre-train.]</td>
<td>3315.500</td>
<td>3239.500</td>
<td>1586.5</td>
<td>0.21251</td>
<td>0.831702</td>
<td>0.219189</td>
<td>0.826503</td>
<td>57</td>
<td>57</td>
<td>0.830148</td>
<td></td>
</tr>
<tr>
<td>STAI X-1 State [post-train.]</td>
<td>2717.500</td>
<td>2742.500</td>
<td>1339.5</td>
<td>-0.07801</td>
<td>-0.937817</td>
<td>-0.078129</td>
<td>-0.937726</td>
<td>52</td>
<td>52</td>
<td>0.935512</td>
<td></td>
</tr>
<tr>
<td>STAI STEN X-1 [post-train.]</td>
<td>2701.500</td>
<td>2758.500</td>
<td>1323.5</td>
<td>-0.18203</td>
<td>0.855557</td>
<td>-0.187251</td>
<td>0.853645</td>
<td>52</td>
<td>52</td>
<td>0.853645</td>
<td></td>
</tr>
<tr>
<td>STAI X-2 Trait [post-train.]</td>
<td>2802.500</td>
<td>2553.500</td>
<td>1122.5</td>
<td>1.33291</td>
<td>0.182561</td>
<td>1.335451</td>
<td>0.181730</td>
<td>50</td>
<td>53</td>
<td>0.182265</td>
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</tr>
<tr>
<td>STAI STEN X-2 [post-train.]</td>
<td>2788.000</td>
<td>2568.000</td>
<td>1137.0</td>
<td>0.47320</td>
<td>0.63606</td>
<td>0.474204</td>
<td>0.635355</td>
<td>57</td>
<td>57</td>
<td>0.635289</td>
<td></td>
</tr>
<tr>
<td>STAI (2012) X-1 State</td>
<td>1881.000</td>
<td>1689.000</td>
<td>846.00</td>
<td>-0.27803</td>
<td>0.780939</td>
<td>-0.279399</td>
<td>0.780292</td>
<td>45</td>
<td>39</td>
<td>0.782112</td>
<td></td>
</tr>
<tr>
<td>STAI (2012) STEN X-1</td>
<td>1840.000</td>
<td>1730.000</td>
<td>805.00</td>
<td>-0.64570</td>
<td>0.518431</td>
<td>-0.70417</td>
<td>0.481361</td>
<td>45</td>
<td>39</td>
<td>0.520313</td>
<td></td>
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<tr>
<td>STAI (2012) X-2 Trait</td>
<td>2026.000</td>
<td>1544.000</td>
<td>766.00</td>
<td>0.9955</td>
<td>0.31946</td>
<td>1.076430</td>
<td>0.321240</td>
<td>45</td>
<td>39</td>
<td>0.321240</td>
<td></td>
</tr>
</tbody>
</table>

Results of the analysis indicate no differences in terms of anxiety level between the group that underwent the SIT and the control group, both after the training and after return from deployment. This lack of differences concerned both the state anxiety variable and the trait anxiety one.

In order to check whether the training had produced an impact on the experimental group, a statistical analysis was conducted by means of the Wilcoxon signed-ranks test. The results are presented in Table 2.

Table 2. Comparison of STAI results in the experimental group

<table>
<thead>
<tr>
<th>Pair of Variables</th>
<th>N</th>
<th>T</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI X-1 State [pre-train.] &amp; STAI (2012) X-1 State</td>
<td>40</td>
<td>205.0000</td>
<td>2.755466</td>
<td>5.80403</td>
</tr>
<tr>
<td>STAI STEN X-1 [pre-train.] &amp; STAI (2012) STEN X-1</td>
<td>26</td>
<td>89.0000</td>
<td>2.704885</td>
<td>6.83603</td>
</tr>
<tr>
<td>STAI X-2 Trait [pre-train.] &amp; STAI (2012) X-2 Trait</td>
<td>41</td>
<td>0.0000</td>
<td>1.358753</td>
<td>4.34678</td>
</tr>
<tr>
<td>STAI STEN X-2 [pre-train.] &amp; STAI (2012) STEN X-2</td>
<td>36</td>
<td>30.0000</td>
<td>5.231621</td>
<td>1.68497</td>
</tr>
<tr>
<td>STAI X-1 State [post-train.] &amp; STAI (2012) X-1 State</td>
<td>38</td>
<td>242.0000</td>
<td>1.365452</td>
<td>6.24460</td>
</tr>
<tr>
<td>STAI STEN X-1 [post-train.] &amp; STAI (2012) STEN X-1</td>
<td>23</td>
<td>85.0000</td>
<td>1.611993</td>
<td>1.07150</td>
</tr>
</tbody>
</table>

The results indicate that a statistically significant drop in STAI value occurred after the training for both variables, i.e. state-anxiety and trait-anxiety.
2.2 Coping with Stress, Temperament and Personality, and Anxiety Level

The effect of personality-related, temperamental and stress-coping-style related variables on training effectiveness, was a difference in anxiety level, measured by means of STAI, which was then examined. For this purpose an analysis of correlation of the CISS, FCZ-KT and NEO results with those of the X1 and X2 scales in STAI was conducted. This analysis was based on the STAI results obtained prior to the training, after, and after return home from deployment. Results for the experimental group were compared with those for the control group. Table 3 presents the pre-training results.

Table 3. Results of statistically significant correlations between style of coping with stress, temperament and personality, and pre-training anxiety level in the experimental and control group.

<table>
<thead>
<tr>
<th></th>
<th>Experimental Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAI X1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( ZW = -0.33 )</td>
<td></td>
<td>( N = -0.36 )</td>
</tr>
<tr>
<td>( WS = -0.36 )</td>
<td></td>
<td>( O = -0.36 )</td>
</tr>
<tr>
<td>( WT = -0.4 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STAI X2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( SSZ = 0.63 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( RE = 0.48 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( WT = -0.45 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( AK = -0.6 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( E = -0.37 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results indicate a negative average correlation between the state-anxiety and briskness, sensory threshold and endurance in the experimental group. In this group there is also a significant dependency between the task-oriented style, and emotional reactivity was obtained, as well as a negative dependence between endurance, activity and extraversion, and trait-anxiety. A particularly strong dependence occurs in relation to activity.

Conversely, there was a negative correlation between neuroticism and openness to experience, and trait-anxiety.

The results demonstrate that both groups differed in terms of temperamental structure and personality of their members. Participants from the experimental group featured a harmonised temperament structure to a larger extent.

Table 4. Results of statistically significant correlations between style of coping with stress, temperament and personality, and post-training anxiety level in the experimental and control group

<table>
<thead>
<tr>
<th></th>
<th>Experimental Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAI X1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( RE = 0.37 )</td>
<td></td>
<td>( N = -0.36 )</td>
</tr>
<tr>
<td>( U = -0.45 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STAI X2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( PE = -0.48 )</td>
<td></td>
<td>( O = -0.45 )</td>
</tr>
</tbody>
</table>

Next the post-training correlation was analysed. Results of this analysis are presented in Table 4. It was found out that dependence had occurred between state-anxiety and emotional reactivity in the experimental group. However, in the control group, a
negative dependence was obtained between anxiety-status and neuroticism, and agreeableness, as well as between anxiety-trait and openness to experience.

This shows that the trait most susceptible to difference in the state-anxiety variable is emotional reactivity.

A statistical analysis of the CISS, FCZ-KT and NEO results in relation to STAI results was conducted after return of the participants from the deployment. These results are presented in Table 5.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experimental Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI X1</td>
<td>RE = 0.31</td>
<td></td>
</tr>
<tr>
<td>STAI X2</td>
<td>SSE = 0.33</td>
<td>SSZ = 0.34</td>
</tr>
<tr>
<td></td>
<td>SSU = 0.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S = 0.34</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Results of statistically significant correlations between style of coping with stress, temperament and personality, and post-deployment anxiety level in the experimental and control group

These results indicate a significant dependence between anxiety-state and emotional reactivity in the experimental, as between anxiety-trait and the emotions-based avoidance style and conscientiousness. Dependence between the task-oriented style and anxiety-trait was found in the control group.

The results demonstrate, first of all, that dependence between emotional reactivity and state-anxiety remained in the experimental group.

2.3. Coping with Stress, Temperament and Personality, and Post-Traumatic Stress Symptoms

An additional statistical analysis of the CISS, FCZ-KT and NEO results in relation to the PCL – M ones that measured symptoms of post-traumatic stress was conducted after the participants returned home from deployment. Results for the experimental group are presented in Table 6 whilst Table 7 shows the results for the control group.

Table 6. Results of the correlation between coping with stress, temperament and personality, and symptoms of post-traumatic stress in the experimental group.
Results in the experimental group indicate an important dependence (average correlation) between intensity of post-traumatic stress symptoms and the emotions-oriented style and emotional reactivity as well as negative dependency between intensity of PTSD symptoms and endurance. On the other hand, in the control group, a link occurred in the form of an average correlation between the task-oriented style, and intensity of post-traumatic stress symptoms. These results suggest that the groups differed in terms of temperamental predispositions and stress-coping styles.

3. Discussion

The results obtained demonstrate that although no differences were observed between the experimental and control group, the training provided had an effect on tension reduction in soldiers who underwent it.

An analysis of relations between individual predispositions and susceptibility to the training demonstrated that the groups were not homogenous. In the experimental group the anxiety level before examination was much more correlated with temperament structure and the results were in agreement with expectations. Emotional reactivity was connected with a high anxiety level while temperamental traits related to a harmonised structure this was inversely proportional.

It seems that this may be related to a defensive attitude demonstrated by the participants who, being in the training situation, could be concerned about the repercussions of their social exposure and stress resistance assessment. It is possible that the participants from the experimental group had to mobilise their additional energetic resources that resulted in a more distinct connection between anxiety and temperament structure in them.

In the experimental group, both after the training and after returning home from deployment, a feeling of tension was connected with emotional reactivity. Thus, it is possible that this temperamental factor is most sensitive to changes experienced by the participants. So a hypothesis may be put forward that highly reactive persons featured a greater susceptibility to the training. Given the connection between emotional reactivity and resistance to stress, described in the literature [10], this result would put highly
reactive persons in a slightly different light, suggesting that the output drop in resistance to stressful situations could be modified by a larger effect of preventive activities such as the SIT research conducted. However, this hypothesis requires further research.

After returning home from deployment, symptoms of combat stress in the experimental group were more connected with the emotions-oriented style and also with emotional reactivity and endurance. However, these results should be treated with caution because of the multitude of factors that may affect the correlations, which occurred.

It would also be interesting to examine the relationships between personality- and temperament-related factors, and susceptibility to SIT, measured by means of the Low Frequency (LF) and Very Low Frequency (VLF) indicators that determine ability for control of physiological arousal. Such an examination would allow for a more precise analysis of individual predispositions for SIT.

References

Section 4

Co-Morbid Issues: Considering the Whole Person in Treatment
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Recent Advances in the Treatment of Comorbid PTSD and Substance Use Disorder

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VA Connecticut Healthcare System, West Haven, CT and Yale University, School of Medicine, Department of Psychiatry, New Haven, CT

Abstract. Comorbidity between posttraumatic stress disorder (PTSD) and substance use disorder (SUD) is common. As a result, the development of integrated treatments addressing both PTSD and SUD are needed. Although there are effective pharmacotherapies for the treatment of PTSD and SUD, there are no proven medications that will treat both conditions. We have conducted two clinical trials testing the safety and efficacy of medication treatments for comorbid PTSD and alcohol dependence (AD). In a 12-week clinical trial enrolling 254 patients with AD and comorbid psychiatric disorders, we compared four treatment conditions: (1) disulfiram and placebo, (2) naltrexone alone, (3) placebo alone, and (4) disulfiram and naltrexone. Patients with PTSD (n= 93) had fewer heavy drinking days and more consecutive days of abstinence when treated with naltrexone, disulfiram, or combination, as compared to placebo. This study demonstrated the efficacy of both disulfiram and naltrexone for the treatment of AD in individuals with PTSD. In the second 12-week study, a total of 88 predominantly male veterans with current diagnosis of AD and PTSD were randomly assigned one of four groups: paroxetine plus naltrexone; paroxetine plus placebo; desipramine plus naltrexone; desipramine plus placebo. Paroxetine was equivalent to desipramine for the treatment of PTSD symptoms. However, desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes. Naltrexone reduced alcohol craving relative to placebo, but did not improve drinking behavior. This study suggests that norepinephrine uptake inhibitors may have efficacy for the treatment of comorbid PTSD and AD.

Keywords. PTSD, alcohol dependence, substance use disorder, comorbidity.

Introduction

Mounting evidence supports a strong association between posttraumatic stress disorder (PTSD) and substance use disorders (SUD). In both clinical and population samples, a high comorbidity between PTSD and SUD has been observed [1]. Parallel to these findings, preclinical and clinical studies support the role of trauma and stress in vulnerability to SUD [2]. Furthermore, neurobiological mechanisms linking PTSD and SUD have also started to emerge [3].

1 Corresponding Author: E-mail; Mehmet.Sofuoglu@yale.edu.
The goal of this paper is to provide an overview of the advances in the treatment of comorbid PTSD and SUD. We first provide a brief background for the comorbidity between PTSD and SUD, followed by an overview of biological mechanisms linking these disorders. We then review some of our recent studies focusing on pharmacological treatment of patients with PTSD and SUD. For more comprehensive review of this topic, several recent reviews are available [3-5].

1. Comorbidity of PTSD and SUD

Substance use disorders include dependence (synonymous with addiction) and abuse. The hallmark of substance dependence is compulsive substance use at the expense of important activities and responsibilities [6]. Substance use continues in spite of the physical or psychological problems caused by its use. In addition, individuals have a desire to stop, but are unsuccessful at attempts to cut down or quit their substance use. Substance abuse, on the other hand, describes a use pattern with social and medical consequences, without the typical compulsive use pattern of substance dependence [6]. In samples of civilian and combat veterans, associations between PTSD and SUD have been described. In a population sample, Breslau has shown that adults with a history of PTSD, compared to those without trauma history, were 4.3 and 4.0 times more likely to have SUD and nicotine dependence, respectively [7]. Overall, in persons with PTSD, estimates of prevalence of SUD ranged from 21.6 to 43.0, compared with 8.1 to 24.7 without PTSD [1]. The rate of current cigarette smoking is estimated to be 45.3% in persons with PTSD, compared to the 22% rate in persons without a psychiatric diagnosis [8]. Smokers with PTSD are less likely to quit smoking than those without PTSD. The ratio of lifetime smokers who are not current smokers is 28.4 and 42.5 in persons with PTSD and without psychiatric diagnosis, respectively [8].

Similar findings have also been observed in clinical samples. Up to as many as 75% of combat veterans met the criteria for lifetime alcohol abuse, or dependence [1]. In a study from multiple treatment centers from Germany, among patients seeking treatment for alcohol and drug dependence, 34 and 30% had comorbid PTSD [9]. It is important to note that the associations observed in these studies were based on cross-sectional data and have not considered the common risk factors for both disorders. To address these limitations, Reed et al conducted a longitudinal study in which 988 young adults were assessed for the emergence of SUD, over a one-year period [10]. In that study, prior PTSD, compared with the no-trauma group was associated with 4.9 times increased risk of emergence of SUD after controlling for common risk factors including childhood conduct problems, risk taking, and family socioeconomic status. This study supports the role of PTSD as a risk factor for the development of SUD.

2. Biological mechanisms

Many researchers investigating the biological mechanisms linking PTSD and SUD have focused on the influence of stress system on drug-seeking and relapse [2]. Addicted persons experience withdrawal symptoms following cessation of drug use. While the physical signs and symptoms of withdrawal may vary depending on the drugs of abuse [11], drug withdrawal states are characterized by negative affective symptoms including dysphoric or symptoms of depression, anxiety, frustration, anger and irritability. These negative symptoms provide a motivation for addicted individuals to take drugs to alleviate the withdrawal state, which is also called negative
reinforcement [2]. The core symptoms of PTSD including blunted emotional responses, hyper arousal, and flashbacks, which may generate a negative emotional state, and thus facilitate the initiation and maintenance of SUD. A recent study examined the influence of PTSD on the severity of drug withdrawal symptoms in nicotine addicted individuals [12]. In that study, cigarette smokers with PTSD, compared to smokers without PTSD, had more severe withdrawal symptoms, including greater urges to smoke following overnight abstinence from smoking. These findings are consistent with the greater difficulty of smokers with PTSD than smokers without PTSD in quitting smoking [8].

In animal studies, induction of experimental stress facilitated initiation of drug self-administration [13]. In humans, stress induction increased craving and drug use behavior [14-16]. In preclinical studies examining the influence of stress on vulnerability to drug seeking behavior, both corticotropin releasing hormone (CRH) and norepinephrine emerged as important mediators [17]. CRH initiates the neuroendocrine response to stress and elevated CRH levels were found in the cerebrospinal fluid of PTSD patients [18, 19]. Many studies have shown that CRH administration enhances the pharmacological effects of stimulant drugs and facilitates stress-induced drug-seeking behavior in rodents [20].

The neurotransmitter norepinephrine modulates many brain functions including attention, arousal and stress response [17]. Patients with PTSD have elevated norepinephrine levels in the cerebrospinal fluid, indicating increased norepinephrine activity [21]. Medications targeting norepinephrine may have efficacy for treating both SUD and PTSD. These include alpha1- and beta-adrenergic antagonists and alpha2-adrenergic agonists. Alpha1-adrenergic agonist prazosin reduces cocaine, alcohol, nicotine and heroin self-administration in rodents [22-24]. Beta-adrenergic antagonist propranolol attenuates the stress induced cocaine and cue-induce nicotine self-administration [25]. Alpha2-adrenergic agonists block the stress-and cue induced self-administration of cocaine and alcohol [22, 26]. These studies support the potential use of noradrenergic medications for comorbid SUD and PTSD [2, 3].

3. Integrated PTSD and SUD treatment

Studies have shown that ongoing SUD and PTSD symptoms may negatively influence each other leading to poor treatment outcomes [9, 27]. It is important that all patients with PTSD are assessed for alcohol and drug use. Integrated PTSD and SUD treatments have increased treatment retention and improved outcomes for both disorders [28]. A recent example of effective treatment integration of patients with PTSD is a study by McFall et al. [29]. In that study, 943 smokers with military-related PTSD were randomized to either integrated care provided by mental health clinicians, or referred to smoking cessation clinics. Those assigned to integrated care were 2.3 times more likely to quit smoking, compared to those who were referred to smoking cessation clinic [29].

4. Pharmacotherapies

Pharmacotherapies for PTSD target symptom reduction. Selective serotonin reuptake inhibitors (SSRIs) are effective in reducing symptoms of PTSD [4]. However, these effects are modest and more effective treatments are clearly needed for the treatment of PTSD. Atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) are commonly used in clinical practice for the treatment of mood and
anxiety disorder. They are used as an adjunctive treatment for PTSD to reduce symptoms of PTSD such as hyperarousal symptoms [4]. A meta-analysis of seven studies found antipsychotics effective in symptom reduction, especially for the symptom of “intrusion” [30]. However, a recent multisite, double-blind placebo controlled study that enrolled military-related PTSD patients did not find efficacy of risperidone in reducing symptoms of PTSD [31]. Benzodiazepine is also commonly used as adjunctive treatment of PTSD to alleviate sleep disturbance, irritability, and other hyper-arousal symptoms [32]. Benzodiazepine, however, did not show efficacy in controlled studies as adjunctive medications for individuals with PTSD [4].

Prazosin, an alpha1-adrenergic antagonist is found effective in improving sleep as well as other symptoms of PTSD in three controlled trials [33-35]. In these studies, prozosin increase the total sleep time and shifted dream content from trauma-related nightmares to more “normal”, less distressing content. Prazosin also improved emotional responses to trauma cues [34]. Multisite trials are underway to test the efficacy of prozosin in patients with PTSD.

4.1 Pharmacotherapies for comorbid SUD and PTSD

Only a few studies have examined the efficacy of comorbid SUD and PTSD [3, 5]. In this section, we will review two studies that have been conducted in our center. In a clinical trial we examine the safety and efficacy of disulfiram and naltrexone in alcohol dependent patients with comorbid psychiatric disorders including PTSD [36]. Although both disulfiram and naltrexone have been approved by the United States Food and Drug Administration for the treatment of alcoholism, the effect of these medications have not been examined in alcohol dependent individuals with comorbid psychiatric disorders including PTSD. A total of 254 veterans with a major Axis I psychiatric disorder and comorbid alcohol dependence were treated for 12 weeks, at three outpatient clinics. Randomization included (1) open randomization to disulfiram or no disulfiram; and (2) double-blind randomization to naltrexone or placebo. This resulted in four treatment groups: (1) naltrexone alone; (2) placebo alone; (3) disulfiram and naltrexone; or (4) disulfiram and placebo. Outcomes were measures of alcohol use, PTSD symptoms, alcohol craving, gamma-glutamyl transferase (GGT) levels and adverse events. Out of 254, 93 patients (36.6%) met DSM-IV criteria for PTSD. Patients with PTSD had better alcohol outcomes with active medication (naltrexone, disulfiram or the combination) than they did on placebo; overall psychiatric symptoms of PTSD improved. Patients with PTSD were more likely to report some side effects when treated with the combination. These findings suggest that disulfiram and naltrexone are effective and safe for individuals with PTSD and comorbid alcohol dependence [36].

In a more recent study, we compared a serotonin uptake inhibitor, paroxetine, to a norepinephrine uptake inhibitor, desipramine, and also evaluated the adjunctive efficacy of the naltrexone, relative to placebo. While paroxetine is approved by the FDA for the treatment of PTSD, naltrexone is approved for the treatment alcohol dependence. A total of 88 predominantly male veterans with current diagnosis of alcohol dependence were randomly assigned under double-blind conditions to one of four groups: paroxetine plus naltrexone; paroxetine plus placebo; desipramine plus naltrexone; desipramine plus placebo. Main outcome measures included standardized scales that assessed symptoms of PTSD and alcohol consumption. Paroxetine was as effective as desipramine for the treatment of PTSD symptoms. However, desipramine
was superior to paroxetine with respect to study retention and alcohol use outcomes. Naltrexone reduced alcohol craving relative to placebo, but it conferred no advantage on drinking use outcomes. Although the serotonin uptake inhibitors are the only FDA-approved medications for the treatment of PTSD, the current study suggests that norepinephrine uptake inhibitors may present clinical advantages when treating male veterans with PTSD and alcohol dependence with PTSD [37].

To summarize, there is a clear need to develop new pharmacological treatments for comorbid PTSD and SUD. In preclinical and clinical studies medications targeting NE show promise as potential treatments for comorbid PTSD and SUD.

Acknowledgments

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References


Secondary Traumatic Stress Among Wives of War Veterans

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Abstract: Previous studies have shown that some wives of war veterans with PTSD develop symptoms of secondary traumatic stress (STS). The aim of this study was to compare the level of present psychological symptoms and perceived quality of life between the wives of veterans with PTSD, without PTSD, and wives of non-veterans. Wives of veterans with PTSD (N=50) were recruited through their partners and war veterans treated for combat related PTSD in Referent Center for Psychotrauma Rijeka, Croatia. Wives of veterans without PTSD (N=50) and wives of non-veterans (N=50) were recruited using the snowballing method. We administrated Sociodemographic questionnaire, Brief symptom inventory, Manchester Short Assessment of Quality of Life and Modified Questionnaire for Secondary Traumatization. Obtained results show that wives of veterans with PTSD have significantly higher level of STS symptoms than wives of veterans without PTSD, and higher level of psychological symptoms and lower perceived quality of life compared to other two groups. Level of STS symptoms is positively correlated with psychological symptoms and negatively with perceived quality of life. Main effect on STS symptoms has the wives’ knowledge of partner’s war traumatic event while the main effect on wives’ psychological symptoms has the presence of PTSD in their husbands. In conclusion, when planning the future interventions for PTSD affected veterans, systemic approach should be considered not only to prevent secondary traumatic stress in partners of war veterans but also to enhance individual functioning of each partner and functioning as a couple.

Keywords: Secondary, Traumatic Stress, Wives, Psychological symptoms, Quality of life, Posttraumatic Stress Disorder, War veterans

Introduction

Nearly a half of the world’s countries have been hit by a war over the past twenty-five years [1]. Many studies have shown that war trauma is associated with an increased rate of mental disorders, with posttraumatic stress disorder (PTSD) and major depressive disorder as the most frequent [2]. PTSD and major depressive disorder may last for years after the traumatic events have ended [3, 4]. Croatia had also gone through a war that had numerous social and health consequences, PTSD amongst them. With its specific symptoms, PTSD exerts a profound effect on social functioning of
war veterans. The PTSD related problems can be seen best in family interactions. Family members, who should be the ones who provide emotional support, are most strongly hurt by the veterans’ mental difficulties [5].

Studies show that people in close contact with traumatized individuals may also develop painful and severe symptoms of trauma [6, 7, 8, 9]. The process is usually called secondary or vicarious traumatization. Secondary traumatization has been explored in partners and other family members of war veterans [10, 11], in members of the ER staff [12, 13], therapists and healthcare professionals working with traumatized people [8, 9, 14].

**The effect of PTSD on intimate relationships**

A series of researches has shown that posttraumatic stress disorder in war veterans poses a risk of developing serious relationship problems. War veterans with PTSD report less satisfaction in their intimate relationships. Their relationships are less cohesive, less expressive and include more conflicts and violence than relationships of war veterans without PTSD [15]. The PTSD-affected veterans’ inability to believe, feel and participate in everyday life reduces their capacity for intimacy. Very often the wives have to take over most of the emotional, practical and financial responsibilities in the family. Solomon [16] describes this as "redistribution of roles and re-division of labor".

Many studies demonstrated that Vietnam War veterans diagnosed with PTSD had more marital and family problems. Divorce rate in families of Vietnam War veterans with PTSD was double their peers without PTSD; family violence and communication and sexual problems were more frequent and problem coping skills were poorer. The wives and the family members more often felt emotional numbness, depression and anger and they more often felt isolated and abandoned. These wives also had an increased risk for developing somatization disorders [18].

**Secondary traumatic stress**

PTSD of a person may have a profoundly upsetting effect on the persons in close contact. Fullerton and Ursano [19] note that such forms of indirect trauma are significantly less explored than the effects of direct trauma. However, secondary traumatization has been attracting more and more interest over the past fifteen years. Figley [6, 20] defined secondary traumatization as behaviors and feelings that result from knowing or hearing about traumatic events experienced by a significant other. Secondary traumatization is a form of stress that develops as a consequence of providing help or wanting to help a traumatized person. Secondary traumatic stress (STS) as the possible outcome of the secondary traumatization process may involve the entire range of symptoms such as intrusive thoughts and images, traumatic memories or nightmares related to the traumatic experience, avoidance, arousal, disturbing emotions and dysfunctionality. It may also include insomnia, a chronic irritability, anger outbreaks, exhaustion, concentration problems and trigger reactions to traumatic stimuli or reminders of traumatic experience of a partner or a significant other [6, 20-23].

Several theories have tried to provide an answer to the question as to why the wives of war veterans feel the symptoms similar to their husbands’ symptoms. Alessi et al. believe that human development does not take place in a vacuum, which is in line with the systemic theories. Henggeler and Borduin [24] say that family is an interdependent
unit whose members influence each other in a circular way. The Couple Adaptation to Traumatic Stress – (CATS) developed by Nelson Goff and Smith [25] offers a systematic definition of how trauma affects individuals and their relationships. The behavior or symptoms of the primarily traumatized partner set off a systemic response that may develop into secondary traumatic symptoms in the other partner. Symptoms of secondary traumatization in the other partner may intensify the symptoms of the partner’s primary traumatization. Adaptation to traumatic stress in a dyad depends on systemic interactions of three primary dimensions: 1) individual functioning, 2) the predisposing factors and resources and 3) couple functioning [25, 26].

A short review of studies on secondary traumatic stress

Nelson Goff et al. [26] examined the partners of American soldiers who had participated in military operations in Iraq and Afghanistan and found that PTSD symptoms of the war veterans were in significant correlation with the symptoms of their wives who had not had any personal experience in the wars.

Dirkwzager, Bramsen, Ader and van der Ploeg [27] explored secondary traumatization in partners of Dutch soldiers involved in peacekeeping missions. The results showed that partners of the PTSD-affected soldiers had significantly higher number of sleeping problems and somatic complaints and more often reported receiving poorer social support and having poorer marital relations as compared to partners of the soldiers without PTSD.

Frančišković et al. [28] conducted research in Croatia aimed at investigating the presence of secondary stress symptoms in wives of Croatian war veterans diagnosed with PTSD. The results demonstrated that 39.3% of the wives satisfied the criteria for secondary traumatic stress disorder based on the DSM-IV criteria for PTSD.

The Referral Psychotrauma Center in Rijeka, Croatia, where the study was conducted, has been providing psychological help to victims of the war for nearly two decades. A large number of the war veterans seeking help raised the question as to how trauma affected the ones who are in close contact with the patients. The aim of our study was to examine the level of secondary trauma in terms of intensity of PTSD symptoms, the level of current psychological symptoms (Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism and the Global Severity Index) and self-perceived quality of life in wives of PTSD-affected Croatian war veterans (group G1) compared to wives of the war veterans without PTSD (G2) and women whose husbands did not participate in the war (G3).

1. Methods

1.1 Procedure

We first contacted the women whose husbands had participated in the war but had not developed PTSD (G2) because these respondents were the least accessible. We selected 50 participants by using the snowballing method. The next step was to find 50 women whose husbands had not participated in the war (G3). We selected women who best matched the group G2 in age and education level.

The third group, G1, consisted of women whose husbands had participated in the war and had been treated with PTSD. First, we chose potential participants by reading
through medical records of PTSD patients treated at the Rijeka Psychotrauma Center. Then we invited the wives of the veterans who had been diagnosed with PTSD but who had not had any other mental disorders or physical disabilities to participate in the research. We examined 150 women; in the order their husbands had applied for a mental health check-up. Of the 150 women, we selected 50 who best matched the G2 and G3 participants in terms of age and education level.

First we obtained socio-demographic information (age, education level, years spent in school, average monthly income, employment status and duration of marriage) and information about the husbands’ participation in the war (duration of deployment, in months, a short description of the husbands’ experience from the battlefield and duties performed in the battlefield) by conducting an interview with the participants. Participants also responded to the questions as to whether they had lived or ended up in the war zone by chance and whether they believed they needed psychological help themselves.

The participants filled out questionnaires in the facilities of the Rijeka Psychotrauma Center. All the three groups filled out the Brief Symptom Inventory (BSI) and the Manchester Short Assessment of Quality of Life (MANSA). Only the participants from the clinical groups responded to the Modified Secondary Trauma Questionnaire. All the participants had previously been informed about the aims of the research and they had all given their written informed consent.

1.2 Participants

Socio-demographic data and information related to the war experience are shown in Table 1. The G1 participants were a mean age of 44.3 years; G2 participants were a mean age of 45.1 and the G3 participants of 46.5. The average education level of the three groups was secondary; the average duration of their marriages was 21.2 years in G1 to 22.9 years in G3. The average monthly income was EUR 970 in G1 to EUR 1232 in G3. The three groups of women did not differ statistically in terms of age (F=1.026; p=0.361), duration of education (F=1.433, p=0.242), duration of marriage (F=0.404, p=0.668) and monthly income (F=1.482, p=0.231). However, there were some statistically significant differences among the participants in employment status (χ²=16.206, p=0.003). Most of the women in the three groups were employed (34% to 39%), but there were more retirees in G3 (18%) than in G1 (6%) and G2 (2%). There were more unemployed participants in G1 and G2 than in G3 (26%, 20%, 4%, respectively).

The groups showed statistically significant differences in terms of how many of the women had lived or had ended up on the war affected areas by chance (χ²=37.719, p=0.000). More than 50% of the G1 participants had lived or had ended up in the war zone by chance, while only a fifth of the G2 participants had reported the same. In contrast, none of the G3 members had lived or ended up in the war affected areas. Further on, participants from the groups G1 and G2 significantly differed in their knowledge of their husbands’ war experience (χ²=17.533, p=0.000). In other words, 90% of the women in G1 knew of at least one traumatic experience of their husbands, while only 52% percent of the women whose husbands had fought in the war, but had not been diagnosed with PTSD, reported the same.

Duration of deployment of the veterans with PTSD (G1) was significantly longer, according to their wives’ reports (t=8.025, p=0.000), as compared to the veterans
without PTSD (G2). The G1 husbands spent an average of 38.4 months in the battlefield; as compared to the average of 15.6 months spend by the G2 husbands.

Table 1. Socio-demographic characteristics of participants whose husbands suffer from PTSD (G1), participants whose husbands do not suffer from PTSD (G2) and the control group whose husbands did not participate in the war (G3)

<table>
<thead>
<tr>
<th></th>
<th>G1 N=50</th>
<th>G2 N=50</th>
<th>G3 N=50</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>M 44.5</td>
<td>43.1</td>
<td>46.5</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>SD 7.61</td>
<td>5.69</td>
<td>8.79</td>
<td>0.361</td>
</tr>
<tr>
<td>Education (in years)</td>
<td>M 11.6</td>
<td>12.1</td>
<td>12.1</td>
<td>0.433</td>
</tr>
<tr>
<td></td>
<td>SD 1.73</td>
<td>1.93</td>
<td>1.43</td>
<td>0.242</td>
</tr>
<tr>
<td>Duration of marriage (in years)</td>
<td>M 21.2</td>
<td>22.2</td>
<td>22.9</td>
<td>0.404</td>
</tr>
<tr>
<td></td>
<td>SD 8.60</td>
<td>6.63</td>
<td>11.35</td>
<td>0.668</td>
</tr>
<tr>
<td>Monthly family income (in Euros)</td>
<td>M 970.3</td>
<td>1,175.92</td>
<td>1,322.15</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>SD 1,147.3</td>
<td>461.03</td>
<td>414.53</td>
<td>0.231</td>
</tr>
<tr>
<td>Employment status</td>
<td>employed N(%)</td>
<td>34(68%)</td>
<td>39(78%)</td>
<td>39(78%)</td>
</tr>
<tr>
<td></td>
<td>retied N(%)</td>
<td>3(6%)</td>
<td>1(2%)</td>
<td>9(18%)</td>
</tr>
<tr>
<td></td>
<td>unemployed N(%)</td>
<td>12(26%)</td>
<td>10(20%)</td>
<td>2(4%)</td>
</tr>
<tr>
<td>Personal experience of living in the war zone</td>
<td>N(%)</td>
<td>26(52%)</td>
<td>10(20%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>p=0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aware of husbands war veteran traumatic experience</td>
<td>N(%)</td>
<td>45(90%)</td>
<td>26(52%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veteran's duration of deployment (in months)</td>
<td>M</td>
<td>38.39</td>
<td>15.64</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SD 14.677</td>
<td>13.513</td>
<td>-</td>
<td>0.000</td>
</tr>
</tbody>
</table>

1.3 Instruments

We used a modified version of the Indirect Traumatization Questionnaire created by Havelka [29] to assess the symptoms of secondary traumatic stress. The questionnaire consists of 16 items relating to symptoms of secondary traumatic stress, which correspond to symptoms of PTSD as defined by the DSM-IV. The first item is presented in the form of a yes/no question of whether the wife knows of at least one traumatic experience of her husband, which corresponds to the criterion A in defining PTSD (presence of traumatic experience). The next four items are related to symptoms of re-experiencing the original trauma (cluster B), the following six refer to avoidance symptoms (cluster C) and the last five are related to symptoms of hyperarousal (cluster D). In the original questionnaire, all questions had dichotomous responses but for the purposes of this research the answering scale was modified. Participants rated their responses on the items corresponding to B, C and D cluster of symptoms on a 0-4 point Likert-type scale (0="not at all" to 4="extremely"). The presence of the three factors was confirmed in the previous studies [28]. Cronbach's Alpha reliability coefficient was 0.89 for re-experiencing symptoms, 0.83 for avoidance and 0.91 for hyperarousal.

To assess psychological symptoms we used the Brief Symptom Inventory (BSI) created by Derogatis [30]. The BSI is a self-report inventory designed for measuring
clinically relevant psychological symptoms in adolescents and adults. It contains 53 items covering nine symptom dimensions: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobias, paranoid ideation and psychoticism; plus three global indices of distress: Global Severity Index, Positive Symptom Distress Index and Positive Symptom Total. Participants rate the extent to which they have been bothered by various symptoms in the past week, including the day of the administration, on a 0-5 point Likert-type scale (0 ="not at all" to 4="extremely"). The inventory is frequently used and reportedly has good metrical features and high reliability. Internal reliability coefficients (Cronbach’s Alpha) range from 0.71 for psychoticism and 0.85 for depression. In our study, Cronbach’s Alpha was 0.80 for hostility and 0.91 for somatization.

Quality of life was assessed by the Manchester Short Assessment of Quality of Life (MANSA) created by Priebe, Huxley, Knight and Evans [31]. MANSA is a 16-item scale assessing the quality of life focusing on satisfaction with life as a whole and satisfaction with particular aspects of life. Four items, made in the form of yes/no questions, are considered objective. The other twelve items are subjective and refer to satisfaction with life as a whole and satisfaction with particular areas: job, financial situation, quality of friendships, leisure activities, accommodation, personal safety, sex life, family relationships, relationships with persons the participant lives with, physical health and mental health. Each item is rated on a seven-point satisfaction scale, from 1="couldn’t be worse" to 7="couldn’t be better". Previous studies demonstrated good internal consistency reliability. In our study, the reliability coefficient was 0.87.

2. Results

2.1 The intensity of secondary traumatic stress symptoms

We conducted t-tests in order to test the differences in the intensity of STS symptoms as a whole and the intensity of B, C and D cluster of STS symptoms between G1 and G2.

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-experiencing</td>
<td>1.97</td>
<td>.83</td>
<td>5.721</td>
<td>.000</td>
</tr>
<tr>
<td>symptoms</td>
<td>1.125</td>
<td>.838</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(B)</td>
<td>.83</td>
<td>.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance</td>
<td>1.47</td>
<td>.72</td>
<td>4.481</td>
<td>.000</td>
</tr>
<tr>
<td>symptoms</td>
<td>.917</td>
<td>.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C)</td>
<td>.72</td>
<td>.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper-arousal</td>
<td>1.56</td>
<td>.58</td>
<td>5.362</td>
<td>.000</td>
</tr>
<tr>
<td>symptoms</td>
<td>1.145</td>
<td>.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(D)</td>
<td>.58</td>
<td>.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.63</td>
<td>.70</td>
<td>5.627</td>
<td>.000</td>
</tr>
<tr>
<td>symptoms of STS</td>
<td>.955</td>
<td>.673</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The t-test results showing the average intensity of secondary traumatic stress symptoms in women whose husbands suffer from PTSD (G1) and women whose husbands fought in the war but did not develop PTSD (G2).
G2 participants (Table 2). The results showed that the women from the group G1 had significantly worse symptoms of STS as a whole (t=5.627; p=.000). Furthermore, these women also had significantly worse symptoms of B (t=5.721, p=0.000), C (t=4.481; p=0.000) and D cluster (t=5.362; p=0.000) relative to the participants from the group G2.

2.2 The intensity of mental symptoms

The one-way ANOVA showed statistically significant differences among the three groups in the following scales: somatization (F=20.386; p=0.001), obsession-compulsion (F=17.048; p=0.001), interpersonal sensitivity (F=13.367; p=0.001), depression (F=19.596; p=0.001), anxiety (F=32.567; p=0.001), hostility (F=13.031, p=.001), paranoid ideation (F=13.288; p=.001), phobias (F=24.767; p=0.001), Psychoticism (F=24.449; p=0.001) and Global Severity Index (F=27.657; p=0.001) (Table 3). The post-hoc analysis showed that the women whose husbands suffered from

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatization</td>
<td>1.77</td>
<td>1.103</td>
<td>.90</td>
<td>.75</td>
<td>20.386</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsession-Compulsion</td>
<td>1.65</td>
<td>1.028</td>
<td>.94</td>
<td>.76</td>
<td>17.048</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpersonal Sensitivity</td>
<td>1.48</td>
<td>.885</td>
<td>.86</td>
<td>.70</td>
<td>13.367</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.52</td>
<td>1.067</td>
<td>.71</td>
<td>.56</td>
<td>19.596</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.83</td>
<td>1.076</td>
<td>.74</td>
<td>.65</td>
<td>32.675</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>1.20</td>
<td>.949</td>
<td>.61</td>
<td>.55</td>
<td>13.031</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phobic Anxiety</td>
<td>1.27</td>
<td>1.580</td>
<td>.49</td>
<td>.31</td>
<td>24.767</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid Ideation</td>
<td>1.64</td>
<td>.962</td>
<td>.94</td>
<td>.86</td>
<td>13.288</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Psychoticism</td>
<td>1.15</td>
<td>.949</td>
<td>.41</td>
<td>.27</td>
<td>24.449</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Severity Index</td>
<td>1.51</td>
<td>.883</td>
<td>.73</td>
<td>.57</td>
<td>27.657</td>
</tr>
</tbody>
</table>

Table 3. Results of the one-way ANOVA and the Tukey post-hoc test for mental symptoms in women whose husbands suffer from PTSD (G1), women whose husbands fought in the war but did not develop PTSD (G2) and women whose husbands did not participate in the war (G3)
PTSD had worse symptoms in the above-mentioned scales, as compared to the women whose husbands did not have PTSD and the women whose husbands had not fought in the war (Table 3).

### 2.3 Self-perceived quality of life

The one-way analysis of variance revealed statistically significant differences among the participants in the MANSA scores ($F=9.097; p=0.001$) (Table 4). The post-hoc analysis showed that the women whose husbands had PTSD had lower self-perceived overall quality of life as compared to the women whose husbands had been in the war, but had not developed PTSD and the women whose husbands had not been in the war. Furthermore, the three groups of women had significantly different perceptions of the quality of particular aspects of their lives. The one-way ANOVA discovered statistically significant differences among the groups when it comes to satisfaction with life as a whole ($F=5.224; p=0.006$), satisfaction with jobs ($F=5.825; p=0.004$), income ($F=6.708; p=0.002$), accommodation ($F=5.291; p=0.006$), personal safety (13.692; $p=0.001$), people they lived with ($F=5.180; p=0.001$), sex life ($F=5.180; p=0.007$) and mental health ($F=7.001; p=0.001$) (Table 4).

<table>
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<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>Mean</th>
<th>SD</th>
<th>F</th>
<th>p</th>
<th>df</th>
<th>Significance</th>
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<td>5.10</td>
<td>5.24</td>
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<td>4.09</td>
<td>1.199</td>
<td>3.23</td>
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<td>4.58</td>
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<td>2.13</td>
<td>0.014</td>
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<td>0.014</td>
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<td>0.014</td>
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<td>3.18</td>
<td>0.007</td>
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<td><strong>PERSONAL LIFE</strong></td>
<td>4.22</td>
<td>4.22</td>
<td>4.22</td>
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<td>0.007</td>
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Table 4. Results of the one-way ANOVA and the post-hoc test for self-perceived quality of life in women whose husbands suffer from PTSD (G1), women whose husbands fought in the war but did not develop PTSD (G2) and women whose husbands did not participate in the war (G3).

The post-hoc analysis determined that the women whose husbands had not been in the war were significantly more satisfied with life as a whole as compared to the women whose husbands suffered from PTSD. The women whose husbands had PTSD and the women whose husbands had been in the war but had not developed PTSD were significantly less satisfied with their jobs compared to the women whose husbands had not been in the war. The women whose husbands had fought in the war did not differ significantly in job satisfaction, regardless of whether their husbands had PTSD or not.
The women whose husbands suffered from PTSD were significantly less satisfied with their accommodation, personal safety, people they lived with, sex life and mental health than the women whose husbands did not have PTSD, and the women whose husbands had not been in the war. The women from the three groups did not show any statistically significant differences in satisfaction with friendships, leisure activities, family relationships and physical health.

2.4 Correlation of secondary traumatic stress, psychological symptoms and self-perceived quality of life

Table 5 shows Pearson's coefficients of correlation of psychological symptoms measured by the Global Severity Index (GSI), self-perceived overall quality of life and the intensity of overall STS symptoms, symptoms of re-experiencing, symptoms of avoidance and hyper-arousal symptoms, for the groups G1 and G2 each. The table also shows the results of testing the correlation coefficient differences between the G1 participants and the G2 participants using Fisher's r to z transformation.

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<th>symptom cluster D</th>
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<td>.477***</td>
<td>.468***</td>
<td>.506**</td>
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<td>z=-1.97, p=.051</td>
<td>z=-0.31, p=.75</td>
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<td>.525**</td>
<td>.352*</td>
<td>.958**</td>
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<td>z=1.94, p=.051</td>
<td>z=1.35, p=.197</td>
<td>z=-0.1, p=.242</td>
<td>z=-1.7, p=.089</td>
</tr>
</tbody>
</table>

GSI – Global Severity Index
QL – self-perceived overall quality of life
* p<0.05, ** p<0.01

Table 5. Pearson’s correlation coefficients of the average intensity of STS symptoms, psychological symptoms and quality of life in women whose husbands suffer from PTSD (G1) and women whose husbands fought in the war but did not develop PTSD (G2) and the results of Fisher’s z test for comparison of coefficients among the groups.

We found statistically significant correlation between symptoms of secondary traumatic stress with psychological symptoms and self-perceived quality of life in both groups of the veteran wives. The exception was the correlation between symptoms of re-experiencing and self-perceived quality of life in women whose husbands had PTSD.

The Global Severity Index was in a statistically significant correlation with the intensity of B, C and D symptom clusters and the intensity of overall STS symptoms. The coefficients ranged from r=0.407 to r=0.613. The testing of the differences between correlation coefficients of mental symptoms and the intensity of STS symptoms did not reveal any statistically significant difference between groups G1 and G2. The result indicated that the higher was the level of psychological symptoms, the greater was the intensity of the overall STS symptoms and certain STS symptoms clusters, regardless of whether the participants’ husbands had PTSD or not.
Self-perceived quality of life was also in a significant but negative correlation with the intensity of STS symptoms, both in G1 and G2. The correlations ranged from $r = -0.331$ to $r = -0.601$. However, we did not discover any significant correlation between re-experiencing symptoms and self-perceived quality of life in G1. The testing of the correlation coefficient differences between self-perceived quality of life and the intensity of STS symptoms did not reveal any statistically significant difference between G1 and G2. However, there was a statistically significant difference between correlation coefficients for symptoms of re-experiencing and self-perceived quality of life ($z = 1.94$, $p = 0.052$). The results suggested that the greater was the intensity of overall STS symptoms, avoidance symptoms and arousal symptoms, the poorer was the quality of life in the two groups, regardless of whether their husbands had PTSD or not.

2.5 Effects of war-related variables on secondary traumatic stress, mental symptoms and self-perceived quality of life

The socio-demographic information (Table 1) shows that apart from the husband’s PTSD, the women also differed in whether they were aware of husband’s traumatic experience or not and in whether they had lived in the war-affected territory themselves or ended up there by chance. We took these variables in consideration in doing the comparison of the women’s STS symptoms, psychological symptoms and self-perceived quality of life. Table 6 shows the results of three-way ANCOVAs in which the average intensity of the overall symptoms of STS, the symptoms of re-experiencing, avoidance and arousal, psychological symptoms and self-perceived quality of life were taken as dependent variables and presence of PTSD, knowledge of husband’s traumatic experience and the wife’s personal war experience were taken as independent variables. In order to control the effect on independent variables, we set duration of the veteran’s deployment as a covariant variable. We did not include the women from the group G3 in this process because their husbands had not participated in the war and had not developed combat-related PTSD.

The results revealed a statistically significant main effect of the wife’s knowledge of the husband’s war-related traumatic experience on the average intensity of the overall STS symptoms ($F (1.99) = 10.092; p = 0.002$), the average intensity of re-experiencing symptoms ($F(1.99) = 14.748; p = 0.000$) and the average intensity of avoidance symptoms ($F(1.99) = 9.760; p = 0.002$) (the variable of the veterans’ deployment was controlled). The other variables and interactions were not statistically significant. We did not find any significant main effects of the variables and their interactions on the intensity of arousal symptoms, even though the overall model was significant ($F (1.99) = 8.045; p = 0.006$).

The veteran’s duration of deployment was a statistically significant covariate for the intensity of the overall STS symptoms, for the intensity of the overall STS symptoms ($F (1.99) = 6.491; p = 0.013$), the intensity of B cluster symptoms ($F (1.99) = 4.083; p = 0.046$) and the intensity of C cluster symptoms ($F (1.99) = 8.754; p = 0.004$). The results suggested that the participants who knew about their husbands war-related traumatic experience, regardless of whether the husbands had PTSD or not and whether the women themselves had a war-related experience, experienced greater intensity of overall STS symptoms ($M = 1.47$, $SD = 0.934$), greater intensity of symptoms of re-experiencing the original trauma ($M = 1.80$, $SD = 1.108$) and greater intensity of avoidance symptoms ($M = 1.34$, $SD = 0.908$), as compared to the women who did not
have any knowledge of their husbands’ war-related traumatic experience (M = 0.57, SD = 0.659; M = 0.61, SD = 0.752; M = 0.61, SD = 0.738). The intensity of the symptoms was in a statistically positive correlation with the husbands’ duration of deployment.

Table 6 shows a statistically significant main effect of the husband’s PTSD diagnosis on psychological symptoms in the Global Severity Index (F (1.99) = 6.552; p=0.012) (the duration of deployment variable was controlled). The other variables and interactions were not statistically significant. The results indicated that the women whose husbands had PTSD had significantly worse psychological symptoms (M = 1.51, SD = 0.883) relative to the women who husbands were not diagnosed with PTSD (M = 0.74, SD = 0.588).

Even though the overall model was significant (F (7.99)=2.362; p=0.029), there were not any significant main effects or interactions for self-perceived quality of life.

### 3. Discussion

#### 3.1 Intensity of STS symptoms among wives of veterans with and without PTSD

Our study found greater intensity of overall STS symptoms and the intensity of particular clusters of STS symptoms in the women whose husbands had PTSD, as compared to the women whose husbands did not have PTSD. The result corresponds to results of earlier studies indicating that the intensity of secondary stress symptoms is in a positive correlation with PTSD symptoms of war veterans [24; 26].

Even though our study does not offer any information about the intensity of PTSD symptoms in the veterans, we may assume that the veterans’ symptoms trigger a systemic response that causes secondary traumatic stress in their partners. This
assumption corresponds to the Couple Adaptation to Traumatic Stress – (CATS) model developed by Nelson Goff and Smith [25]. Identification with the ill partner and empathy may cause similar disturbances in the wives, which may explain why the wives of war veterans with PTSD report greater symptoms of STS than the wives of war veterans without PTSD. Projective identification may account for the ways of transmission of the primary symptoms from the victim onto people in close contact [25]. Victims of trauma often experience problems with self-esteem, guilt and other negative self-attributes. In order to preserve the image of self, the traumatized persons project the bad image of self onto the partner or other family members and create an interpersonal process that results in the partner developing the same thoughts and feelings.

3.2 Intensity of psychological symptoms among wives of veterans with PTSD, veterans without PTSD, and wives whose husband are not war veterans

Further on, the results of our study showed that wives of PTSD-diagnosed war veterans have significantly higher level of psychological symptoms as compared to the other two groups of respondents. The wives of PTSD-diagnosed war veterans reported a greater number of physical disturbances, obsessive-compulsive thoughts and behaviors and symptoms of depression, anxiety and psychoticism. They reported greater interpersonal sensitivity and they were more prone to phobias and paranoid ideation as compared to the women whose partners did not suffer from PTSD and the women whose partners had not participated in the war. The participants whose husbands did not suffer from PTSD did not show any statistically significant differences in the levels of psychological symptoms as compared to the participants whose husbands had not participated in the war. The result was in line with our expectations.

Earlier studies have already demonstrated that wives of Vietnam War veterans had more depression and anxiety symptoms and more physical symptoms relative to wives of the war veterans without PTSD [24, 15]. Another study showed that wives of Israeli war veterans had more somatic symptoms, obsessive-compulsive problems, anxiety symptoms, paranoid ideation and psychoticism than the controls. Alessi et al. [24] explained the increased level of emotional problems in wives of war veterans with PTSD – over-functioning of the wives and their full-time care for the family makes them feel burdened and dissatisfied, which increases stress, sensitivity to depression and loss of identity.

3.3 Intensity of psychological symptoms among wives of veterans with PTSD, veterans without PTSD, and wives whose husband are not war veterans

Our study also revealed that wives of PTSD affected war-veterans had lower scores in self-perceived quality of life scales as compared to the other two groups of respondents. The women whose husbands had not been in the war reported the greatest satisfaction with all aspects of life.

The participants whose husbands had PTSD were significantly less satisfied with life as a whole, jobs, income, accommodation, personal safety, people they lived with, sex life and mental health than the participants whose husbands had not participated in the war. The dissatisfaction with jobs, income and accommodation of the G1 participants may be explained by several objective factors. They were more often unemployed as compared to the control group and, even though the difference was not
statistically significant, they had lower monthly income than the G2 and G3 participants.

The lower level of satisfaction with personal safety, people they lived with, sex life and mental health in the participants whose husbands had PTSD may be accounted for by the effect of the victim’s PTSD on the family members. When it comes to personal safety, many studies showed that war veterans with PTSD were more prone to irritability, aggression and family violence [32]. Anger problems may lead to impulsive outbursts and violent and destructive behaviors after which the family members continue to live in fear. The unpredictable nature of anger outbursts underlines the tension, anxiety, hypervigilance and the feeling of “walking on egg shells” in the family. Wives of veterans suffering from PTSD say they too have become cautious and distrustful and often experience exaggerated startle response [14]. Alessi et al. [23] explain these wives' low satisfaction with people they lived with by a lack of social and emotional support from their ill partners and family members. Families of war veterans very often reduce their social contacts in order to protect the veteran from potentially upsetting situations, which results in further downsize in social support available [33; 34].

According to researches, partners of Vietnam war veterans with PTSD were less satisfied with their intimate relationships [15]. A study on Croatian war veterans diagnosed with PTSD showed that they had decreased sexual activities, reduced sex drive and an increased erectile dysfunction compared to the healthy controls [35]. The veterans most often stated their health problems and their wives’ health problems as reasons for the sexual difficulties. The veterans’ reduced capacity to believe, feel and participate in everyday life also impairs their capacity for intimacy. It was not surprising that the participants whose husbands had PTSD were less satisfied with their mental health than the other participants. Earlier studies dealing with the effect of PTSD on war veteran wives also showed that the wives had more psychological symptoms than women whose husbands did not have PTSD and women whose husbands had not participated in a war.

3.4 Correlation between STS symptoms, psychological symptoms and quality of life

The testing of the relationships among the variables indicated that there was a statistically significant correlation among the symptoms of STS, psychological symptoms and self-perceived quality of life. The symptoms of STS and psychological symptoms were in a positive correlation, while self-perceived quality of life was in a negative correlation with STS symptoms and the observed psychological symptoms. This finding proved that symptoms of PTSD in war veterans were associated with emotional difficulties in their wives [36], lower satisfaction in marital relations [37] and symptoms of STS [5; 25]. Moreover, all variables observed in the study were not only in a statistically significant, but also in moderate to high correlation. This may be interpreted by the effect of an intrapsychological process of the transmission of traumatic symptoms from the veteran onto the emotional life of the wife. The CATS has already proved the significance of the circular relationship of individual functioning and couple functioning [25].
3.5 Influence of war-related variables on STS symptoms, psychological symptoms and quality of life

The three-way analysis of covariance revealed the main effect of the wife’s awareness of the husband’s traumatic event on the intensity of STS symptoms and particular clusters of STS. This was in line with our expectations, considering the etiological correlation. Still, it was surprising that there was not any significant effect of the veterans’ PTSD and the wives’ personal war experience on STS. Nearly a half of our participants whose husbands had PTSD had lived at some point in the war zone. According to the CATS, personal traumatic experience is a predisposing factor for developing STS. Unresolved traumatic experiences of any of the partners intensify the relationship conflicts and increase the partners’ sensitivity for primary and secondary traumatization effects. Our study did not examine the characteristics of the participants’ personal war experience, however, it is possible that some did not experience war related trauma and some hide their own war trauma compared with that of the war veterans which may account for the lack of its significant effect on the symptom intensity. Even though the G2 veterans had not been diagnosed with PTSD, this study did not explore whether they too had certain symptoms or symptoms of other comorbid disorders. Our results showing the main effect of the wife’s knowing about the husband’s war experience on the frequency and the intensity of STS symptoms may be in line with the theoretical concept of secondary traumatic stress according to which knowing of one person’s trauma was enough for the partner to develop symptoms similar to PTSD. However, more research has to be conducted in order to confirm the theory.

The participants whose husbands’ duration of deployment was longer experienced more overall STS symptoms and more avoidance symptoms. Duration of trauma exposure is a risk factor for the development of PTSD and is associated with a greater intensity of PTSD symptoms [38], which are transmitted onto the wives.

Our war veteran patients at the Psychotrauma Center often admit that they have not told their wives about their experiences from the war. They rarely share their painful war-related memories with people who have not had such experiences. They are afraid that their family members would be upset or would not be able to provide support and understanding. Our study suggests that not knowing about the trauma is truly a strong protection against developing secondary stress symptoms. Even so, the wives are exhausted by trying to break through the “wall of silence” erected by their husbands and feel helpless because they are unable to help their partners. The wives’ support groups always raise the subject of fantasizing about the husbands’ war experiences (“who knows what awful things he did in the war”). These fantasies tend to grow and block the communication with the veteran. When they finally find out about the veterans’ experiences, they feel relieved since the fantasies they had were much worse. Mere awareness of the partner’s war trauma without an open communication and emotional support may cause more difficulties between the partners. This finding underlines the importance of a systemic approach in treating psychotraumatized families.

Our study demonstrated that the veterans’ PTSD produced a significant main effect on psychological symptoms of their wives, regardless of the veterans’ duration of deployment. Living with a PTSD-affected person is hard and depression, anxiety, social isolation and other symptoms are a frequent systemic response of the other partner. In line with the findings of Alessi et al. [23], Matsakis [17] and Lyons [39], our
experience in working with the war veteran wives showed that family dysfunction and the sense of responsibility for the husbands’ state were very frequent subjects in the beginning of the group therapy. The wives usually begin the therapy thinking that the aim is to help their husbands. They often believe their problems are insignificant compared with their husbands’ and that they are the ones who should provide help. They try not to upset their husbands, they observe their husbands’ behavior and take over all family responsibilities. When they finally shift the focus onto themselves, they discover how discouraged and said how they truly feel.

According to our results, awareness of the husband’s trauma, presence of PTSD in the wives and personal war experience of the wives had not had any significant effect on the self-perceived quality of life. The finding may be explained by the fact that many other factors that have not been examined in the study influence the perception of the quality of life. The wives of the veterans seeking help at the Psychotrauma Center often say that the quality of their lives is impaired by the husband’s mental state. Their husbands cannot stand crowded spaces, standing in line, family gatherings… For this reason, the wives usually miss social events such as weddings, theater shows, even ordinary walks. They often do not share beds because of the veteran’s sleeping problems. Some of the women even experienced being physically attacked by their husbands who thought the wives were the enemies from their nightmares. Nevertheless, most of these wives say they love their husbands and cannot imagine living without them. Both the veterans and the wives believe in the sanctimony of marriage.

3.6 Methodological limitations

The study has several methodological limitations. First, we used reachable samples that were relatively small and did not allow for result generalization since it is not clear to which extent they represent the general population of war veterans and their families. The future research should examine variables related to the war veterans’ trauma (the level and category of traumatization, intensity of symptoms) and presence of comorbid disorders. In addition, the further research should explore the relationship between intensity of particular symptom clusters in the veterans and the wives’ symptoms. Another limitation of the study is the lack of focus on traumatic experiences of the wives who had lived or ended up in the war zones since there is a chance that they too have developed PTSD. The advantage of the study is that it included wives of war veterans without PTSD. The advantage of the study is that it included wives of war veterans without PTSD.

3.7 Clinical implications of results

Posttraumatic stress disorder is a chronic illness affecting the persons in close contact with the patient. Our study confirmed our experiences from clinical work with the war veteran wives. The initial idea in working with the veteran wives was to inform them about posttraumatic reactions of their husbands. However, we encountered “hidden” patients – the women who are also deeply hurt and also struggle with a series of problems. Clinicians dealing with psychotrauma should bear in mind that living with a traumatized individual may cause secondary stress reactions in the partner. The therapy should include the wives for two reasons: they are the source of support for the PTSD-diagnosed veterans and they are likely to develop secondary symptoms of traumatic stress. A systemic approach in the treatment could improve both individual and couple functioning.
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