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PREFACE

The guest editors are pleased to present this special edition on the topic of leveraging technology in military and Veteran mental health. The articles in this supplement reflect the ongoing work of the NATO Human Factors and Medicine Research Task Group 279 (NATO HFM RTG-279), *Leveraging Technology in Military Mental Health*. The task group comprises clinician scientists, defence scientists, and subject matter experts from multiple nations, including Australia, Canada, the Netherlands, and the United States. Its purpose is to review existing and emerging technologies, such as big data/machine learning, neuroimaging/biomarkers, genomics, mobile and online interventions, simulation and serious gaming, and neurostimulation – and to examine their potential across domains inclusive of research, education, training, and clinical care. RTG-279 studies these technologies to determine their applicability and suitability for use in the military and Veteran mental health setting for the prevention, diagnosis, treatment, and prediction of military mental health disorders. The articles in this supplement are the result of deliberations that occurred in Toronto, Ontario, in October 2017, and in Amsterdam, the Netherlands, in February 2018.

The rapidly advancing technology sector represents the greatest opportunity for advancing military mental health in over a century. Across the NATO alliance, military partners are contending with a significant mental health burden, particularly in areas such as posttraumatic stress disorder (PTSD) and suicide. Incorporating technological innovation offers an opportunity for a novel approach to mental health care. Leveraging advances in technology is one aspect of an ongoing and concerted effort to mitigate the devastating effects of mental illness in the military and Veteran population.

Oncology, cardiology, radiology, and surgery have made incredible advances over the past several decades, most notably through leveraging advances in materials science, data science, drug development, and technology. Mental health has long lagged behind other fields of medicine in the application of such advances. Despite this, mental health now appears to be on the cusp of a new era in which big data, biomarkers, neuroimaging, mobile and online interventions, simulation and "serious gaming" will likely augment or replace conventional approaches across the key domains of military mental health. Taking advantage of these emerging developments will contribute to greater force readiness and enhance the treatment of the ill and injured.

In this edition, we discuss how neuroimaging could be used to understand further the brain regions involved in mental health conditions relevant to the military population, such as PTSD. Such an understanding could lead to the use of neuroimaging as a more objective marker of mental illness, particularly for monitoring response to treatment. Beyond the research potential for neuroimaging, additional patient and clinician education could facilitate more clinically relevant use of neuroimaging findings, with an aim to "make the invisible disease, visible" and further assist in destigmatizing mental illness.

We also explore genomics, a field of study that promises great advances for mental health, from risk stratification to gene therapy. Our Toronto meeting focused more narrowly on pharmacogenomics, a technology that examines how genetic variants affect medications prescribed to an individual. Pharmacogenomics was reviewed in the context of precision medicine for drug safety, efficacy, and efficiency of providers through the reduction of trial and error.

While neuroimaging and genomics can be considered biomarkers of sorts, this supplement also devotes space to the investigation of more traditional biomarkers typically found in blood, urine, and saliva. We felt this exploration was important for military mental health, as it assists in the paradigm shift that will allow these debilitating conditions to be seen as diseases of the body, and not simply of the mind. In PTSD, for example, abnormalities in the body's stress reaction and immune response may shed light on the biological underpinnings of the disorder and, eventually, lead to novel prevention and treatment approaches.

Gamification of mental health interventions, virtual reality, full-body haptic suits for military training, sensory reality pods, and computer-aided therapy are also reviewed in this supplement. The Amsterdam meeting provided a significant opportunity for members of NATO HFM RTG-279 to experience technologies through hands-on demonstration. This experiential approach facilitated an appreciation for the truly immersive nature of some of these technologies. Specifically, the group had the opportunity to interact with a

sensory reality pod that has been used in children's hospitals and burn centres. The pods allow users to temporarily escape to realistic scenes of a beach or mountain top, accompanied by all the sights, sounds, and smells of their chosen destination. While further research is needed to understand and advance these innovations, it was exciting and inspiring for the group to see the potential benefit of these immersive technologies.

As a group, we appreciate that mental health is far from realizing the true potential of online interventions for the education, training, and treatment of mental health conditions. There are many potentially helpful online interventions and applications that exist, and it is understood that the gamification of these interventions may increase uptake and efficacy. While we are hopeful about the future of such interventions, we also understand that much work is needed before we can fully realize the potential of these and other technologies.

We recognize that the technologies described in this special edition are by no means an exhaustive list, but rather examples that can demonstrate potential advances in the field of military and Veteran mental health. It is also clear that the technologies are at various stages of maturity and readiness for use in clinical settings. As an example, the magnetoencephalography (MEG) scanners used for non-invasive biomarker discovery of mental health conditions will continue to be in limited supply in the near future, and will not likely become a standard diagnostic tool. However, MEG may be an ideal research tool to demonstrate real-time electrophysiological processes of the brain. Perhaps one day, surrogate quantitative electroencephalography (qEEG) could create an office-based approximation of MEG.

Other technologies, such as virtual reality (VR), pharmacogenomics, and online applications are likely mature enough that aspects of these technologies can be integrated into – and will likely enhance – our current clinical approaches. VR seems a natural extension of exposure therapy, and could also be used in other ways, such as enhanced guided meditation. Pharmacogenomics has current demonstrated utility in pain, psychiatric, and cardiovascular disease and represents a potential step toward personalized medicine for mental health. Online tools and apps bring a total removal of geographic – and most temporal – boundaries for patients. They also appear to represent an increasingly preferred method of communication for our target population. These technologies may aid in avoiding the barriers to care that exist in traditional approaches and, in some cases, remove the need for a clinician entirely. In our estimation, additional advances in online tools and apps are more likely to result in a decreased burden on the health care system, rather than obviating the need for clinicians.

Biomarkers offer substantial potential for improving mental health care, including an understanding of how mental illness impacts the complex homeostatic systems within the body – an obvious priority. A disorder such as PTSD is ripe for such inquiry: it has been in existence in its present form for nearly four decades, and yet there is no medication specifically designed for its treatment. Biomarkers may help us to construct an understanding of military mental health beyond a fear-based paradigm to one that reflects a complex interplay between stress, immune function, and the wide array of bodily systems likely involved. This understanding is much more likely to lead to treatment approaches targeting specific underlying abnormalities, instead of the current way we, as a field, have approached PTSD for the past four decades.

The guest editors wish to thank the publishers of the *Journal of Military, Veteran and Family Health* (*JMVFH*) for the opportunity to produce this special edition. We would like to consider it the first of many conversations as we help accelerate the evolution of mental health. Let NATO HFM RTG-279 – and this special edition of inspiring articles – be a call to arms for those in the mental health community to embrace and leverage technology in order to better understand and care for the military and Veteran population suffering with mental health conditions.

Col Rakesh Jetly, *Co-Editor*
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Regulating posttraumatic stress disorder symptoms with neurofeedback: Regaining control of the mind

Andrew A. Nicholson[a], Tomas Ros[b], Rakesh Jetly[c] and Ruth A. Lanius[d]

ABSTRACT

Neurofeedback is emerging as a psychophysiological treatment where self-regulation is achieved through online feedback of neural states. Novel personalized medicine approaches are particularly important for the treatment of posttraumatic stress disorder (PTSD), as symptom presentation of the disorder, as well as responses to treatment, are highly heterogeneous. Learning to achieve control of specific neural substrates through neurofeedback has been shown to display therapeutic evidence in patients with a wide variety of psychiatric disorders, including PTSD. This article outlines the neural mechanisms underlying neurofeedback and examines converging evidence for the efficacy of neurofeedback as an adjunctive treatment for PTSD via both electroencephalography (EEG) and real-time functional magnetic resonance imaging (fMRI) modalities. Further, implications for the treatment of PTSD via neurofeedback in the military member and Veteran population is examined.

Key words: amygdala in PTSD, brain wave oscillations, EEG neurofeedback, emotion regulation, fMRI neurofeedback, military, NATO, neurofeedback, personalized medicine, PTSD, Veterans

RÉSUMÉ

Introduction : La rétroaction neurologique apparaît comme un traitement psychophysiologique qui permet l'autorégulation par la rétroaction en ligne des états neuronaux. **Méthodologie :** Les nouvelles approches de médecine personnalisée sont particulièrement importantes pour le traitement du syndrome de stress post-traumatique (SSPT), car la présentation des symptômes et les réponses au traitement sont hautement hétérogènes. **Résultats :** Il est démontré que le fait d'apprendre à contrôler des substrats neuronaux précis grâce à la rétroaction neurologique donne des résultats thérapeutiques chez des patients présentant un vaste éventail de troubles psychiatriques, y compris le SSPT. **Discussion :** Le présent article souligne les mécanismes neuronaux sous-jacents à la rétroaction neurologique et examine des données convergentes sur l'efficacité de la rétroaction neurologique comme traitement d'appoint au SSPT, à la fois par l'électroencéphalographie (ÉEG) et l'imagerie par résonance magnétique fonctionnelle (IRMf). De plus, on y étudie les conséquences de la rétroaction neurologique pour le traitement du SSPT dans la population de militaires et de vétérans.

Mots-clés : amygdale en cas de SSPT, médecine personnalisée, militaires, oscillations des ondes cérébrales, OTAN, régulation émotionnelle, rétroaction neurologique, rétroaction neurologique par ÉEG, rétroaction neurologique par IRMf, SSPT, vétérans

THE NEED FOR NOVEL ADJUNCTIVE TREATMENTS AND PERSONALIZED MEDICINE IN PTSD

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that can develop in the aftermath of psychological trauma.[1] The incidence of PTSD in all public safety personnel rescue workers[2] worldwide is 10%. An alarming national study in Canada found that 44% of public safety personnel screened positive for symptom clusters consistent with one or more mental health disorders.[3] Similarly, 13% of returning Canadian Armed Forces personnel are diagnosed with

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deployment-related mental disorders, including PTSD.[4] In addition, a cross-sectional World Health Organization survey, conducted in 11 countries, found that PTSD was associated with 20.2% of sexual assault cases.[5] Currently, common treatments for PTSD consist of psychotherapy, pharmacotherapy, or a combination thereof. However, dropout rates from psychological therapies, such as trauma-focused cognitive behavioural therapy and eye movement desensitization, are an important consideration for the military and Veteran population,[6,7] where a recent systematic review reported an average dropout rate of one in three patients among Veterans.[7] In community-based settings, only 56% of patients with PTSD received a minimally adequate dose of psychotherapy.[8] A cross-national meta-analysis study suggests that psychotherapy is reported to be successful in only about 60% of cases.[9] Pharmacological treatment can also be effective in PTSD, however, research suggests a substantial portion of patients (41%) fail to respond to this type of intervention.[10,11] Further, it has been suggested that PTSD treatment models must extend beyond one-size-fits-all conceptualizations and adopt a personalized medicine approach to treatment if they are to adequately reflect the evidence base and the complexity of PTSD in Veteran populations.[12]

Importantly, neurofeedback with both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) represent an emerging adjunctive treatment that allows patients to self-regulate neural states. The underlying benefit of this treatment practice is that one can directly entrain and regulate neural activity along with associated psychological symptoms.[13–15] In a systematic review of biofeedback for psychiatric disorders, 70% of the studies reported a statistically-significant clinical improvement in the treatment of depression or anxiety disorders.[16] Furthermore, with regard to patients with PTSD, a recent cross-national systematic review found that all 10 neurofeedback studies, which included military members, demonstrated positive improvements on at least one PTSD symptom.[17]

Novel adjunctive treatments are particularly important for the treatment of PTSD, as it is a highly heterogeneous disorder, where symptom severity and the predominance of certain symptoms greatly differs between individuals, especially in more chronic cases over time.[1,18] Based on diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*), a classification manual used by mental health professionals, there are more than 600,000 symptom combinations or ways in which a person can present with PTSD.[1,18] Moreover, a dissociative subtype of PTSD has been defined in which individuals present with additional symptoms of depersonalization and derealization, with associated abnormal neural circuitry in emotion regulation and fear-responding regions.[1,19–22]

Given the diversity of brain circuits that may be involved in PTSD, modern neurofeedback technology may facilitate a more personalized approach to medicine when treating patients with PTSD and could also help to improve symptoms in those individuals previously resistant to treatment. The current review will focus on the fMRI and EEG signals that are used for neurofeedback, together with studies that demonstrate converging neurobiological evidence for their use as treatments in patients with PTSD.

INTRODUCTION TO NEUROFEEDBACK

Neurofeedback is non-invasive approach used in the treatment of a wide range of neuropsychiatric disorders, including PTSD.[13,14,16–18,23] Many different neurofeedback protocols and methods exist, where treatment flexibility may be particularly advantageous in PTSD, as it is a heterogeneous disorder with a wide range of symptoms.[1,18,19,22] Neurofeedback involves a brain-computer interface that provides real-time feedback of brain activity that individuals learn to regulate using a "closed-loop" paradigm.[13,14,24] Typically, the neural signal is fed back to the person as an auditory or visual signal. The individual receives positive feedback each time progress is made toward normalizing aberrant neural activity.[14,18] Clinicians are able to target specific neural dynamics in the brain, related to PTSD symptom presentation and maintenance, which allows patients to self-regulate pathological states.[18,25] Neurofeedback protocols can be used with fMRI neuroimaging to precisely target localized brain regions and related brain networks, whereas EEG neurofeedback is used to regulate more global signals, indicative of large-scale brain oscillations.[13,14] Notably, EEG neurofeedback has also recently been used to target more specific subcortical regions of the brain.[26–28] Neurofeedback represents a closed-loop design, meaning continuous sensory representations of brain activity are provided to individuals in real-time with the aim of controlling this activity.[13,14] Neurofeedback can be conceptualized as a "virtual mirror for neural dynamics occurring within the brain", in which this interface allows for the modification of such dynamics and their corresponding psychological state(s).[13]

In terms of mechanisms, the direct causal pathways that mediate neurofeedback are yet to be elucidated fully. However, several theories exist. Briefly, neurofeedback has been proposed to involve Hebbian plasticity, homeostatic plasticity, and structural plasticity within the brain.[13,14,18,29] Neuroplasticity is a concept that is widely supported by research within the field, in which neurofeedback may not only alter the strength of neural circuitry connections and activity within the synapse, but may also directly modulate abnormal brain oscillations.[13,14,18] In support of structural changes occurring in response to neurofeedback,[30,31] a recent fMRI study reported post-training microstructural changes with regard to white matter pathways and grey matter volume among areas involved in the sustained attention neurofeedback task.[29] Finally, in support of homeostatic plasticity, EEG neurofeedback has been shown to result in a homeostatic rebound of brain wave oscillations, which has been associated with the normalization of abnormal brain circuitry in patients with PTSD and acute symptom alleviation.[32] In terms of implementing neurofeedback treatment interventions specifically in patients with PTSD, several neurophysiological measures have been identified, which represent key targets for modulation/intervention via neurofeedback.

WHAT ARE THE NEURAL TARGETS FOR MODULATION IN PTSD?

Intrinsic connectivity networks (ICNs) have been shown to be particularly important for proper neural functioning in humans. Specifically, the main ICNs consist of the default mode network (DMN), central executive network (CEN) and salience network (SN), where dysfunction in these three core networks plays a significant role in a broad range of psychopathology.[33] These ICNs have been shown to be abnormal in PTSD and are hypothesized to be related to specific symptom presentations within the disorder, including altered self-referential processing and social cognition (DMN),[34,35] cognitive dysfunction (CEN),[36–38] as well as dysregulated arousal/hypervigilance and chronic threat monitoring (SN).[33,35,37,39–50] Neuroimaging studies in PTSD suggest an over-engagement of the SN, failure to properly recruit emotion regulation and executive functioning areas within the CEN, and a breakdown of functional connectivity within the DMN.[45,51] Indeed, neurofeedback has been proposed as a potential avenue by which to normalize these network abnormalities in PTSD.[45]

Recent studies suggest covariation between alpha-wave oscillations in the brain and changes in the aforementioned ICNs[52,53] that are particularly implicated in PTSD.[45] Alpha oscillations (8–12Hz) are easily measurable with EEG and correspond to a state of resting wakefulness correlated to the DMN,[54,55] where patients with PTSD are known to display decreased DMN connectivity at rest in key hubs of this network.[40,45,46] In conjunction, PTSD patients display abnormally reduced alpha oscillations, proposed to be a global index of chronic hyperarousal.[13,56–58] Taken together, alpha-wave oscillations are frequently a target for EEG neurofeedback due to their associations with symptoms of hyperarousal in patients with PTSD, along with their ability to modulate autonomic activity related to the stress response[13] and ICN dynamics.[32]

Additionally, studies have repeatedly found that PTSD is associated with less activation in the medial prefrontal cortex (mPFC), which contributes to a loss of top-down regulation on emotion generation areas such as the amygdala, corresponding to PTSD symptoms of hyperarousal vivid-reexperiencing, and emotion undermodulation.[19,20,22,59–69] PTSD symptoms of hyperarousal have been correlated with negative mPFC-amygdala coupling,[64] where PTSD patients display reduced PFC-amygdala connectivity as compared to controls, corresponding to reduced regulation of emotion centres during the resting state.[70]

Observations of these altered patterns of neural functioning have driven efforts to develop novel treatment interventions that target both large-scale neural oscillations, as well as localized brain regions implicated in PTSD symptomatology. Taken together, common targets for treating PTSD via neurofeedback largely consist of regulating directly abnormal alpha-based brain oscillations related to ICNs, as well as directly regulating amygdala activation and associated top-down recruitment/control from the mPFC.[18,28,32,71,72] Interestingly, empirical studies with fMRI and EEG neurofeedback signals evidence overlapping neurobiological mechanisms, where both approaches have been shown to lead to plastic changes in ICN and amygdala connectivity. Specifically, real-time fMRI neurofeedback targeting amygdala downregulation in PTSD patients may lead to increased connectivity of the amygdala with PFC emotion regulation areas as well as a plastic changes within ICNs (DMN, CEN, and SN).[71,72] Similarly, alpha-based EEG neurofeedback also leads to plastic changes within ICNs, with associated reductions in

hyperarousal and a shift in amygdala connectivity away from innate defence and fear-processing areas, toward PFC emotion regulation areas.[28,32] These converging mechanisms underlying EEG and fMRI neurofeedback are explored in the subsequent sections.

REAL-TIME fMRI NEUROFEEDBACK IN PTSD

Real-time fMRI neurofeedback (rt-fMRI-nfb) involves learning to increase or decrease activity in specific cortical or subcortical regions and has been used to modulate neural correlates underlying psychopathology.[14] Several studies have examined the capacity to regulate emotion processing by targeting neurofeedback of the amygdala using rt-fMRI-nfb in both healthy individuals[73–78] and psychiatric populations, including borderline personality disorder (BPD),[79] major depressive disorder,[80–82] and PTSD.[71,72,83,84]

The amygdala is a region associated with the processing and generation of emotions,[85–87] where dysregulated amygdala activation has been shown to be central to the development and maintenance of PTSD symptoms.[19,22,46,51,67,68,88] Indeed, attenuated top-down regulation from the mPFC with concomitant amygdala hyperactivity is a neural signature critical to symptoms of emotion undermodulation (i.e., hyperemotionality), hyperarousal, and re-experiencing.[19,20,22,46] Notably, direct amygdala regulation via rt-fMRI-nfb has been shown to also affect activation in PFC areas involved in emotion regulation, as well as to enhance amygdala-PFC connectivity.[74–76,89] Neurofeedback regulation of the amygdala may offer a way to therapeutically normalize the abnormal cortico-subcortical pathways maintaining PTSD.

Nicholson et al.[71] presented the first demonstration of successful amygdala downregulation using rt-fMRI-nfb in patients with PTSD. Here, patients were able to downregulate both right and left amygdala activation during a symptom provocation paradigm in which patients viewed words associated with their trauma.[71] Importantly, patients were also able to learn to regulate their amygdala activation on a subsequent transfer trial without neurofeedback.[71] Here, increased activation in the dorsolateral and ventrolateral PFC was observed in trials where patients were instructed to downregulate their amygdala.[71] Interestingly, these regions are known to be related to emotion regulation and executive functioning, while their activation was negatively correlated with PTSD symptoms during neurofeedback training.[71] Furthermore, increased functional connectivity between the amygdala and the PFC was found during neurofeedback training. This study suggests that neurofeedback may be a therapeutic protocol for dampening amygdala hyperactivity and restoring emotion regulation PFC regions in patients with PTSD. These results parallel other rt-fMRI-nfb studies in healthy individuals, where self-regulation of the amygdala, as compared to control regions, was shown to increase activation in emotion regulation PFC regions, as well as enhance amygdala-PFC connectivity.[74–76,89–91] Elsewhere, it has also been shown that using rt-fMRI-nfb to enhance the connectivity between the PFC and the amygdala during threat exposure in highly anxious individuals resulted in reduced anxiety in the absence of feedback.[92]

Finally, in terms of underlying mechanisms, an analysis exploring directional connectivity in a PTSD sample including military members suggested that amygdala downregulation involved both top-down and bottom-up information flow with regard to observed PFC-amygdala connectivity.[71] These results support the hypothesis that emotion regulation may be underpinned by a reciprocal loop of information processing, in which information flows in a bi-directional manner between the amygdala and PFC during amygdala downregulating neurofeedback.[14,71,92,94] Taken together, these studies suggest that rt-fMRI-nfb may be an effective means of decreasing amygdala hyperactivity and enhancing PFC activity/connectivity in order to regulate emotion states. Interestingly, increased PFC activation has also been reported when examining neural activity, post-treatment, among PTSD patients.[11,88,95,96]

In another Canadian research study, Nicholson et al.[72] also provided evidence that amygdala downregulation via rt-fMRI-nfb leads to plastic changes within ICNs, which, as previously mentioned, represent neural targets highly implicated in PTSD that are known to be associated with symptom presentation.[34,40,45,46,97] In this study, that included military members with PTSD, amygdala downregulation was associated with increased recruitment of the left CEN over neurofeedback training runs, a finding supported by increased dorsolateral PFC activation during the downregulate condition, specifically.[72] Critically, the literature suggests decreased recruitment and functional connectivity within CEN emotion regulation PFC regions among PTSD patients,[37,38,45,98] where attenuated regulatory activation in the PFC is associated with PTSD symptoms of emotion undermodulation (i.e., hyperemotionality) and amygdala hyperactivation.[19,20,22] This neurofeedback protocol

may represent a therapeutic strategy to restore activity in emotion regulation regions within the CEN in an attempt to counterbalance severe emotion undermodulation that is observed in PTSD.[72] In the same study, DMN recruitment related to self-referential processing and autobiographical memory was stabilized during neurofeedback runs.[72] Individuals with PTSD have been shown to maladaptively recruit the DMN during tasks that require cognitive control.[97] Hence, stabilization of the DMN may represent a normalization of neural dynamics within this network; that is, a decrease from the response typically observed in PTSD patients.[72] This normalization may allow patients to increase recruitment of the CEN involved in executive regulation, resulting in more control over emotion generation centres in the brain (e.g., amygdala). Taken together, these recent studies[71,72] provide exciting, preliminary evidence that fMRI neurofeedback involving downregulation of the amygdala in PTSD is associated with measurable changes in ICNs and emotion regulation regions,[71,72] effects similar to those observed using EEG signals for neurofeedback in patients with PTSD.[28,32]

EEG NEUROFEEDBACK IN PTSD

EEG neurofeedback consists of regulating electrocortical oscillations in real-time, also known as brain waves. Historically, the EEG signal was the first to be used for neurofeedback in order to regulate neural activity and corresponding pathological brain states in patients with PTSD,[28,32,99–101] culminating in a recent randomized controlled trial in patients with chronic PTSD.[102]

Peniston and Kulkosky[100] reported one of the first studies that demonstrated significant reductions in PTSD symptoms following the regulation of alpha brain waves using EEG neurofeedback in Veterans with PTSD. After training to increase "slow" brain waves (i.e., alpha and theta waves), only 20% of PTSD patients had a recurrence of PTSD symptoms over a 30-month period, consisting of monthly follow-up assessments, in contrast to 100% of the control group.[100] Furthermore, the neurofeedback group also displayed more significant improvements on the Minnesota Multiphasic Personality Inventory (MMPI) scales, as compared to controls.[99] More recently, a mechanistic study on alpha-based neurofeedback in PTSD patients was found to rescue alpha oscillations post-training, which was directly associated with significant reductions in hyperarousal symptoms.[32] Interestingly, this neurofeedback protocol also lead to changes in ICNs highly associated with PTSD symptomatology.[32,45] This included plastic modulation of the DMN involved in PTSD alterations in self-referential processing and autobiographical memory, as well as alterations within the SN involved in the detection of salient threat in the environment and hypervigilance.[32,45] Notably, this was the first study to show that key brain networks underpinning PTSD can be volitionally modulated by EEG neurofeedback with outcomes on immediate symptomatology.[32] Importantly, these results are supported by other alpha-based, controlled neurofeedback studies in healthy individuals, which display lasting changes in cortical plasticity post neurofeedback.[103,104]

Relevant to EEG neurofeedback targeting hyperarousal symptoms in patients with PTSD, a subsequent study from a Canadian laboratory aimed to investigate amygdala functional connectivity before versus after treatment with alpha-based neurofeedback.[28] Here, prior to neurofeedback treatment, PTSD patients displayed stronger amygdala connectivity to areas implicated in threat, emotion, and fear processing, as well as trauma memory retrieval areas (brainstem periaqueductal gray and hippocampus, respectively). Interestingly, after a 30-minute session of alpha-based EEG neurofeedback, the amygdala shifted connectivity to PFC emotion regulation areas involved in top-down executive functioning.[28] This switch in amygdala connectivity was positively associated with reduced hyperarousal among patients and negatively correlated to PTSD symptom severity. In a wider context, the results were consistent with neurocognitive models of PTSD emotion undermodulation, which suggest that PTSD symptoms manifest from weakened top-down cortical regulation of the subcortically hyperactive amygdala and limbic system.[22] Critically, this study represents a therapeutic "tuning" of neural dynamics toward increased top-down regulation over the limbic (amygdala) and midbrain (periaqueductal grey) systems with associated acute symptom alleviation.[28,105]

In accordance with this model, EEG neurofeedback training of amygdala-correlated activity leads to emotion regulation improvements in soldiers during combat training.[26] Taken together, EEG neurofeedback represents a non-invasive way to normalize dysregulated activation in emotion regulation areas of the PFC, as well as in limbic and midbrain brain structures involved in innate fear and reflexive responding to trauma (amygdala and brainstem periaqueductal grey), with the aim

to correct neural patterns of emotion undermodulation in PTSD.[28]

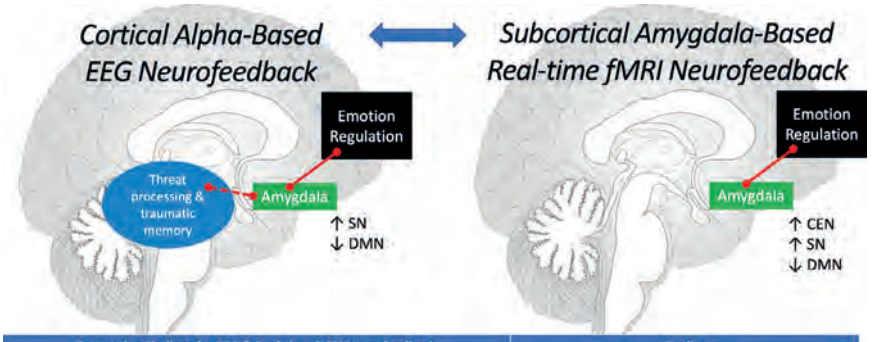
In support of this, a recent randomized control trial on alpha-based EEG neurofeedback in patients with chronic PTSD showed that, as compared to the control group, neurofeedback treatment produced significant improvements for both PTSD symptoms and capacity for emotion regulation.[102] Neurofeedback led to significant reductions in the number of patients meeting criteria for PTSD — from 88.9% to 27.3% in the experimental neurofeedback group — that was sustained in a one-month post-treatment follow-up.[102] Participants in this study consisted of a number of traumatized individuals with PTSD who had not responded to at least six months of trauma-focused psychotherapy.[102] Only a very small amount (4%) of participants in the active treatment condition reported side effects of increased flashbacks,[102] although additional research is needed to elucidate further potential side effects of neurofeedback in trauma samples. Another study demonstrated that 30 sessions of alpha-based EEG neurofeedback lead to increased cognitive functioning and decreased symptoms of depression among PTSD patients.[101] Notably, whereas most evidence-based therapies for PTSD focus on the processing of trauma memories, the target of neurofeedback is neural regulation, stabilization, and homeostasis. Since cognitive self-regulation disruptions have been identified as an obstacle for psychotherapy-based treatments, neurofeedback may be especially beneficial for PTSD patients who are highly anxious, dissociated or dysregulated, and who may not tolerate or respond to other forms of treatments.[22,102,106] Taken together, empirical evidence for both EEG and fMRI neurofeedback modalities suggest that modern neurofeedback technology may facilitate a more personalized medicine approach when treating patients with PTSD and may utilize similar neural mechanisms/pathways to achieve these therapeutic results.

CONVERGING EVIDENCE FOR REAL-TIME fMRI AND EEG NEUROFEEDBACK IN THE TREATMENT OF PTSD

Interestingly, both fMRI and EEG modalities demonstrate very similar neurobiological mechanisms in terms of normalizing disrupted brain circuitry in PTSD. Both amygdala-targeted rt-fMRI-nfb[71,72] and alpha-based EEG neurofeedback[28,32] lead to (1) plastic modulation of ICNs associated with PTSD symptom presentation; (2) functional changes in amygdala connectivity; and (3) increased PFC activation and functional connectivity to key limbic structures indicative of increased top-down control of emotion generation regions (Figure 1). In addition, neurofeedback appears to shift amygdala functional connectivity away from fear-processing and defence regions and towards emotion regulation regions, an effect which is negatively correlated to PTSD symptoms and alpha rhythm, and is associated with increased calmness among PTSD patients.[28,32,71,72]

Relevant for the implementation of neurofeedback locally in the clinic and remotely among deployed military members, EEG neurofeedback is a relatively inexpensive and mobile tool for administering neurofeedback. Furthermore, EEG-based neurofeedback treatment settings are arguably more comfortable environments than the fMRI scanner. Nonetheless, fMRI studies are also important for investigating anatomically localized neural mechanisms underlying neurofeedback. Hence, a convergence of EEG and fMRI neurofeedback modalities are critical for the clinical integration of neurofeedback for PTSD treatment. Indeed, scientists in the field of neurofeedback have begun to use simultaneous EEG/fMRI recordings to define patterns of electrical recording that correlate to highly specific subcortical targets normally only measurable with fMRI.[26,27] Importantly, when targeting the amygdala via EEG neurofeedback, results suggest modulation of neural pathways comodulated during amygdala-based targeted rt-fMRI-nfb.[26,27] Furthermore, correlations between amygdala fMRI activity and frontal EEG asymmetry during amygdala-based rt-fMRI-nfb training in patients with depression also suggests that EEG and fMRI-based neurofeedback methods have overlapping mechanisms of modulation.[81] Specifically, the study by Zotev et al.[81] suggests that EEG-based neurofeedback on frontal EEG asymmetry in the alpha band may be compatible with amygdala-based targeted rt-fMRI-nfb. It has also been suggested that a combination of the two methods could enhance emotion regulation training in patients with other psychiatric disorders.[81]

In terms of future directions, multiple researchers in Ruth Lanius' laboratory are analyzing a 20-session randomized controlled trial of alpha-based EEG neurofeedback in patients with PTSD to compare against sham neurofeedback and healthy controls. fMRI data collected throughout the clinical trial will also be analyzed to elucidate further specific neural mechanisms related to changes in symptomatology. In this study,



Converging Findings for EEG & Real-time fMRI Neurofeedback	Studies
Increased recruitment of emotion regulation areas and increased connectivity between emotion regulation regions and the amygdala.	Nicholson et al., 2016a; 2016b; 2018
Decreased amygdala connectivity with threat, fear and defense processing areas, as well as regions implicated in trauma memory.	Nicholson et al., 2016b
Plastic modulation of intrinsic connectivity networks during and after neurofeedback.	Kluetsch et al., 2014; Nicholson et al., 2016a; 2016b; 2018

Figure 1. Converging evidence for neurobiological mechanisms underlying both EEG and real-time fMRI neurofeedback

Solid red lines indicate increased functional connectivity, while broken red lines indicate decreased connectivity between brain regions. Alpha-based EEG neurofeedback that targets abnormal cortical oscillations leads to a shift in amygdala connectivity toward emotion regulation areas and away from threat, fear, and defence processing regions, as well as areas implicated in trauma memory. Decreased DMN activity during EEG neurofeedback is associated with a homeostatic normalization of such activity, with increased SN connectivity and decreased hyperarousal in PTSD patients. Amygdala-based real-time fMRI neurofeedback that targets a localized brain region highly implicated in PTSD emotional responses, which similarly involves increased amygdala connectivity to, and activation within, emotion regulation areas. Furthermore, downregulating the amygdala in PTSD patients is associated with increased CEN and SN recruitment as well as normalized DMN recruitment. In sum, both modalities of neurofeedback lead to a reorganization of amygdala functional connections, in addition to increased emotion regulation activity and plastic modulation of ICNs.

EEG = electroencephalography; DMN = default mode network; SN = salience network; CEN = central executive network; ICN = intrinsic connectivity network; PTSD = posttraumatic stress disorder.

it will also be critical to examine PTSD heterogeneity, and unique responses to treatment among PTSD and its dissociative subtype.[1,19–22]

In summary, observations of altered patterns of neural functioning within PTSD patients have driven efforts to develop novel treatment interventions that target both abnormal brain oscillations and localized anatomical brain regions. Both fMRI and EEG neurofeedback modalities display common evidence for underlying neurobiological mechanisms, where both have been shown to lead to plastic changes in ICNs, as well as changes in emotion regulation regions and amygdala connectivity. In conclusion, PTSD is a debilitating disorder with complex symptomatology and psychopathology, as well as a high degree of comorbidity. Among military members and the Veteran population in Canada, it is clear that PTSD can be difficult to treat and that current therapies are not always effective for all patients. Growing evidence suggests neurofeedback represents a novel adjunctive treatment for PTSD, in addition to a wide range of other psychiatric disorders.[13,18] In light of the promising studies reviewed in this article, neurofeedback offers a novel way to retrain brain circuits under physiologically normal conditions, with associated reductions in symptoms. As such, there is an urgent need for further investigation of neurofeedback in order to fully validate and define the neural mechanisms underlying the therapeutic effect for PTSD. The result of such scientific efforts could lead to a frontline, non-invasive and modern method for treating PTSD and related psychiatric disorders, for military personnel and Veterans.

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New perspectives on the neurobiology of PTSD: High-resolution imaging of neural circuit (dys)function with magnetoencephalography

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ABSTRACT

Introduction: Combat-related posttraumatic stress disorder (PTSD) is increasingly conceptualized in psychiatry as a disorder of dysfunctional neural circuits. Advances in neuroimaging have enabled the study of those networks non-invasively. PTSD is currently assessed using subjective self-reporting to inform crucial decisions, such as fitness to deploy, but objective markers would aid in diagnosis and return-to-deployment decisions. **Methods:** Magnetoencephalography (MEG) allows investigation of neural circuit function via imaging of brain waves (known as neural oscillations) that index information processing in the brain and would prove a reliable, objective, biomarker. These measures of brain function establish how regions communicate to form brain circuits that support thinking and behaviour. **Results:** Studies into intrinsic brain function, both during rest and when engaged in a task designed to tap into cognitive dysfunction, have found these neurobiological mechanisms are disrupted in PTSD and are a reliable objective marker of illness. We now know that these alterations in brain function are directly related to core symptoms of PTSD and comorbid cognitive-behavioural challenges. **Discussion:** Continued characterization of neural function using MEG and related methods will advance understanding of the neurobiology underlying PTSD; allow for the identification of biomarkers that, coupled with machine learning, will aid in diagnoses; provide individualized therapeutic targets for neurostimulation; predict treatment outcomes; and track disorder remission in military personnel and Veterans who are disproportionately affected by this devastating illness.

Key words: brain dynamics, brain oscillations, functional brain imaging, functional connectivity, magnetoencephalography, NATO, neural circuits, PTSD

RÉSUMÉ

Introduction : Le syndrome de stress post-traumatique (SSPT) lié au combat est de plus en plus conceptualisé en psychiatrie comme un trouble des circuits neuronaux dysfonctionnels. Les progrès de la neuro-imagerie ont permis d'étudier ces réseaux de manière non invasive. Actuellement, le SSPT est évalué en fonction d'autodéclarations subjectives pour éclairer des décisions cruciales, telles que l'aptitude à être déployé. Des marqueurs objectifs contribueraient pourtant au diagnostic et aux décisions de retour en déploiement. **Méthodologie :** La magnétoencéphalographie (MEG) permet d'explorer la fonction des circuits neuronaux par l'imagerie des ondes cérébrales (qu'on appelle des oscillations neuronales), lesquelles référencent le traitement de l'information dans le cerveau et constituent un biomarqueur fiable et objectif. Ces mesures de la fonction cérébrale déterminent le mode de communication entre les régions pour former des circuits cérébraux qui appuient la pensée et le comportement. **Résultats :** Les études sur la fonction cérébrale intrinsèque, à la fois pendant le repos et pendant une tâche conçue pour puiser dans la dysfonction cognitive, ont établi que ces mécanismes neurobiologiques sont perturbés en cas de SSPT et représentent un marqueur objectif fiable de maladie. On sait maintenant que ces altérations de la fonction cérébrale sont directement liées aux symptômes fondamentaux du SSPT et aux problèmes cognitivo-comportementaux comorbides. **Discussion :** Les caractéristiques continues de la fonction neuronale d'après la MEG et des méthodes connexes feront progresser les connaissances sur la neurobiologie de l'affection, permettront de déterminer les biomarqueurs qui, couplés avec l'apprentissage machine,

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contribueront au diagnostic, fourniront des cibles thérapeutiques personnalisées en neurostimulation, prédiront les résultats des traitements et suivront la rémission du trouble auprès du personnel militaire et des vétérans, qui sont démesurément touchés par cette maladie dévastatrice.

Mots-clés : circuits neuronaux, connectivité fonctionnelle, dynamique cérébrale, imagerie cérébrale fonctionnelle, magnétoencéphalographie, oscillations cérébrales, OTAN, SSPT

INTRODUCTION

Shell shocked

Posttraumatic stress disorder (PTSD) has variously been called war neurosis, soldier's heart, shell shock, and battle fatigue[1] throughout the ages, but it is found in all walks of life in times of trauma or stress,[2,3] such as natural disasters, war, torture, terrorism, physical, sexual, and/or social abuse.[4] Most people will experience a deeply traumatic event first-hand during their lifetime, and anyone can suffer from PTSD. It does not differentiate, but occurs far more frequently among military personnel and Veterans,[5,6] likely due to their increased exposure to highly, and often repeated, traumatic experiences. Up to a third of these individuals meet diagnostic criteria for the disorder,[4,7] while in the general population, prevalence is approximately 10%.[4,7] Symptoms include intrusive thoughts (i.e., reliving a traumatic experience and nightmares); avoidance behaviours (i.e., becoming emotionally or physically withdrawn); heightened states of vigilance (i.e., the feeling of always being on edge); and dysfunctional cognition, behaviour, and/or mood (i.e., changes in thinking and feeling).[3] The nature of symptoms can vary dramatically between individuals and can be predicted to some degree by personality or previous exposure to trauma.[8] Not only are the primary symptoms debilitating, but there are secondary and often subtle impairments in everyday aspects of cognition, behaviour, and well-being, functioning that most people take for granted. This can have a huge impact on an individual's quality of life, as well as placing an enormous burden on an already strained healthcare system.

Furthermore, PTSD is also associated with increased levels of unemployment, divorce, and homelessness.[9,10] The primary diagnosis of PTSD is often compounded by comorbid conditions such as anxiety and depression, which require their own specific treatment regimen and can make a differential diagnosis and intervention especially difficult. Moreover, it seems mainstream psychotherapy and treatment do not work as effectively in Veterans, given their unique training and life experience.[11] Could a better understanding of neurobiology in this group provide an explanation for the type of PTSD they experience? Would this allow for movement away from one-size-fits-all therapies and toward individualized treatment plans that address the unique etiology of PTSD in military personnel and Veterans?

Mental health challenges, including PTSD, mild traumatic brain injury, anxiety, and depression, have a significant impact on service members. Currently, there is an over-reliance on subjective self-reporting to inform crucial decisions, such as fitness to deploy. However, due to stigma or otherwise, patients are often reluctant to report symptoms. Objective markers that aid in "Go/No Go" decisions will enhance the fighting strength of the Canadian Armed Forces (CAF) and its members, protect individuals, and reduce stigma.

Waves, circuits, and networks

As neuroscience advances and the understanding of neurobiology improves, so too has insight into the etiology, pathogenesis, and neural substrates of PTSD. Increasingly, as with other psychiatric and neurological illnesses, PTSD is framed within the context of dysfunctional brain networks and circuitry.[12] It is understood that specific circuits that control specific cognitive and behavioural functions can be dysfunctional – either innately, perhaps due to genetics, or through environmental factors, like an injury, or any combination of reasons or influences – and that this dysfunction can give rise to psychological deficits, mental and/or neurological disorders.

Non-invasive brain imaging has played a pivotal role in uncovering the neurobiological circuitry involved in psychiatric illness, driven by magnetic resonance imaging (MRI), which can image brain anatomy. This technological revolution – along with extensive preclinical work – led to the neurocircuitry model of PTSD,[13] which posited that the emergent behaviour and cognitive phenotypes of PTSD primarily arise from the interactions among three key neurobiological structures in the brain: the amygdalae, prefrontal cortices, and hippocampi. This theory states the following: that exaggerated amygdalae activity is responsible for maladaptive fear

responses and conditioned associations with traumatic stimuli; that the frontal cortices do not sufficiently suppress reflexive fear and startle responses and fail to extinguish dysfunctional attention and orienting responses; and that atypical hippocampal functioning is responsible for the consolidation and recollection of episodic memories that underlie traumatic re-experiencing and nightmares. Crucially, Rauch et al.[13] proposed that it is not just the maladaptive functioning of these areas in isolation that cause the symptoms of PTSD, but how they connect and communicate with one another, particularly with regards to frontal-amygdalae and amygdalae-hippocampi circuits and interactions.

Research has begun to elucidate the underlying neurobiological abnormalities of PTSD; however, the Holy Grail of psychiatry, and particularly in the treatment of serving personnel and Veterans, would be the identification of unique, non-invasive imaging measures – putatively, biomarkers or fingerprints – that can objectively distinguish those with a disorder from those without. A natural extension of that would be the identification of specific markers that would guide tailored intervention.

METHODS

Making the invisible visible

There has been a move in biological psychiatry to explain disease mechanistically by directly imaging phenomena generated by brain activity, such as electromagnetic signals. Using the increased temporal sensitivity of these methods allows for exploration of the dynamics of neural activity at behaviourally relevant time scales and provides an understanding of the mechanisms of maladaptive brain function that explain how psychopathology can emerge. In line with a shifting consensus in psychiatry, it is understood that psychopathology, in part, reflects dysfunctional brain circuits, and magnetoencephalography (MEG) represents a potent tool for evaluating function in those circuits. MEG measures minuscule changes in magnetic field strength generated by naturally occurring electrical currents in the brain that result from neuronal activity when a person is thinking.[14]

Neurophysiological studies have been less common than the use of fMRI in studies of PTSD, yet they reveal important functional abnormalities to which other more common methods are blind. Neurophysiological imaging, such as MEG (Figure 1A) and electroencephalography (EEG), have confirmed the role of neural oscillations in mental health challenges. Neural oscillations are a functional mechanism the brain uses to process information[15] and to move information around the brain and form circuits, known as functional connectivity. Functional connectivity is the broad term given to measures of brain network function and was popularized by early fMRI studies,[16] yet neural oscillations are only directly measurable using electrophysiological modalities such as EEG and MEG. Neural oscillations are critical to the coordination and integration of information that travels between functionally specialized areas. This mechanism evolved to organize brain circuits spontaneously and dynamically to support goal-directed cognition and behaviour needed for everyday interaction with one's environment.[15,17,18] Moreover, different mental states and behaviours are coded by the different frequencies of oscillations, which vary systemically across different brain regions and in response to cognitive demands, with circuits at different frequencies occurring at both local levels and global (i.e., brain-wide) spatial scales.[19] In essence, neural oscillations and the frequencies at which they operate are a multiplexing method for the brain to process information, and in turn, generate thinking and behaviour.

RESULTS

Neural oscillations and networks in PTSD

The use of MEG as a method has been applied to the study of PTSD, and suggests that disturbances to neural function that impact circuits and networks underlie the development of symptomology and sequelae in this disorder.[20–28] Sophisticated analyses offer a window into brain dysfunction and can reveal mechanistic insights into the underlying microcircuitry that is responsible for functional impairment in a variety of psychiatric disorders, across a variety of frequency ranges, that are thought to play functionally specialized roles in cognition and behaviour. A number of studies have used tasks that incorporate emotionally-relevant or threatening stimuli in examining neural oscillatory activity.[21,29–31] Perception of emotionally-charged combat-related pictures, similar to scenes experienced by those who were deployed and subsequently took part in the studies, have been found to evoke increased neural oscillations in the left hippocampus and amygdala,[32] suggesting their key role in memory and recollection. Elevated amygdala activity has also been observed in soldiers with PTSD for the processing of threatening faces – activity that was

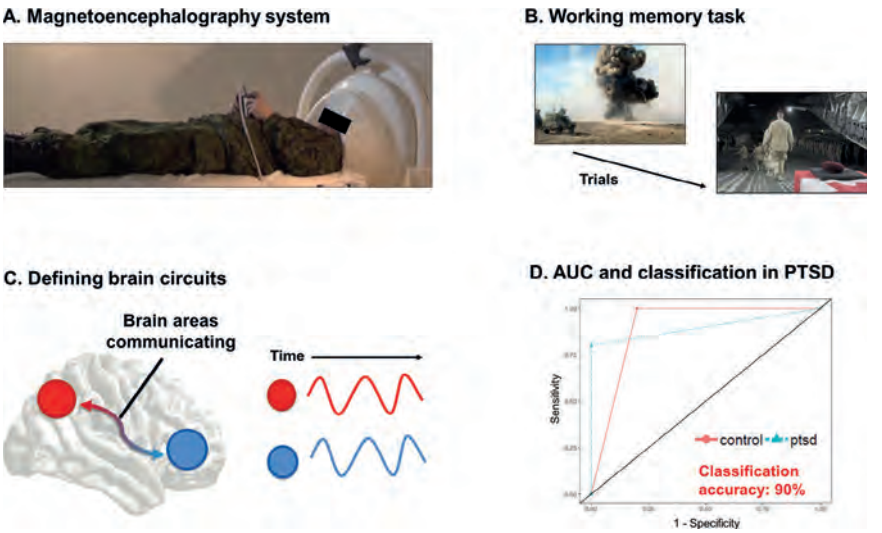

Figure 1. **(A)** Magnetoencephalography system. MEG can be used for non-invasive biomarker identification of mental health challenges in armed forces members and Veterans. The MEG system measures brain function, is completely non-invasive, quiet, non-claustrophobic, fast, and better tolerated than other traditional neuroimaging techniques. Here, a participant lies supine in the scanner with a button response box that they use to make choices in a cognitive paradigm (a memory task in this case, but any number of behavioural or emotional protocols are possible). **(B)** Example slides shown in a working memory task tapping traumatic re-experiencing, shown while inside the MEG scanner, and designed to activate brain networks involved in memory and emotion. **(C)** A short scan allows us to measure brain function and circuits while forming networks that communicate via neural oscillations; these control how the areas talk with one another (e.g., during activation of memory and emotional regions). **(D)** Advances in machine learning algorithms allow us to delve deeply into data for features that can classify an individual case – in this example, we can detect individuals with PTSD at 90% accuracy, compared to participants who were traumatized but did not develop PTSD. The tolerability, sensitivity, and specificity of MEG holds exceptional promise for understanding PTSD, improving diagnostics, and – with longitudinal data – providing a prognostic capability for identifying mental health challenges.

absent during the perception of neutral expressions – suggesting rapid and sustained amygdala oscillations subserve threat assessment[31] and that this activity underlies the neurobiological cause for biases in attention toward danger. In other studies, attention training has been found to directly reduce PTSD symptom severity and modulate associated neural oscillations in several tasks that tap key deficits in PTSD.[33]

Building on the premise that neural oscillations are markers of dysfunction, other studies have shown that neural synchrony, a measure of brain communication and information processing, is atypical in this population and tied directly to negative alterations in cognition, one of the symptom clusters of PTSD. Facets of executive function are known to be compromised in PTSD, a particular complaint of military personnel suffering from PTSD. One such domain is cognitive flexibility, the ability to switch one's train of thought between differing concepts. In a task-switching paradigm (that is, one that taps mental flexibility), soldiers with PTSD show a comparable ability to deal with relatively easy flexibility demands compared to a control cohort, but a reduced ability to deal with difficult rule changes on the fly. When they were able to do these shifts correctly, however, the brain showed elevated oscillatory activity that suggests the brain circuits have to over-engage to cope.[27]

In another study, soldiers with PTSD showed an affective memory bias in visual working memory and delayed recognition task (Figure 1B), exhibiting a reduced ability to correctly identify neutral stimuli after a delay period, but a comparable ability to recall affective stimuli (war-related) when compared to combat-matched peers without PTSD. Again, neural activity was elevated, suggesting a dysfunctional memory system in the brain that is unnecessarily biased or weighted toward remembering traumatic memories, to the detriment of remembering other events.[34]

Implicit threat-perception is adaptive in war but can be detrimental in day-to-day civilian life. Studies using tasks designed to tap this process using threatening faces embedded in an impulsivity task have shown dysfunctional brain responses in soldiers with PTSD. When shown happy faces, no additional neural response was elicited in PTSD, when compared to trauma-exposed peers, but when shown threatening and angry faces, a

fear network in the brain would light up, involving the amygdalae and orbitofrontal cortex.[34] This revealed the brains of military personnel with PTSD were highly attuned to implicit threat, with attention resources biased to such stimuli, driven by an engaged fear network that rapidly processed and prioritized threatening emotional expressions in others, again, to the impairment of typical function. Crucially, these responses are stable over time, in line with stable symptoms.[35]

Other recent studies with the brain at rest in PTSD have examined the role of large-scale (e.g., brain-wide) circuits, rather than regional differences (Figure 1C). Neuronal oscillations and synchrony appear to be directly associated with PTSD and specific symptom clusters. High-frequency oscillations, known to aid in memory function and recall, are found to be anchored in the left hippocampus and distinguish those with PTSD from trauma-exposed controls. These signatures were directly related to PTSD symptom severity, and these functional biomarkers in other areas of the brain, such as the medial frontal areas, were associated with the severity of comorbid depression and anxiety.[25] Furthermore, it was found that triggering and traumatic stimuli, comprised of photographs taken from the war zone in which the soldiers served, could induce changes in neural synchrony in the highly traumatized control group that then resembled the activity of the PTSD group. This exposure to traumatic reminders led to increases in connectivity in brain regions and networks associated with fear conditioning and memory (i.e., amygdalae, hippocampi, etc.). This suggests this brain activity is highly plastic, modifiable by experience, and provides a target for personalized therapy. If those brain rhythms can be normalized, a reduction in PTSD symptoms may be possible.

Further work showed those brain circuits were hyperconnected in PTSD and involved frontal and temporal regions of the brain (Figure 1C), between and within networks (i.e., including the default mode network [DMN], salience, visual [VIS], and dorsal attention network [DAN]). These circuits are involved in remembering the past, thinking about the future, arousal, awareness of self and one's surroundings. Crucially, these differences were found prior to the exposure of affective and triggering stimuli,[26] but could be modulated by those stimuli, suggesting this brain dysfunction is highly amenable to intervention.

Other studies have shown that low-frequency oscillations are also reduced in PTSD and that these patterns of connectivity could differentiate those with PTSD, not only from a trauma-exposed control group but also from those with mild traumatic brain injury (mTBI) and a civilian control group.[36] Importantly, this suggests that measures of neural activity could uniquely distinguish patient groups with common complaints or overlapping symptoms, aiding in a differential clinical diagnosis. Moreover, when pre- and post-triggering scans were compared (i.e., before and after viewing traumatic imagery), changes in neural function evoked by affective imagery were attenuated in the PTSD group, compared to their combat-exposed peers. This was due to an intrinsic and general hyperconnectivity/elevated neural function during the baseline (at rest) scan. This suggests that participants' brains were already engaged and hyperactive, even before viewing traumatic and affective reminders.[36] Additionally, MEG has also revealed a general decrease in brain network organization, where a departure from organized local circuits to disorganized large-scale connectivity[37] is seen. In other words, the brain networks in PTSD are less ordered.

In summary, these studies show that brain function, and specifically neural activity, indexed via non-invasive imaging of oscillations, is dysfunctional in PTSD. These regional changes in brain function, and the brain-wide circuits that regional interactions subserve, are directly related to the core behavioural phenotypes of the disorder. Moreover, they capture the root of negative alterations in cognition, such as problems with memory, attention, and impulsivity, an often-overlooked problem in PTSD. These issues create trouble with day-to-day functioning and can severely reduce a person's quality of life. Importantly, it seems like neural circuit function, particularly function within, and communication between those three key brain structures discussed above – the amygdalae, the hippocampi, and prefrontal cortex – explain many of the reported issues with emotional reactivity, traumatic re-experiencing, avoidance behaviours, and negative mood. These signatures now provide targets in space, time, and frequency in the brain for directed stimulation and neuromodulation, a burgeoning hope in pursuit of precision medicine that has already shown promise in disorders of depression and anxiety.[38]

DISCUSSION

Future directions and applications

Recently, there has been increased interest in developing transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) interventions for PTSD. These

techniques directly modulate neural oscillations and circuits through electrical or magnetic stimulation delivered to the brain. MEG is ideally placed to identify targets of dysfunctional neural activity for sites of stimulation and track the interventional change in individual patients. As already shown, attention control treatment indirectly modulates neural oscillations in line with reductions in symptoms.[30] Could directly modulating these phenomena have the reverse effect and modify dysfunctional behaviour and thinking?

TMS is a safe and completely non-invasive neurostimulation technique that achieves this via the principle of electromagnetic induction. TMS generates tiny electrical currents in a localized region of the brain, modulating the function of neurons in that area. Shielded coils of wire are placed close to the scalp, and a current is passed briefly through the coil, either as a single pulse or train of pulses (repetitive TMS: rTMS). These pulses generate rapidly changing magnetic fields around the coil that modulate neural activity in the region beneath the coil. They travel effortlessly through the scalp and skull, which makes TMS an easy, painless, non-invasive way to stimulate the brain. rTMS has a unique role in understanding how the brain works. Brain imaging techniques such as MEG record brain activity and can tell where and/or when activations occurred. However, they cannot tell if a specific activation is necessary for a given thought or behaviour (i.e., they are purely correlational in deducing brain function). rTMS, on the other hand, can be used to infer causal relations between brain function and behaviour. It can be used to turn specific brain networks on or off, depending on the type of stimulation used, for a fraction of a second. Therefore, rTMS allows for the establishment of causality between brain activations and different types of sensory, motor, and cognitive functions, and allows us to examine whether particular networks are required (or not) to perform a specific task.

Recent years have seen the TMS technique increasingly used in a therapeutic setting, as clinicians seek to mitigate the huge burden of brain disorders by using alternatives to traditional CBT or pharmacological interventions. These neurorehabilitation approaches are increasingly emphasized, given their efficacy in otherwise treatment-resistant cases. rTMS has been rapidly leveraged in adult mental health centres across the country as a therapeutic intervention and is now a Health Canada approved treatment for depression.[38] It is being investigated for use in other disorders, such as autism and PTSD, with preliminary findings showing promising results.[39,40] It achieves this by altering brain function for a sustained period by administering stimulation (<1 hour usually, and as little as 6–10 minutes with refined pulse sequences) to areas of the brain that are underactive or overactive, gradually returning them to healthy patterns of activity.

These pulses can strengthen or weaken the synaptic connections between neurons and fundamentally and safely alter the wiring and plasticity of the brain. These enduring changes in neural connections modulate long-term patterns of brain activity, reversing the abnormal function associated with disease. Mounting evidence has shown it is efficacious in treating a wide variety of neurological and psychiatric diseases, including major depressive disorder, anxiety, post-concussive syndrome, stroke, multiple sclerosis (MS), and motor neuron disease.[38,41–44] These studies have targeted brain regions derived from group-level meta-analyses. Given the heterogeneity of neuropsychiatric disease, and the unique challenges military and Veteran populations present in their treatment needs, individualized targets for precision medicine is critical in ensuring timely care, reducing patient burden and costs. Key to addressing this one-size-fits-all problem is an integration with advanced neurophysiological techniques (including MEG) to define specific regions in patients for stimulation, as the effects of rTMS depend on which brain area is stimulated, and no two patients are exactly alike – despite being diagnosed with the same condition. For example, two patients diagnosed with PTSD might show distinct symptom profiles and benefit from different stimulation protocols (e.g., anxiety and depression vs. memory deficits).

Given this, TMS is often combined with navigation devices that allow accurate localization of the stimulated area. This equipment accurately combines a patient's anatomical MRI image with the position of the coil in space to directly target an underlying brain region. MEG will be able to identify hotspots of abnormal brain oscillations in military personnel and Veterans with PTSD, target those areas with rTMS via a neuro-navigation tool, and stimulate the areas specific to the patient to normalize brain rhythms or re-establish normal networks. Soon, it will be possible to integrate stimulation protocols with neuroimaging to identify brain-based biomarkers (i.e., oscillatory signatures of disease) in individuals, to apply precision medicine and to track treatment efficacy over time. This multi-modal research will address the problem of "everyone-fits-the-mould"

approaches to mental health treatment, a particular problem in the military health service.[11]

While more invasive, deep brain stimulation (DBS) also shows promise in therapy for treatment-resistant and severe cases of PTSD, this would be reserved for the most extreme cases. Canadian institutes are leading the way in this research, with a small-scale study being spearheaded at Sunnybrook Hospital, funded through the Government of Canada's Veteran and Family Well-Being Fund. Again, MEG shows promise in identifying the neural targets that could be modified and ameliorated by DBS therapy.

Rapid developments in MEG technology also promise an increasing use in the field of PTSD research, and that of psychiatric conditions more generally. With the advent of machine learning and pattern classification algorithms, MEG data hold the potential to aid in the objective diagnosis of PTSD, to prognosticate outcome, and to guide individualized treatment strategies. Already, studies using MEG connectomics data, like those described here, are able to reliably identify with over 80% accuracy those with mTBI,[45] and preliminary data using a similar approach provides a robust and reliable way to differentiate those with PTSD from those who were exposed to trauma, but do not have PTSD, at around 90% accuracy (Figure 1D). Crucially, those with traumatic exposure exhibited subthreshold PTSD symptoms, suggesting that MEG data might elucidate subtle neurophysiological differences in individuals who have experienced trauma.

Particularly in a longitudinal context, this approach promises to improve predictions of treatment outcomes and help clinicians determine when it is appropriate to return to work/play/deployment. MEG could be used as a screening tool to identify military personnel who may have pre-existing neurophysiological risk factors for the development of PTSD following traumatic exposure. For example, soldiers might be scanned during training and before deployment in much the same way eyesight or physical fitness is assessed. Similarly, exciting developments in mobile cryogen-free systems, via optically pumped magnetometers, also have the potential to be deployed by first-responders or during battlefield deployment[46] to assess the impact on brain function during battlefield deployment.

Conclusions

MEG has played a significant part in our understanding of the neurobiology and pathophysiology of PTSD and will continue to be a potent tool in studying mental illness generally. Its ability to examine neuronal function and brain dynamics at an incredibly rapid timescale, together with its ability to resolve the functional circuits of the brain, have provided powerful explanations for the core behavioural phenotypes of PTSD. Moreover, it has also proven useful in mapping the often subtle neurophysiological abnormalities that contribute to peripheral and comorbid cognitive sequelae of posttraumatic reactions. Furthermore, in combination with rapid progress in advanced analytics, such as artificial intelligence and machine learning for diagnostics, treatment strategies like targeted neuromodulation and rehabilitation, and advances in cryogen-free, room-temperature sensors, MEG will continue to contribute to our understanding of PTSD and aid in the development of individualized medicine and enhance the operational readiness of troops.

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Using VR-based interventions, wearable technology, and text mining to improve military and Veteran mental health

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ABSTRACT

Introduction: Virtual reality (VR)-based interventions, wearable technology and text mining hold promising potential for advancing the way in which military and Veteran mental health conditions are diagnosed and treated. They have the ability to improve treatment protocol adherence, assist in the detection of mental health conditions, enhance resilience and increase a patient's motivation to continue therapy. **Methods**: This article explores five cutting-edge research projects designed to leverage VR-based interventions, wearable technology, and text mining to improve military and Veteran mental health. A computer-animated virtual agent provides online coaching for posttraumatic stress disorder (PTSD) patients in their own homes to enhance treatment compliance. A head-mounted display safely immerses PTSD patients in a virtual world to relive past experiences and associate them with new meanings. Gaming and simulation technology are tested as a way to improve resilience and performance in military members in deployment-related scenarios. Guidelines are developed for the creation of wearable assistive technology for military members and Veterans. Text mining is explored as a way to assist in the detection of PTSD. **Results**: VR-based therapy, gaming and simulation, wearable assistive and sensory technology, and text mining hold promise for diagnosing, monitoring, and treating military mental health conditions. **Discussion:** The five research projects presented have made promising contributions to the field of military and Veteran mental health, either by advancing diagnostic trajectories, contributing to therapy or enhancing the process by developing new approaches to delivering preventive or curative care.

Key words: military and Veteran mental health, NATO, PTSD, simulation technology, text mining, virtual reality, VR-based interventions, wearable technology

RÉSUMÉ

Introduction : Les interventions en réalité virtuelle (RV), les technologies prêt-à-porter et l'exploration de texte offrent le potentiel non négligeable de faire progresser le diagnostic et le traitement des troubles de santé mentale chez les militaires et les vétérans. Elles peuvent améliorer l'adhésion au protocole de traitement, contribuer au dépistage des troubles de santé mentale, accroître la résilience et améliorer la motivation du patient à poursuivre le traitement. **Méthodologie** : Le présent article explore cinq projets de recherche de pointe conçus pour stimuler l'utilisation des interventions en RV, de la technologie prêt-à-porter et de l'exploration de texte afin d'améliorer la santé mentale des militaires et des vétérans. Un agent virtuel animé fournit un encadrement en ligne au domicile même des personnes présentant un trouble de stress post-traumatique (TSPT), afin de favoriser l'adhésion au traitement. Un visiocasque immerge les patients ayant un TSPT en toute sécurité dans un monde virtuel pour leur faire revivre des expériences et les associer à donner de nouveaux sens. Les jeux vidéo et la technologie de simulation sont mis à l'essai pour améliorer la résilience et le rendement des militaires dans le cadre de scénarios liés au déploiement. Des directives sont en cours d'élaboration relativement à

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la création de technologie d'assistance prêt-à-porter pour les militaires et les vétérans. L'exploration de texte fait l'objet de recherches pour contribuer à dépister le TSPT. **Résultats** : Les traitements en RV, les jeux vidéo et la simulation, le port de technologie d'assistance ou de technologie sensorielle prêt-à-porter et l'exploration de texte se révèlent prometteurs pour le diagnostic, la surveillance et le traitement de troubles de santé mentale chez les militaires. **Discussion :** Les cinq projets de recherche présentés apportent une contribution prometteuse au domaine de la santé mentale des militaires et des vétérans, que ce soit en faisant progresser les trajectoires diagnostiques, en contribuant au traitement ou en améliorant le processus grâce à de nouveaux modes de prestation des soins préventifs ou curatifs.

Mots-clés : exploration de texte, interventions en RV, OTAN, réalité virtuelle, santé mentale des militaires et des vétérans, technologie prêt-à-porter, technologie de simulation, TSPT

INTRODUCTION

This article presents five cutting-edge research projects that are designed to leverage VR-based interventions, wearable technology and text mining.

METHODS

1. Virtual coaching

Posttraumatic stress disorder (PTSD) has a high impact on quality of life[1] and, although effective treatments exist,[2] barriers to care still prevent many survivors of trauma, including military members and Veterans, from receiving the care they need.[3] Some of these barriers could be removed with the help of technology, such as systems that allow for participation in online therapy at home. Such systems provide a cost-effective, privacy-sensitive and accessible option for therapy, but also have challenges. One main challenge is the ability to provide patients with personalized support, a factor particularly relevant to exposure therapy for PTSD, as it requires patients to actively confront individualized fears. Virtual agents (computer-generated, animated, virtual human characters) are one way to address this issue, as they have been shown to improve treatment compliance and even treatment outcomes in other domains[4] (Figure 1). However, using a virtual agent for PTSD treatment has its own unique challenges. Therefore, the technology for the Virtual E-coaching and Storytelling for PTSD (VESP) therapy project sought to investigate how a virtual agent could enhance treatment compliance by informing, assisting and motivating patients.

Psychoeducation is an important part of exposure therapy for PTSD, as it provides information to patients about why it is helpful to confront traumatic memories.[5] In standard therapy, such information is usually presented by a therapist. A virtual agent could verbally present this information, but technology also offers other options, such as allowing patients to read the text on screen. Presentation by a virtual agent might increase trust in the agent and reading the text may allow a user to better remember the information. To study this further, an experiment was performed where participants were

Figure 1. Four different virtual agents

presented with psychoeducation about expressive writing. One group received the information verbally from a virtual agent, while the other group read text from a computer screen. Afterward, a virtual agent asked both groups to select a negative memory to write about. Data shows that, while participants' attitudes toward the agent and recollections of information presented influenced how well they adhered to the task, neither of the groups was directly affected by the way in which the information was presented. However, when controlling for these two factors, the group that received the information textually showed better adherence than the group that received the information verbally from the virtual agent.[6]

The core of exposure therapy for PTSD is the recollection of memories. Given the difficulty of this task, assistance can be very helpful. One potential way for a virtual agent to offer personalized assistance is through asking the right questions. To equip a virtual agent with knowledge on which questions are relevant, at the Technical University in Delft, an ontology was created for traumatic memories. This ontology provided the virtual agent with information about the types of locations, objects and people that are likely to be associated with the memories. Additionally, the ontology stored information about questions relevant to the locations, people and objects. In a study involving recollection of holiday memories, a similar ontology was shown to increase the level of detail provided in answers to an agent's questions.[7]

Due to the difficult nature of exposure therapy, it is important that patients are motivated, as sometimes, symptoms get worse before they get better. To offer personalized motivational messages, a virtual agent requires knowledge of what to say in a particular situation. For this reason, experts were asked to provide motivational statements for imaginary patients who had a specific type of symptom progression and a specific level of trust in a good therapy outcome.[8] Using this input, a motivational system, capable of generating personalized messages, was built. A recent study showed that motivational messages can improve reported motivation and trust, and that personalized motivational messages are particularly important in situations where symptoms initially worsen.[8]

The three studies discussed demonstrate how a virtual agent can inform, assist and motivate patients during home-based, online treatment of PTSD. The multi-model memory restructuring system (3MR) is one version of a home therapy system involving a virtual agent. The system operates with a digital diary to describe memories (Figure 2) and also has a virtual environment where memories can be recreated.[5] This work shows how a virtual agent can help increase detailed memory recollection, adherence to treatment protocol and motivation to continue therapy, with an eventual goal to improve treatment outcomes in home therapy for PTSD as it is thought that this engages patients in performing therapy, and by spending time with it facilitates recall. Moreover, it helps structure and contextualize past experiences.

2. VR Exposure-based Rehabilitation in Immersive Contexts (ERIC): A novel high-tech way to personalize exposure-based treatment of PTSD using VR

Virtual reality (VR) with a head-mounted display (HMD) is a technique that can be used to actualize/

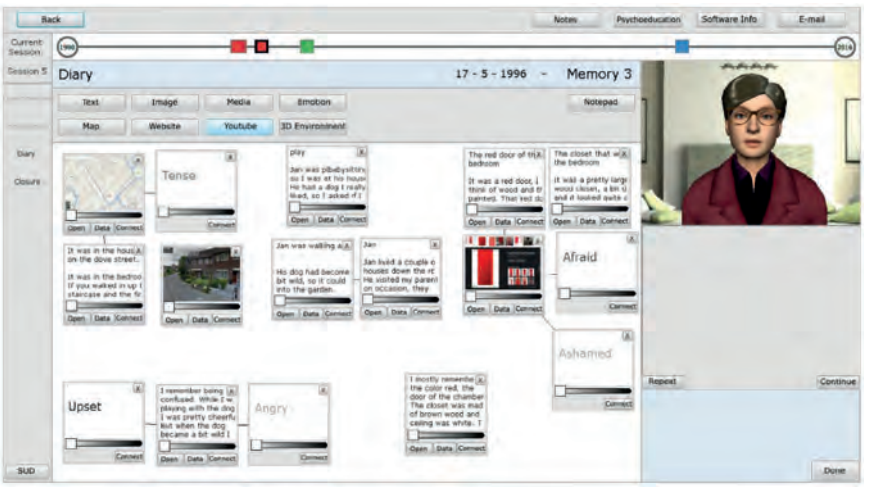

Figure 2. Digital diary to describe memories is a virtual environment in which memories can be recreated

realize the objective of interaction and engagement in a scenario that has taken place in the past. This has benefited the military and Veteran population to simulate battlefield experiences at various locations in the world and personalize experiences. With modern techniques, such as eye tracking, voice-to-text, wearable sensing devices and a protocol based on exposure, an immersive treatment can be offered that has a strong capacity for eliminating anxiety-conditioned experiences and reconsolidating dysfunctional cognitive schemes. Fragmented relaxation exercises can also be built into VR so patients can create a phased exposure. Finally, there is a narrative element in the VR environment that can provide new meaning to experiences and store them in a personal document.

VR is an advanced form of human-computer interaction[9] that enables users to interact with computers and digital content in a more natural and sophisticated manner compared to what is provided by standard keyboard or mouse devices. Immersive VR can be produced by combining computers, HMDs, body-tracking sensors, specialized interface devices, and real-time graphics to immerse a participant in a computer-generated, simulated world that changes in a natural and intuitive way using head and body motion. This project (named below) offers a novel way to provide graded exposure in a virtual world. Novel VR exposure-based therapies are increasingly reliant on immersion and gamification. Typical HMD systems allow for an immersive world that provides participants with the ability to explore sensations, feelings and memories in a safe environment, and interact with elements that remind them of the distant past. The Military Mental Health Care of the Dutch Armed Forces developed a novel VR-based interactive system built on layers of immersion in a virtual world. The project was exposure-based and focused on immersion and guided imagery with personal pictures. The approach was similar to the novel 3MR,[10] except this system is used in a sedentary position.

VR with HMD is a technique that can be used to actualize/realize the objective of interaction and engagement with a scenario that has taken place in the past.

Sometimes, patients cannot properly enter an imaginary state. Even when they can, a therapist cannot always imagine exactly what they see. As a result, the patient often has to describe both their feelings, as well as the imaginary vision being experienced. This may affect the patient's ability to remain immersed in the imagined state. In close co-operation with the Military Mental Health Care Unit of the Royal Netherlands Army, the Simulation Centre of the Netherlands Armed Forces in Amersfoort built a VR demonstrator, called the Exposure-based Rehabilitation in Immersive Contexts (ERIC). Using ERIC, a patient can be immersed in a chosen, safe virtual world, such as a beach, study or forest, while seated in a chair. The patient is seated at a table that houses a series of control elements, including a radio, objects to reduce fear, and has visual and verbal 3D contact with a therapist through a virtual TV. The patient is asked to organize a series of self-selected photos into a book and supply them with cognitive and affective stamps (Figure 3). The therapist will help with ordering and rating the cognitions associated with the trigger images and will follow the patient's gaze with a built-in eye tracker. The patient will learn to tolerate traumatic affect and identify cognitive associations with trigger images, while having the ability to control their exposure.

Exposure will be offered through a stepped approach and relaxation exercises can be used in the virtual world. Several techniques are available to practice self-control under conditions of increasing exposure, including biofeedback (visualization of heart rate alterations to mitigate fear), battle breathing and relaxation exercises such as listening to music. Sessions are designed to allow participants to control exposure in the immersive virtual contact. Since the connection between the subject and the therapist is virtual, this approach can be used either in standard settings, where the patient and therapist are in the same physical location, or from a distance, when the patient and therapist cannot be in the same physical location due to travel time or other reasons.

This project is a work in progress, aimed to optimize personalization for military members and Veterans with PTSD.[11] Future directions include: implementing text to speech to capture connotations for images, including triggers to reduce fear, controller-free interaction, event logging, external sense stimulation with heat, wind and smell, and more. During development, the product will be tested by the Military Mental Health Care Unit and will be validated by an official military authority for operational use.

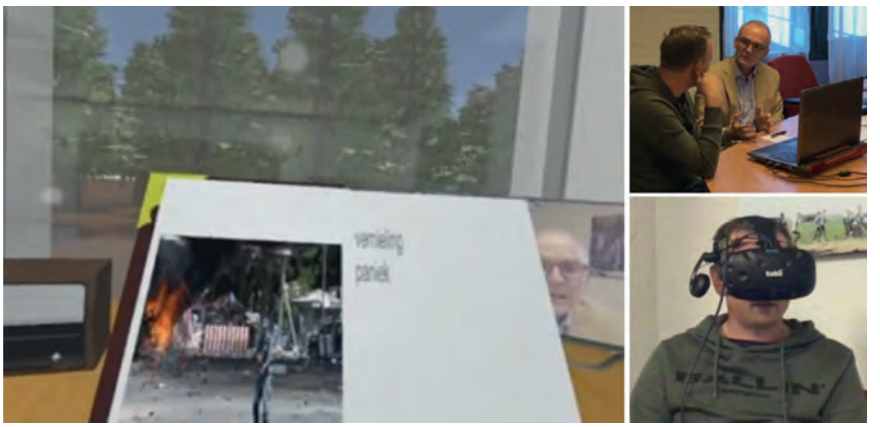

Figure 3. VR view from the HMD of a patient. A book on a table displays self-selected images. The self-selected images are displayed on the left page. Text to describe memories and emotions connected to the images can be added on the right page. A computer screen on the table of the patient (left) allows for virtual contact with the therapist. The window outside displays a virtual world that can be changed according to needs. Behind the book there is a radio where the patient's favorite music can be played, serving as reminders for the images displayed. Between images, there is opportunity to play distractor games, or perform relaxation techniques. This environment is calibrated to increase the overall immersion of the experience to maximize engagement. On the right are pictures of the setting of the intervention.

VR = virtual reality; HMD = head-mounted display

3. VR gaming and simulation to induce, measure, and gather feedback on the stress response of soldiers: Project AMPERE (augmenting military performance and resilience enhancement)

Dealing with high levels of emotional, cognitive and/or physiological stress is an essential skill of soldiers, since their profession requires performing in complex and high-pressure environments. At the same time, enhancing military resilience and troop performance, ensuring a high level of operational readiness among forces, and providing the best care for military personnel, is one of the most important challenges.[12,13] The Dutch Ministry of Defence launched a research program that examined innovative approaches in resilience and performance education and training. The development of both VR gaming and simulation technology, along with applied miniaturized sensor and monitoring technology, presents a great opportunity for advancing performance in the physiological and psychological resilience of military members who may experience high levels of stress and associated underperformance during deployments. This important opportunity can be harnessed by combining these technologies, as VR gaming and simulation have the potential to introduce military scenarios relevant to the context of future deployments, as well as familiarize soldiers with tasks and duties that induce controllable and relevant stress levels in soldiers. Sensor and monitoring technology can be set to measure, classify and provide feedback on stress responses and has the potential to educate and train soldiers experiencing increases in stress how stress impacts their performance, and how to cope with – and regulate – the impacts of stress. Based on this, a VR simulation and measurement environment were developed by the Netherlands Organisation of Applied Scientific Research (TNO) containing a controllable Virtual Reality Monitoring (VRM) platform.

The VRM platform is comprised of oculus rift goggles to simulate a relevant military task environment (a military patrol mission) and to increase soldiers' immersion within the virtual simulation. Next, muscle stimulation equipment was attached that generated a pain sensation to increase stress and distraction from the task. A fan was synchronized to the screenplay to simulate an airstream whenever the patrol vehicle moved. A game controller was provided to participants to answer questions related to the task in order to measure their performance. The VRM monitoring apparatus consisted of an array of sensors and devices to measure heart rate (HR), heart rate variability (HRV), blood pressure (BP), galvanic skin response (GSR),[14] and saliva cortisol using salivettes.[15] Deriving from HR and BP measures, cardiac output (CO) and total peripheral resistance (TPR) were calculated to classify stress in challenge and threat responses.[16] During task execution, a cognitive

task performance score (CPS) was registered and digitized questionnaires were used to assess mental responses, such as the Dutch version of the State and Trait Inventory[17] and the General Self-Efficacy Scale[18] to assess emotional state. Finally, the threat and challenge state were assessed to attempt to correlate the physiological with the psychological classification of threat and challenge.[19] Sixty-three cadets of the Royal Dutch Academy volunteered to participate during the initial validation experiment and to undergo the simulated military patrol scenario.

Results showed the VRM platform setting is able to increase physiological (HR, CO, TPR, and GSR) responses. Moreover, several psychological outputs, such as state anxiety scores, were correlated with physiological responses (cortisol samples), and the cognitive task performance scores showed a significant increase or decrease per participant. The main impact of the VRM platform was measured in the beginning of the scenario, as the cadets engaged the new environment and had to adapt to the VR task and context. In addition, at the end of the scenario, when the patrol was ambushed, physiological and mental responses increased, to some extent. Although group analyses of variance revealed no significant indices of challenge or threat, in-subject analyses showed a number of participants were challenged to perform well and three even showed indices of being threatened. These results will now be used by the Royal Dutch Academy to develop profiles of soldiers with higher or lower response rates to the simulated stress environment, in an effort to develop tailor-made VR training interventions.

4. Wearable assistive technologies as integrated design solutions: From the lab to the real world

In the field of Veteran mental health and well-being, many new wearable assistive technologies are emerging. These technologies enable the measurement of physiological and behavioural stress markers that can effectively predict a person's experienced level of stress. Predictive stress models, based on neurological data that can be used to control such wearables, are also being introduced. Despite these promising technological developments, there are still barriers to use when it comes to creating assistive technologies that can function in the context of everyday life.

Developing wearable assistive technologies as integrated design solutions would allow these technologies to move into the real world. Assistive technologies should be developed as integrated technical solutions that can function in unpredictable settings. This requires a different approach to technology development, as compared to optimizing the performance of systems, which typically requires testing (isolated) functions in controlled lab environments. Assistive technologies should be developed for those that will actually use them. The technologies should be comfortable to wear, user-friendly, socially accepted and non-stigmatizing. This can be achieved by adopting a human-centered design approach that is sensitive to the socio-cultural contexts in which these technologies will be used.

Three design guidelines to develop wearable assistive technologies into integrated design solutions

Three guidelines to develop wearable assistive technologies into integrated design solutions are proposed below. These insights come from design research conducted at Delft University of Technology in the context of health care innovation.[20,21] When wearable assistive technologies are designed according to these guidelines, there is a higher chance they will be used,[22] and thus able to make a positive impact on people and health care practices (Figure 4).

Guideline 1: Wearable assistive technologies should be appealing

The sensorial and semantic appeal of the technology is important to users considering their acceptance and

Figure 4. Relaxation training glove intended to be friendly, intuitive, and respectful. Design by Felix Quadvlieg

use.[23] Wearable technologies should feel comfortable on the body and should be easy to carry. They should be easy to use, which depends on how the user interface is designed and showcases the functions of the technology. Its form and interactivity should be consistent and should clearly communicate its function. Lastly, wearable assistive technologies can even be enjoyable to use. The materials used in the design can be beautiful, and the manner in which the device functions can be motivating, increasing the likelihood of use.

Guideline 2: Wearable assistive technologies should be respectful

Wearable assistive technologies should not replace human skills but empower users by enhancing sensitivities and capabilities. Designers and technologists require an empathic understanding of people who find themselves in challenging life situations, acknowledging the type of support required, and how technology can assist users in supporting themselves.[24] Wearable assistive technologies should be developed to provide support in respectful and collaborative ways, avoiding situations in which technology dominates or overpowers the user. Designing wearable assistive technologies that provide users with a mechanism to follow, overrule, or ignore notifications, is one way in which technology can be designed collaboratively.[25]

Guideline 3: Assistive technologies should be socially appropriate

Wearable assistive technologies are perceived to act appropriately when they are designed with awareness of the socio-cultural contexts in which they will be used. For example, wearable assistive technologies that are visible as technical devices, and perhaps produce noise, will not be appropriate for use in public settings. Potential feelings of embarrassment and stigma may prevent adoption by users,[25] although benefits of use are clear. Understanding how wearable assistive technologies are socially integrated also contributes to their appropriateness. These technologies have a presence in family life, and may be shared among peers or colleagues, or used to mediate a client-therapist relationship. In such cases, consideration needs to be given to privacy and sociability in order to determine appropriateness.

5. Text mining

The information age has made it easy to store and process large amounts of data, including both structured data (e.g., responses to questionnaires) and unstructured data (e.g., natural language or prose). As an additional source of information in assessments, textual data has been increasingly used by cognitive, personality, clinical, and social psychologists in attempt to understand human beings.[26,27,28] The question of how to handle textual data, and how to combine it with structured data in psychiatric and psychological assessments, remains a major theme to be explored. Two main research questions can be asked: (1) How can applying text mining to narratives, collected in the framework of psychiatric and psychological assessment, be used to make classification decisions (e.g., PTSD)? and (2) How can the outcome of text mining and the item response theory (IRT)-based outcomes of responses to questionnaires be simultaneously modelled to validate the text mining procedure and enhance the quality of the measurement and classification procedure? In an attempt to answer these questions, three research methodologies were applied in this study: text mining for handling unstructured data, IRT for handling structured data, and the combination of these two methods using a Bayesian framework.

RESULTS

A new intake procedure was developed for assisting in the detection of PTSD. It combined the use of advanced text mining techniques and item response modelling in one framework. The research mainly consisted of three parts: a computerized text classification of patients' self-narratives to screen for PTSD, exploring the generalizability of diagnostic criteria for PTSD in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*) using item response modelling, and combining textual assessment of patients' self-narratives and structured interviews in the PTSD identification process. Using 300 self-narratives collected online, a textual assessment method based on the DSM already distinguished people at high or low risk of developing PTSD. The text mining approach resulted in a high agreement (82%) with the psychiatrists' diagnoses and reveals some expressive characteristics in the writings of PTSD patients.[29] Although the results of text analysis were not completely analogous with the results of structured interviews in diagnosing PTSD, it was concluded that the application of text mining is a promising addition to assessing PTSD in clinical and research settings.[29] The generalizability of DSM-5 diagnostic criteria for PTSD to various subpopulations can be explored using IRT techniques. In addition to identifying differential symptom functioning related

to various background variables – such as gender, marital status and educational level – it is also important to evaluate the impact on population inferences made in health surveys and clinical trials, and on the diagnosis of individual patients. It was concluded that the DSM-5 diagnostic criteria for PTSD did not produce substantially biased results in the investigated subpopulations, and there should be few reservations regarding their use.[30]

Considering the positive effects of either text mining or IRT, as discussed above, a combination of two methods was proposed to further strengthen the benefits from both sides. Text mining and item response modelling were used to analyze patient writing and response to standardized questionnaires, respectively. The whole procedure was combined in a Bayesian framework, where the textual assessment functions as an informative prior for the estimation of the PTSD latent trait. Results show that, by adding textual prior information, the detection accuracy is increased, and the test length can be shortened.[30]

This model was adapted from psychiatric datasets to an Internet dataset that consisted of both textual posts and responses to scales related to self-monitoring skills on Facebook.[31] The importance of validating data collected from the Internet was emphasized and the relationship between self-monitoring skills and textual posts on Facebook wall was explored. Textual analysis was conducted via both structured and unstructured approaches. To link the results from these two approaches, the keywords extracted by text mining techniques were mapped onto the framework of Linguistic Inquiry and Word Count (LIWC), a commonly used psychology-related linguistic software package.[32] The variable of the word "family" was found to be the most significant predictor in LIWC. Emoticons and Internet slang were extracted as the most robust classifiers in the unstructured textual analysis. The conclusion was drawn that textual posts on Facebook walls could partially predict users' self-monitoring skills. The accuracy rate is expected to enhance if variables from LIWC, and keywords extracted from text mining, can be used in combination in future studies.

Finally, it can be concluded that the work is important, as the introduction of text mining provides a new perspective to handle structured and unstructured data in a common framework. Text mining, together with IRT, is expected to be a promising tool in psychological and psychiatric assessments in the future.[33] A next critical step is the implementation of this new approaches in current practices of screening and mental health care.

DISCUSSION

The five cutting-edge research projects presented here are designed to leverage VR-based interventions, wearable technology and text mining. They have made promising contributions to the field of military and Veteran mental health, either by advancing diagnostic trajectories, contributing to therapy or enhancing the process by developing new approaches to delivering preventive or curative care.

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COMPETING INTERESTS

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REVIEW

Leveraging technology to improve military mental health: Novel uses of smartphone apps

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ABSTRACT

Introduction: Smartphones have made promising contributions to the field of military mental health by providing novel app-based approaches to enhance training and deployment, data collection, and creating social domains for participants to share information and perform research. **Methods**: This article reviews four applications designed specifically for military members and Veterans that increase mental health literacy, overcome barriers to care, and enhance well-being and performance. **Results:** The Road to Mental Readiness (R2MR) app is an on-the-go training tool based on cognitive behavioural theory (CBT). Unit Victor connects Veterans in a secure chat environment and provides information on available supports. UrMMIND is a pre-deployment tool designed to reinforce healthy behaviours and teach coping techniques. iFeel passively collects and analyses individual smartphone data to detect early signs of depression. **Discussion**: Mobile apps are playing an ever-increasing role within health care and, when designed and integrated correctly, can yield many benefits. While security and privacy need to be carefully weighed and addressed, they hold the potential to empower the end user in a range of novel ways that were not possible before.

Key words: mental health apps, military mental health, NATO, PTSD, trauma resilience, Veterans

RÉSUMÉ

Introduction : Les téléphones intelligents apportent une contribution prometteuse au domaine de la santé mentale des militaires grâce à des approches par application novatrices pour améliorer la formation, le déploiement et la collecte de données et créer des domaines sociaux où les participants peuvent dialoguer et effectuer des recherches. **Méthodologie** : Le présent article passe quatre applications en revue, conçues expressément pour les militaires et les vétérans en vue d'accroître la littératie en santé mentale, vaincre les obstacles aux soins et améliorer le bien-être et le rendement. **Résultats** : L'appli *En route vers la préparation mentale* (RVPM) est un outil de formation « instantané » qui repose sur la théorie cognitivo-comportementale (TCC). *Unit Victor* permet aux vétérans d'échanger dans un environnement de clavardage sécurisé et fournit de l'information sur les mesures de soutien offertes. *UrMMIND* est un outil utilisé avant le déploiement pour renforcer des comportements sains et enseigner des techniques d'adaptation. *iFeel* collige et analyse passivement les données contenues dans les téléphones intelligents de chacun pour déceler les premiers signes de dépression. **Conclusion** : Les applis mobiles jouent un rôle croissant dans le milieu de la santé, et lorsqu'elles sont conçues et intégrées correctement, elles peuvent apporter de nombreux bienfaits. Leur sécurité et leur confidentialité doivent être soigneusement soupesées et respectées, mais les applis ont le potentiel d'habiliter l'usager de diverses façons qui n'auraient pas été possibles auparavant.

Mots-clés : applications en santé mentale, OTAN, résilience aux traumatismes, santé mentale des militaires, TSPT, vétérans

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INTRODUCTION

Smartphones have made promising contributions to the field of military mental health by providing novel app-based approaches to enhance training and deployment, data collection, and creating social domains for participants to share information and perform research.

METHODS

This article reviews four applications, designed specifically for military members and Veterans, that increase mental health literacy, overcome barriers to care, and enhance well-being and performance.

RESULTS

Research and development of the Road to Mental Readiness (R2MR) mobile application

Mental health and resiliency training are priorities for the Canadian Armed Forces (CAF). Thus, the Road to Mental Readiness (R2MR) training program was developed in 2008 to increase mental health literacy, overcome barriers to care, and enhance well-being and performance. Leveraging concepts from similar programs implemented by the U.S. Navy Seals, the U.S. Army BATTLEMIND and the United States Marine Corps (USMC) Combat Operational Stress Control (COSC) program, R2MR was developed as classroom-based resilience training for members and their families across the career and deployment cycle.[1] R2MR is currently the largest mental health and resilience training initiative in the CAF. It is being shared with other Canadian government departments and several military allies.

Perceived improvements following R2MR classroom-based training have been documented for mental health literacy, stress management skills and attitudes toward mental health treatment,[2] yet it has been shown that repetitive application and practice of the skills in the training environment is essential for retention and effectiveness.[3] As such, in an effort to expand and modernize training, and to examine health and wellness in a military context, the CAF designed and developed a mobile application. The R2MR app (Figure 1) is an on-the-go training tool to help manage stress responses, improve short-term performance and long-term mental health outcomes, as well as to promote treatment-seeking behaviours.[4]

The main objectives of the R2MR app are to complement the current R2MR training, to turn R2MR skills into life skills, and to individualize R2MR skills. The content of the app is based on cognitive behavioural theory (CBT) and allows for repeated practice. Specifically, six modules, goal setting, self-talk, visualization, tactical breathing, attention control and working memory, allow users to build CBT-based personal training scenarios to help them achieve mental health objectives. The mental health continuum model module enables users to self-monitor using a visual spectrum, as well as provide access to additional resources for further care.

The R2MR app enables the individualized application of learning and provides the opportunity to leverage the unique technological features of the smartphone. Reminders and gamification (e.g., badges) have been implemented as notifications to potentially enhance motivation for behaviour change. In addition, users can be directed to seek help via GPS location, utilizing integrated maps, and direct dialing. Further, wireless connection (via Bluetooth to wearable sensors) allows for the evaluation of biofeedback on learning and training. The effectiveness of biofeedback (e.g., heart rate) on techniques learned during the R2MR training is currently being evaluated to examine how this feature

Figure 1. Screenshots of the R2MR app highlighting its utilization of the advanced features of the smartphone (including GPS, heart rate biofeedback, etc.)

R2MR = Road to Mental Readiness

influences the ability of the user to reduce stress and optimize performance.

As part of the development and validation process of the R2MR app, a human-centred design was ensured to meet the needs of intended users. Expert review was sought to ensure that the app abided by established mobile design principles[5] and conducted a series of usability studies. Using the concurrent "think aloud" method on Canadian civilians and CAF members, significant insight was gained into the users' internal model, which guided further updates of the app. These updates are crucial to enhance the user experience in order to encourage behaviour change for each population. Specifically, CAF participants, in comparison to civilian participants, were more accepting of the app as a prescribed training tool and were more focused on their progress relative to others, potentially due to their group mentality and competitive mindset. Alternatively, civilians were more open to customizable settings and delivery of training.[6,7]

The R2MR app has been released on iTunes and Google Play so that it is available to all CAF members and civilians. Making the app available online provides a unique opportunity to crowdsource anonymous user analytics and feedback for future research. Further, the R2MR app will be used as the foundation for future work on leveraging immersive digital technologies for mental health and resilience training and therapy.

Development of a novel app for Veterans: Description of No Worries Company and Unit Victor

The No Worries Company was founded by Royal Netherlands Army Veteran Hans Nagtegaal, who is half Dutch and half Canadian. After 10 years of service, Nagtegaal experienced difficulty transitioning out of the Army and adjusting to civilian life. He missed the comradery and the bond he felt with his peers. Whenever Nagtegaal struggled during a difficult time, he felt the need to be around people who knew what he had been through. With the help of private funding, several years of research, and discussions with Veterans and Veterans' organizations, the No Worries Company and its app, Unit Victor, were created.

No Worries Company, with the help of Enviu, developed Unit Victor as a platform for Veterans. It is the result of a two-year research project into the needs and characteristics of Veterans and the Veteran Landscape. As part of this research, many interviews with Veterans were conducted, and the Veterans Institute (Netherlands), as well as the Nationwide Care System for Veterans (Netherlands), were consulted for advice. Many research papers have informed an understanding of the possibilities of sensing moral injury and mental wellness/health through smartphone applications. Early research projects conclude that is it possible to identify indicators of mental well-being – depression, mood and stress – with a smartphone, based on automatically collected data.[8]

Through Unit Victor, No Worries Company aims to help Veterans take the first step toward help by identifying early signals of stress-related behaviour and creating an environment where Veterans can support each other when needed.

During the development of Unit Victor, it became clear that additional research was required for identifying early stages of stress through smartphone data. An additional research project that focuses on this will be conducted separately. It is expected that the development of this additional research will most likely span multiple years. However, the development of the platform that strengthens bonds, provides information, and enables buddy support, has already been completed.

Unit Victor version 1.0 (Figure 2) was formally presented to the Inspector-General of the Royal Netherlands Armed Forces, Lt-Gen Hans van Griensven, on Oct. 25, 2018. As of June 2019, more than 1,500 Veterans were using Unit Victor daily, and that number continues to increase. Many additional functionalities, options, and updates have been added to Unit Victor since its release, based on user feedback.

Three core functions of Unit Victor

1. **Connect** Veterans in a secure chat community: The community is a safe, secure environment only for Veterans. In the Dutch version, participants are cross-checked against the Veterans Institute Database. Unit Victor stimulates the social connection of Veterans and leverages the unique bond that servicemen and women build.
2. Provide relevant **information** on the most important organizations for Veterans, including governmental organizations that offer support and relief, as well as private initiatives that offer help (i.e., job search, discounts, etc.). Offer the latest **news** on Department/Ministry of Defence, Department/Ministry of Veterans Affairs and No Worries Company. In the following months, this will be

Figure 2. Screenshots of Unit Victor

expanded to include news from Veteran organizations and service clubs for Veterans. The possibility of adding **eHealth** modules, such as Headspace and Mind-district, is also being explored.

3. **Self-monitoring.** The stimulation of awareness of one's mental and physical health is an important part of Unit Victor. The first step is insight through the status of habits. By tracking physical activity and phone usage, changes in habits can be observed. Furthermore, users can gain more insight and awareness by providing anonymized data. All participants add to the group average.

Train UrMMIND application: A user story describing the applied use of a smartphone application for advancing deployment preparation

Based on the Canadian R2MR application (according to an unpublished draft by Granek and Boland on the research and development of the R2MR mobile application [unreferenced]), the Netherlands developed a smartphone application tailored to the future national mental health curriculum. The aim of the UrMMIND app is to provide the individual military member with ongoing reinforcement of coping with daily stressors, as well as reinforcement of healthy behaviour (sleep monitoring, combat breathing techniques, stress regulation, e.g., through heart rate variability training). This is specifically tailored to be used in the phase before deployment. The R2MR application demonstrated the possibilities of this concept.[4]

The UrMMIND platform is designed to motivate individual soldiers to better integrate the skills that are learned and to apply them on a regular basis to day-to-day stressors. The training binds various elements that are presented to them in a way that allows the soldiers to better engage and own the material that is provided. The platform will be an added dimension to the impact and effectiveness of in-person training. A first-person perspective of the applied use of the UrMMIND app for military personnel is described below:

> Pte 2nd Class Joanna Vermeer, 26, has served with the Dutch Forces for four years. She is a mother of two children, ages 5 and 6, and wife to Jan, 26, a bicycle engineer. Vermeer recently acquired a military driver's licence for heavy (18 tons+) logistic trucks and was assigned to 140 Heavy Transport Battalion, in the centre of the Netherlands, as a driver. It was announced her platoon would be deploying to Masar I Sharif in northern Afghanistan for six months to

join the NATO Resolute Support Mission. The unit started deployment preparation. During its first meeting, Vermeer's platoon commander explained the tasks of the platoon and introduced the pre-deployment process. In addition to the planning of shooting exercises and tests, extra scheduled physical health checks, including different inoculations, extra fitness training programs, and the mental health training curriculum was programmed. A link to the UrMMIND app was provided.

UrMMIND introduced the mental health curriculum, scheduled the times that the psychologist of the Military Mental Health (MMH) department would come to the unit and explained the first steps of preparation that Vermeer was to complete on her own. Items to be self-completed included a checklist for practical preparations, such as arranging childcare; scheduling medical checks and different vaccinations; scheduling a training week away from the base, and so on. The platform checked if Vermeer had informed primary and secondary family contacts, and advised how to provide unclassified mission-specific information that is meant to be shared with family and friends.

Approximately one month later, Vermeer and the unit were visited by a psychologist, and the MMH curriculum was initiated. After the psychologist provided basic information about risk factors and discussed the impact of being deployed, the next steps and available resources to identify issues were discussed. A number of tools within the UrMMIND app were demonstrated and discussed. After the meeting, Vermeer completed short questionnaires to describe and assess her mental state.[9] She also used the cognitive performance test, in which the user is challenged with a vigilance test. During the tests, physical responses are measured, and feedback is provided to evaluate performance when the user is relaxed and/or tense. In the weeks that followed, Vermeer used the sleep monitor, in combination with a wristband motion watch[10] that provided information about total sleep time and a single subjective item about the sleep quality[11] for reliability and applicability. The mobile platform takes readings through Bluetooth, so Vermeer was not hindered by any wires. Although total sleep time seems sufficient, Vermeer's scores were consistently low on sleep quality. The platform suggested she seek help from a specialist and provided her with contact information and the location of the right person within MMH.

During the meeting with the MMH psychologist, Vermeer recognized she was insecure about her upcoming tour. She had trouble finding proper childcare close to home and was advised to talk to personnel who recently returned from deployment for reassurance and to get connected to the military support unit that manages childcare. Furthermore, based on data from the platform and the sleep diary, Vermeer was advised to change some of her sleep behaviours, to use the breathing training application and the coping flexibility toolbox on the app, to learn relaxation techniques, and to find and practice other coping styles to combat stressful situations.

Throughout the pre-deployment process, the input provided by Vermeer was further monitored and used to define benchmarks and inform the group's readiness evaluations.

Digital phenotyping – The case of mobile monitoring of trauma resilience and iFeel

The widespread use of smartphones opens new possibilities for objective, continuous, passive, and inexpensive behaviour monitoring. This kind of monitoring can be developed to assess deviations in human behaviour related to psychiatric disorders such as depression. Disorders like posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are closely associated with decreased activity, social withdrawal, sleep disturbances and diurnal variation. All of these are expressed and detectable with smartphone functions (number of calls, data usage, etc.).[12] Hence, the usage of smartphones can be a proxy for activity, behaviour, and social interaction. A smartphone app that collects and analyzes behaviour has the potential to detect early signs of depression. Intervention at those early stages is a key element for secondary prevention in MDD.

Over the past two decades, there has been an increased awareness of the psychological consequences of modern military operations. These injuries include, but are not limited to, PTSD, MDD, and substance use disorder (SUD), and can have a devastating effect on individuals, their families and the militaries themselves. Militaries have invested a lot of resources aimed at preventing, identifying and treating these illnesses. Despite these efforts, problems continue to occur, such as suicide and the loss of well-trained soldiers due to ineffective treatments, or an inability to identify problems early enough to provide timely access to evidence-based care.

The extensive use of supercomputers (smartphones), and the vast amount of information they contain, has rendered cellular devices a massive database for

personalized behavioural, social and day-to-day activities. The current study aims to use these computers as a proxy for behaviour to identify the digital phenotype of PTSD patients and to use this identified pattern for resiliency and secondary prevention in high-risk populations.

Once downloaded, the mobile Monitoring of Trauma Resilience (mMTR) app, iFeel.PTSD, will collect general and anonymous information about the behavioural patterns of the participants. This will include: communication patterns (e.g., number and frequency of phone calls, excluding phone numbers; number and frequency of messages from instant message conversations; duration of instant message conversations, excluding content; changes in persons contacted by the user; diurnal time of calls, SMS, etc.), activity patterns (e.g., total distance accumulated, excluding geographical positioning; device usage, such as Wi-Fi and data), diurnal variation and potential sleep changes surmised through screen lock/unlock. All data is completely anonymous with no identifiable information, and the servers are located in Germany.

The iFeel.PTSD app harness smartphone usage and passively collects different behavioural measures was developed to find correlations between changes in the behaviour (as measured by the mobile system usage pattern), and mood fluctuations among PTSD and MDD patients. In conjunction with a supporting website, it also enables the collection of clinical data about patients' moods. In future studies, patients who have suffered from PTSD will be invited to download the iFeel app and will be monitored for a year. Correlations between some behavioural smartphone usage patterns and the level of symptoms and levels of depression experienced, as measured by a patient's Visual Analog Score (VAS)[13] and by the patient's caregiver's education, will be monitored.

The intention is to correlate between behavioural patterns (as measured via smartphone usage) and PTSD assessments (conducted monthly by the caregiver and bi-monthly by the individual). As a result of this process, a large database will be created. If successful, the data gathered will provide an unprecedented wealth of information about parameters and behaviours that are relevant to PTSD. Scientific analysis of this data may lead to the development of digital phenotypes of resilience among PTSD Veterans. iFeel is an essential step toward improving our understanding of the feasibility and acceptability of large-scale remote measurement technology (RMT) of data collection and determining the clinical utility and predictive ability of RMT to predict relapse in the breakdown of resilience (Figure 3).

DISCUSSION

Conclusion

Smartphones have made promising contributions to the field of military mental health. Various platforms have provided novel app-based approaches to enhance training and deployment, data collection, and created social domains for participants to share information and also to perform research. A range of novel apps relevant to the military were reviewed and serve as examples of a range of possibilities to improve mental health. From

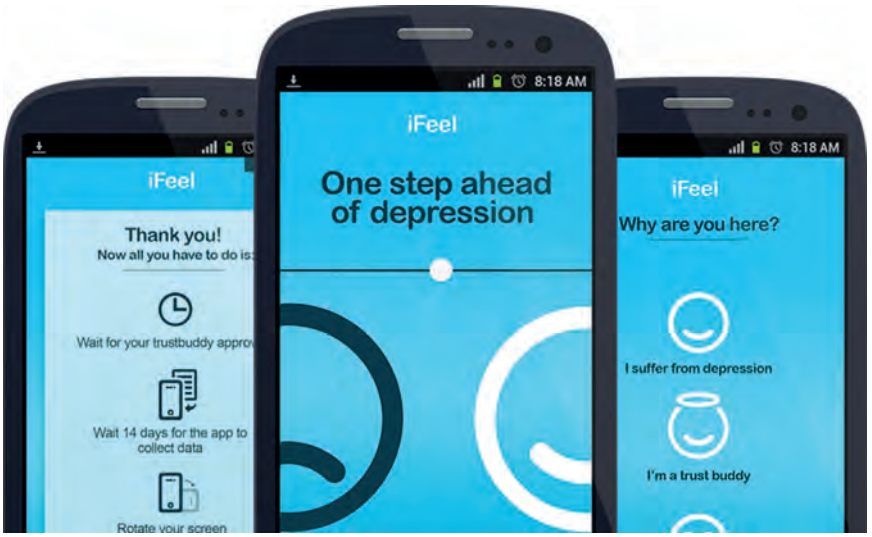

Figure 3. Screenshots of the iFeel app highlighting its utilization of the smartphone

this article, it is clear that mobile apps are playing an ever-increasing role within health care and – when designed and integrated correctly – can yield many benefits. While security and privacy need to be carefully weighed and addressed, smartphone-based apps hold the potential to empower the end user in a range of novel ways that were not possible before.

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Pharmacogenomics: A primer for the military mental health provider

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ABSTRACT

While the basics of pharmacokinetics and pharmacodynamics have not changed much in the past two decades, the world of pharmacogenomics has seen much advancement and refinement. These advances have improved the clinical utility and applicability for those caring for individuals with a range of conditions. Indeed, there are now simple clinical tests that can tell a provider potentially useful information about clinical decisions regarding prescribing practices. This article reviews the basics of pharmacokinetics and drug interactions before covering the concepts of pharmacogenomics and pharmacogenomics testing. Further, it discusses the topic of pharmacogenomics testing as it relates to the practice of military mental health providers. It explores several case scenarios to aid in clinical relevance and understanding. This article also addresses the issue of baseline pharmacogenomic testing; A recent Canadian military example and an in-depth table of commercially available pharmacogenomic tests are provided.

Key words: drug interactions, military mental health, NATO, pharmacogenomic testing, pharmacogenomics, pharmacokinetics

RÉSUMÉ

Les principes de base de la pharmacocinétique et de la pharmacodynamique n'ont pas tellement changé depuis vingt ans, mais le monde de la pharmacogénomique a beaucoup évolué et s'est beaucoup amélioré. Ces progrès en ont accru l'utilité clinique et l'applicabilité pour les soins de diverses affections. En effet, il existe désormais des tests cliniques simples dont les résultats peuvent fournir aux dispensateurs de soins de l'information au potentiel très utile sur les décisions cliniques relatives aux pratiques de prescription. Dans le présent article, les auteurs revoient les principes de base de la pharmacocinétique et des interactions médicamenteuses avant d'aborder les concepts et les tests de pharmacogénomique. Ils traitent également des tests de pharmacogénomique dans le contexte de la pratique des dispensateurs de soins aux militaires en santé mentale. Plusieurs scénarios de cas sont abordés pour contribuer à la pertinence clinique et à la compréhension. Le présent article porte également sur l'utilité d'un test pharmacogénique de référence, donne l'exemple récent d'un militaire canadien et contient un tableau détaillé de certains tests pharmacogénomiques sur le marché.

Mots-clés : Interactions médicamenteuses, OTAN, pharmacocinétique, pharmacogénomique, santé mentale des militaires, tests pharmacogénomiques

INTRODUCTION

Most can easily recall from medical school scrambling to remember the deluge of facts being presented – the seemingly countless hours trying to remember list after list of facts, including long lists of drugs with their specific uses, classes, mechanisms of action, side effect profiles, contraindications, metabolic sites, and myriad other details. Along with this, trying to make the clinical

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connections between these disembodied facts and the suffering patient soon to be seen on clinical rotations. Making such clinical connections is one of the tougher skills, from a learning, implementation, and teaching perspective. With the completion of training and over a decade as board-certified physician, the integration of the *knowledge* and *art* aspects of medicine has become easier. The ability to recite a litany of facts about each drug is no longer a vital skill, unlike the days under the looming threat of the next exam. Having a general sense of each drug – including its side effect profile, the "must know" facts such as contraindications, and an overall picture of use – is likely sufficient for most clinicians for most drugs in most clinical settings. After learning the basic information about the drugs, the majority of the learning is the art, rather than the science, of medicine. The "art" includes the rapport building, the gentle nudges toward one therapy (or toward remaining in therapy), recognizing returning symptoms (possibly before patients do), knowing the limitations, and (hopefully) remaining humble about skill limits no matter how well trained. Within this art of the practice of medicine lies the challenge of incorporating pharmacogenomics – particularly for clinicians who were not trained in it during medical school.

Pharmacogenomics has been an area of increasing interest and improving technology over the past decade. Indeed, the last decade has seen the addition of new lab tests, new mechanistic understanding, and the advent of a consortium dedicated to translating pharmacogenomic understanding for clinical practice. In light of these advances, and with the desire to help facilitate increased understanding for pharmacogenomics, particularly among those who care of military and Veterans, this article will attempt to address some basic topics around pharmacogenomics, interspersed with clinical case scenarios.

WHAT IS PHARMACOGENOMICS?

At the most basic level, bodies interact with medicine (pharmacodynamics) and also process and remove chemicals (pharmacokinetics). In particular, pharmacokinetics processes are core lessons for any medical profession, typically in a beginning pharmacology course, and often go by the mnemonic MADE (metabolism, absorption, distribution, and elimination). Pharmacogenomics is the interplay of genetics and these biological interactions between compounds and various bodily processes. The most well-known and clinically relevant of these areas, currently, when it comes to pharmacogenomics, is metabolism. Metabolism is a basic bodily process that alters a compound in preparation for removal, often through the addition or removal of something such as a methyl group. Genetics determine an individual's baseline level of pharmacokinetics (i.e., metabolic activity). Genetics would also determine the baseline level of pharmacodynamics (i.e., the function of serotonin receptors). Pharmacogenomics is the relationship of underlying genetics to both pharmacokinetics and pharmacodynamics. At this point, most of the knowledge around pharmacogenomics and pharmacogenomics testing relates to pharmacokinetics and, more specifically, to metabolism. The most well-known class of metabolic enzymes is that of the cytochrome P450 enzymes. These enzymes are the major metabolizers of the available drugs in use in medicine today.

WHAT ARE DRUG–DRUG INTERACTIONS?

Drug–drug interactions occur when one drug affects the pharmacokinetics or pharmacodynamics of another drug. Most of these interactions occur within the area of metabolism. One drug affects the metabolic rate of another drug when taken at the same time, resulting in altered plasma levels of a drug. Drugs can affect one another through *inhibition* or *induction*.

Inhibition occurs when one drug decreases the metabolic activity of another drug, most often through inhibition of the metabolic site. Inhibition usually occurs very quickly and lasts for the duration of the administered drug. For example, the antifungal ketoconazole is a potent inhibitor of CYP3A4. Co-administering ketoconazole and alprazolam (a substrate of CYP3A4) would result in higher plasma levels of alprazolam than expected over a longer period of time, as the normal metabolism of alprazolam would not occur and the drug would accumulate. In this case, a patient may only experience some increase in sedation or relaxation, but such additional effects can be severe. When they occur in specific contexts, like driving, it can be life-threatening. Once the ketoconazole is discontinued – for example, after a three-week course of antifungal treatment – then the CYP3A4 inhibition will also cease.

Induction, in terms of a drug interaction, occurs when one drug increases the metabolic activity of the enzymatic pathway for another drug, most often through the creation of additional enzymes. Induction, because it involves creating additional enzymes, can take up to several weeks to reach full effect. For example, if a

patient on a stable and effective dose of buspirone, a CYP3A4 metabolized drug, began a course of carbamazepine (which induces CYP3A4), it is unlikely the patient would initially notice any changes. However, over a few weeks, as the metabolic activity of CYP3A4 is increased, due to additional copies of the enzyme becoming available, the patient would begin to notice less effect from the buspirone. Anxiety symptoms may start to appear, or a general sense of tension may return. Regardless, the increased metabolic activity at CYP3A4 would result in decreased plasma levels of buspirone, and likely decreased or loss of therapeutic efficacy. For many drugs that cause induction, there is a dose-dependent relationship so that changes – in some cases, even a modest change – in dosage will shift the amount of induction caused. Drug–gene interactions, analyzed by pharmacogenetics, are conceptually similar to drug–drug interactions, and may provide more nuanced insights.

WHAT IS PHARMACOGENOMICS TESTING, AND WHAT DOES IT DEMONSTRATE?

Pharmacogenomic testing is simply a test of the underlying genetics of a specific pharmacokinetic or pharmacodynamic action within the body. These tests are often part of a group of tests, for example, for a suite of metabolism sites within the cytochrome P450 system. A handful of these tests have undergone the testing requirements to become commercially available, while others have remained in the research space. It is beyond the scope of this article to discuss all available testing (both commercial and research), so a discussion of some of the commercially available tests is included and the article attempts to focus on some basic information about pharmacogenomic testing.

What pharmacogenomic testing reveals very much depends on the test. Most commonly, pharmacogenomic testing demonstrates the baseline metabolic activity of a given enzyme for a patient, as compared to the typical metabolic activity seen in other humans. There are, in general, four levels of metabolic activity: poor metabolizer, intermediate metabolizer, extensive metabolizer, and ultra-rapid metabolizer.[1] There is variation within each of these categories, creating the potential for a broad spectrum of variation in metabolic activity. Considering the baseline of two functioning alleles for a given enzyme, we can easily see this mapping onto the four categories. A poor metabolizer is likely to have one non-functioning allele along with a hypomorphic allelic variant that is not a high throughput version of the enzyme. An intermediate metabolizer might have two copies of moderately active enzymes or one normal throughput and one non-functioning allele. Extensive metabolizers likely have two functioning alleles, while ultra-rapid metabolizers most likely have extra copies and/or a variation that increases the production of the functional enzyme.

Pharmacogenomic testing reveals the number and type of a patient's alleles and offers the best current knowledge on the typical metabolic activity level of that allele. The resulting reports are sometimes geared toward simple messaging strategies that sum up the information, or the report may simply list the alleles and the expected level of metabolic activity. Most commercial products try to strike a balance between providing detailed information and a summative approach that may be more clinically useful.

WHEN SHOULD A PATIENT RECEIVE PHARMACOGENOMICS TESTING?

Three possible scenarios might lead a clinician to pursue pharmacogenomics testing for a patient. Two of three scenarios are in keeping with current clinical norms, while the third is controversial and not supported by the literature available at this time. The first and most common reason for pursuing pharmacogenomics testing is treatment resistance. The second scenario is when something notable has occurred or is about to occur, such as a recent diagnosis of a complex disorder requiring complicated therapies, or a pending intervention such as surgery. The third scenario is simply to obtain the information as a means of establishing a baseline for a patient so that all future therapies are more informed.

PHARMACOGENOMIC TESTING FOR THE TREATMENT-RESISTANT PATIENT

Probably the most common reason for pursuing pharmacogenomic testing is a patient not responding to multiple interventions. In consultations on this topic, another factor that clinicians mention as consideration for pharmacogenomic testing is when a patient is not experiencing any side effects, despite high medication doses, or they are experiencing near intolerable levels of side effects at very low doses, but not benefiting from the drug. Notably, plasma level testing is often a wise first step, as it confirms that a patient is taking a medication and can provide initial evidence as to whether there is a pharmacogenomic issue. Plasma levels can be obtained for any pharmacologic compound, and estimated

therapeutic windows for plasma levels are available for most compounds of relevance.

Case study 1: "My meds just aren't doing anything"

A 33-year-old, otherwise healthy male military service member with a history of previous deployments was seen for symptoms of depression and posttraumatic stress disorder (PTSD). Over the first year of treatment, the patient had tried paroxetine, sertraline, and venlafaxine without success. He had no side effects from the three medications, despite having been on fairly high doses, and is vehement about being compliant with treatment. A detailed history of the patient's responses to medication finds he also receives little benefit from diphenhydramine, nor does he find it sedating at "regular" doses, requiring him to take as much as 100 mg to feel sedated. The clinician pursued pharmacogenomic testing after first ordering a plasma level for the patient's current medication, venlafaxine, which came back at well below expected levels.

Pharmacogenomic testing showed the patient to have multiple alleles for a highly active version of the CYP2D6 enzyme, meaning he is an ultra-rapid metabolizer at 2D6. The rate of elevated CYP2D6 activity, secondary to allelic variation, is about 1%–2% of the population for those of European, South Asian, and East Asian heritage, while those of African descent have elevated CYP2D6 activity in about 9% of the population.[2] Paroxetine, sertraline, venlafaxine, and diphenhydramine all have metabolism at 2D6. Typical doses, and even high normal doses of these medications, are likely to result in sub-therapeutic plasma levels of the drug and, thus, a perceived lack of efficacy from these medications.

For this patient, given the multiple highly active copies of CYP2D6, the dose required to achieve a benefit would likely be well above currently approved maximums. Such dosing should only be undertaken with a very clear strategy resulting from an in-depth discussion with the patient. Alternatively, the clinician could consider a medication for which the patient has normal levels of metabolism, possibly something metabolized primarily through CYP3A4 or CYP2C19.

PHARMACOGENOMIC TESTING FOR A PATIENT WITH A PENDING SURGERY OR COMPLEX DIAGNOSIS

Another common reason for clinicians to consider pharmacogenomics testing for a patient is in the case of a notable event, such as an upcoming surgery, or if the patient has had a recent complex diagnosis. Such events trigger a series of testing in preparation for, or in response to, the event and may include pharmacogenomics testing. In this scenario, the real question for a clinician when it comes to pharmacogenomic testing is, "What are the likely treatments and what pharmacokinetic or pharmacodynamic measures of physiologic function are important for potential treatments?" In these cases, the likely interventions, potential outcomes, and usual pathways forward are known to any experienced clinician. The goal is to align the experience of the clinician with the potential predictive value of pharmacogenomics testing. For instance, a patient with an upcoming surgical intervention who faces a modest recovery period involving some expected pain and rehabilitation would potentially benefit from pharmacogenomic testing in order to better predict ideal post-operative pain management choices.

Case 2: "I'm getting surgery in a couple weeks, and I hate the recovery"

A 48-year-old female recently retired military service member with a history of depression, hypertension, and orthopedic problems – stemming from her time in service – arrived for a regular appointment. During the appointment, the patient disclosed she was scheduled for surgery in a few weeks for one of her orthopedic problems. The patient was very nervous and unhappy about having the procedure, given her previous experience. She reported a number of previous orthopedic surgeries during which she had difficulties post-operatively due to both poor pain management and excessive sedation from her medications. Given the patient's poor previous experiences, the clinician ordered pharmacogenomic testing to better tailor the patient's post-operative pain management regimen.

Pharmacogenomic testing showed this patient to be a moderate-to-poor metabolizer at CYP2D6. In addition, she was taking duloxetine for depressive symptoms, which is a known inhibitor of CYP2D6. It is likely that the patient was previously treated post-operatively with hydrocodone, one of the most commonly prescribed drugs in the United States,[3] and a pro-drug that requires activation via metabolism at CYP2D6. Her baseline level of moderate-to-low activity at CYP2D6 would likely be exacerbated by the presence of duloxetine, as it substantially inhibits CYP2D6 activity.[4] Post-operative management of this patient would be better served by a drug such as morphine or fentanyl

in the acute post-operative period, followed by a transition to another non-pro-drug narcotic pain medication, or transition to non-narcotic treatments. Awareness of the patient's underlying pharmacogenomics can make a substantial difference for future surgeries. Additionally, providing the patient with information to understand her condition will help her manage her expectations.

PHARMACOGENOMIC TESTING AS A BASELINE

The final potential consideration for pharmacogenomic testing is as a baseline for individual patients. One important reason to consider pharmacogenomic testing at a population level is that as many as 70% of drug treatments initiated are ineffective or cause problematic side effects.[5] Up to 30% of this failure rate is caused by underlying pharmacogenomics.[6] Notably, pharmacogenomics is only a third of the issue. Other issues, such as drug–drug interactions, along with unknowns regarding a patient's pharmacodynamics, likely play a substantial role.[7] Still, such pursuits are worthwhile. To date, the literature is mixed with some successes, including a composite score approach utilizing 2D6 pharmacogenomic data. This composite score[8] predicted an antidepressant response in a Caucasian cohort. A systematic review showed promise for the clinical utility of pharmacogenomics, but the evidence was insufficient to support improved clinical outcomes or cost savings.[9] A more recent meta-analysis showed modest support for improved response and remission rates when treatment includes pharmacogenomic guidance.[10] Of note, these efforts were concentrated in specified populations, such as individuals with depression, rather than the general population. Evaluations in a generalized population would require substantially larger research efforts to assess the potential value of pharmacogenomic testing for treatment guidance, health outcomes, and cost containment.

A RECENT CANADIAN ARMED FORCES (CAF) EXAMPLE

The CAF completed an implementation trial of pharmacogenomics in March 2019. Over 360 tests were administered on three military bases within primary care, mental health, and dental clinics over an 18-month period. Target conditions were not pre-determined as this was a naturalistic study; however, the range of conditions included depression, PTSD, acute pain, chronic pain, and complex medical conditions (i.e., cardiovascular). Further data analysis will occur, with publications and reports expected to follow. In preliminary analysis, Maj Wayne Willmott has yielded indications that there was great satisfaction with pharmacogenomics as a tool by the entire care team, including prescribers, patients, and pharmacists (material from an unpublished draft report by Col Rakesh Jetly on the implementation of pharmacogenetics [PGx] at CAF base medical and dental clinics [unreferenced]). When used, it appears the tool has the expected potential to increase drug safety and improve clinical efficiency. A host of unintended positive outcomes emerged, including perceived increased patient engagement and a more robust team-based approach, bringing together prescribers, pharmacists, and patients. From the same draft report, there was also an indication of increased confidence in managing complex disorders for some professionals, such as nurse practitioners and physician assistants.

The CAF will now, like many other organizations studying pharmacogenomics as a potential tool, determine next steps, including identifying a user group and best practices for use. These lines of thinking and discussion are consistent with, or similar to, the scenarios previously described for when pharmacogenomics should be considered and ordered by clinicians.

CONCLUSION

Pharmacogenomics represents a burgeoning field with substantial potential for benefiting clinicians as they care for individuals suffering from mental health disorders. The rapid nature, and perceived complexity, of the topic can seem like a barrier to clinicians considering the use of such tests for treatment guidance or investigating potential reasons for treatment resistance. The reality is such testing is relatively straightforward, after initial familiarization. There are only a handful of commercially available tests, some of which are listed in Table 1. The websites for many of these tests provide good information on the potential utility of available tests. Some even provide continuing medical education about pharmacogenomics to help providers who may be overwhelmed by the topic.

For references, the most dependable is the Clinical Pharmacogenetics Implementation Consortium (CPIC) which produces rigorous guidelines on how available genetic tests should be used to guide treatment and whether a clinician should order such a test.[11] These guidelines represent some of the best information to make decisions regarding testing. In addition to

Table 1. Some of the commercially available pharmacogenomics tests

Test name	Company	Company location	Product	
			Pharmacokinetic tests	Pharmacodynamic tests
Amplis	CNSDose	Melbourne, Victoria, Australia	Proprietary Pharmacokinetic Polygene Pathway Interpretive Formula*	
Genecept assay	Genomind, Inc	King of Prussia, Pennsylvania, United States	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5	SLC6A4, CACNA1C, ANK3, 5HT2C, MC4R, DRD2, COMT, ADRA2A, MTHFR, BDNF, OPRM1, GRIK1
GeneSight	Assurex Health	Mason, Ohio, United States	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A4, UGT2B15	COMT, ADRA2A, MTHFR, OPRM1
Pillcheck	GeneYouIn	Toronto, Ontario, Canada	CYP1A2, CYP2B6, CYP2C8,CYP2C9,CYP2C19, CYP2D6, CYP3A4/5,DPYD, TPMT, SLCO1B1, UGT1A1, UGT2B15	ADRB2, IFNL3, F2, F5, OPRM1, VKORC1
PGxOne	Admera Health	South Plainfield, New Jersey, United States	ABCB1, CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4/5, CYP4F2, DPYD, SLC6A4, SLCO1B1, UGT1A1, UGT2B15	ACE, ADRA2A, AGTR1, ANKK1, APOB, APOE, ATM, CDA, CES1, CNR1, COMT, DRD1, DRD2, ERCC1, F2, F5, FAAH, G6PD, GRIK4, HFE, HLA-B, HTR1A, HTR2A, HTR2C, IFNL3, ITPA, KIF6, LDLR, MTHFR, NAT2, NOS1AP, NQO1, OPRM1, SCN2A, TPMT, VKORC1
PGxPredict	Transgenomic	Omaha, Nebraska, United States	ABCB1, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5	F2, F5, MTHFR, VKORC1

Note: Information regarding commercially available tests is derived from publicly available information through company websites, scientific journal articles, and direct inquiries.

accessing CPIC guidelines, it is also a good reference for drug interactions that lists both pharmacokinetic interactions, mostly via CYP450, and pharmacodynamics interactions. There are also a number of good texts on the market.

Beyond accessing CPIC guidelines, and purchasing a good reference book, clinicians should understand the outputs provided by tests ordered. Each commercial test aggregates information differently, resulting in a variation in reporting. Becoming familiar with how different reports are structured, and what information, especially assumptions, is contained within each report can be vital to optimizing the use of these reports. This is especially true, given that most of the commercially available tests report as if the patient is on one drug, or only one drug is being considered. Pharmacogenetic testing showing high levels of CYP2D6 activity is important to know, but must be considered in the broader context of other medications, or ongoing health conditions that may play just as critical a role in affecting pharmacokinetics as a patient's underlying pharmacogenetics.

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Biomarkers for military mental health: Insights, challenges, and future prospects

Shawn G. Rhind[a], Gary Wynn[b], Eric Vermetten[c] and Rakesh Jetly[d]

ABSTRACT

Mental health is increasingly being recognized as both a leading cause of disability worldwide and an important area of opportunity for biological breakthroughs. A major limitation in the current diagnosis and management of severe psychiatric conditions is the exclusive reliance on subjective clinical information in the absence of available laboratory tests. A lack of objective biomarkers that reliably identify mental health disorders, and which could serve as targets for diagnosis, treatment response monitoring, and the development of novel therapeutics, remains a fundamental challenge of psychiatry today. Although clinical tests are well established in other areas of medicine, their development in psychiatry has been relatively slow. So far, no biomarkers or other risk markers are available to create profiles to enhance prediction and therapeutic selection in psychiatry. As novel *'omics*-based technologies – such as genomics, proteomics, and metabolomics – and advanced imaging modalities enable researchers to probe the molecular to systemic underpinnings of various disorders, opportunities arise to explore the biological basis for mental health and disease. It is anticipated that specific alterations in blood-based molecular biomarkers, such as DNA, RNA, protein, and metabolite levels, will lead to standardized tests to facilitate diagnosis as they reflect the underlying etiology and mechanisms of disease. They may also pave the way for earlier and more effective treatment and monitoring of patients. Ultimately, the coordinated effort of relevant civilian and military stakeholders – including researchers, physicians and funders – together with standardization initiatives, will be vital to overcoming existing challenges to advance personalized mental health care using sensitive and specific biomarkers.

Key words: big data, biomarker detection, biomarker development, biomarkers, mental health disorders, military members, multi-omics, precision medicine, PTSD

RÉSUMÉ

Il est de plus en plus établi que la santé mentale est à la fois une cause majeure d'incapacité dans le monde et une possibilité importante de percée biologique. La dépendance exclusive envers l'information clinique subjective en l'absence de tests de laboratoire est une limite substantielle au diagnostic et à la prise en charge de troubles marqués. L'absence de biomarqueurs objectifs pour dépister les troubles de santé mentale avec fiabilité, qui pourraient cibler le diagnostic, la surveillance des réponses thérapeutiques et la mise au point de nouvelles thérapeutiques, demeure une difficulté fondamentale de la psychiatrie moderne. Même s'il existe des tests cliniques bien établis dans d'autres secteurs de la médecine, leur mise au point est relativement lente en psychiatrie. Jusqu'à maintenant, il n'existe aucun biomarqueur ni aucun autre marqueur de risque pour créer des profils qui permettront de mieux prédire et choisir des thérapeutiques en psychiatrie. Puisque de nouvelles technologiques « omiques », telles que la génomique, la protéomique et la métablomique, et l'imagerie avancée permettent aux chercheurs de sonder les fondements moléculaires et systémiques de divers troubles, il est possible d'explorer les principes biologiques de la santé mentale et de la maladie mentale. On anticipe que des altérations précises aux biomarqueurs moléculaires à base de sang, tels que les taux d'ADN, d'ARN, de protéines et de métabolites, favoriseront la création de tests standardisés pour faciliter le diagnostic, car ils reflètent l'étiologie et les mécanismes sous-jacents de la maladie. Ils peuvent aussi ouvrir la voie à un traitement plus précoce et plus efficace et à la surveillance

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des patients. Au bout du compte, il sera essentiel de coordonner les efforts d'intervenants civils et militaires (y compris des chercheurs, des médecins et des bailleurs de fonds), combinés aux initiatives de standardisation, pour vaincre les difficultés actuelles et faire progresser les soins personnalisés en santé mentale à l'aide de biomarqueurs sensibles et précis.

Mots-clés : Biomarqueurs, détection des biomarqueurs, développement des biomarqueurs, médecine de précision, mégadonnées, militaires, SSPT, troubles de santé mentale

INTRODUCTION

A quest of contemporary medicine is to provide improved patient care through early intervention and individualized treatments. This is particularly relevant to military mental health, in which a heavy burden of psychological distress and trauma is common. The discovery and development of biological markers (biomarkers) has seen widespread success in various medical fields – notably for conditions such as cancer, heart disease, and diabetes – and this has had a significant impact on condition management and treatment. Biomarkers are present in all parts of the body, including bodily fluids and tissues, and they can be detected on imaging studies or upon examination of various organs. Advances in biomolecular diagnostic technologies have enabled the discovery of an array of molecular biomarkers and are helping in the definition of their role in the pathomechanisms of disease. However, the development of biomarkers to diagnose and predict treatment response for mental health disorders has not kept pace with advances in other areas. No biological indicators are routinely used for major psychiatric disorders. This represents a significant impediment to improving care and developing new treatments for these common and debilitating conditions.

Scope of the problem

Involvement in armed combat or warfare has a profound impact on the mental health and well-being of military personnel and non-combatant civilians.[1–3] According to the World Health Organization's (WHO) Global Burden of Disease study, mental health disorders account for a large portion of the non-communicable global disease burden. An estimated 450 million people worldwide are currently suffering from such conditions, placing mental health disorders among the leading causes of ill-health and disability.[4] Both military and civilians suffer from a similar set of disorders and psychological consequences caused by extreme trauma, including posttraumatic stress disorder (PTSD), major depressive disorder (MDD), anxiety, addictions, dissociation, psychosocial dysfunctions, and suicidal behaviour.[5–8] Indeed, allied military population-based findings show that mental health disorders represent the most important source of medical and occupational morbidity among active-duty soldiers and Veterans.[9–15] Likewise, combat exposure is associated with high utilization of mental health services and mental health disorders are a leading cause of attrition from military service.[16–18] The mental health consequences of military service are dramatically evidenced by high rates of suicide in soldiers and Veterans.[19–21] In fact, the need to cope with rising numbers of mental health casualties of war and conflict continues to spur biomedical innovations in mental health care and research.[1,22]

Collectively, these findings emphasize that mental health disorders are common, disabling, and costly to society at large. Still, these data are just estimates, confounded mainly by the way in which mental health conditions are classified and diagnosed.[23,24] Despite an urgent medical and societal need, no clinically validated biological tests exist for any mental health disorders that can rapidly and reliably delineate normal from disease states or one disease from another.[25]

The ongoing challenge of diagnostic nosology in mental health

It is widely accepted that diagnosis is the rate-limiting step in clinical psychiatry and that the management of mental health disorders is hampered by incomplete knowledge of the biological underpinnings of these illnesses.[26,27] Despite scientific advances in the neuroscience of psychiatric conditions, there remains widespread frustration with the pace of progress in understanding and treating mental health.[28] Thus, there is an ongoing need to expand basic, translational and clinical research to better understand the workings of the brain and why things go wrong.

Current diagnostic categories, as codified in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[29] and the *International Statistical Classification of Diseases and Related Health Problems*, 11th revision (ICD-11)[30] emphasize clinical utility but do not address the biological validity of these classifications.[31] Instead, they define categories using cut-off criteria based on the presence or absence of observed signs/

symptoms in clinical interviews.[32,33] This situation is distinct from other medical diagnostic concepts that are typically linked to specific pathobiological alterations, and it is exacerbated by the lack of an objective biological gold standard for psychiatric diagnoses.[34]

Classification systems based on symptomatology and consensus currently serve a vital role in providing a common language for health providers that ultimately leads to improved clinical care.[35] However, a notable limitation of symptom-based diagnosis is that categories are overtly heterogeneous, incorporating many combinations of symptoms under each category. The boundaries between disorders can be poorly defined due to overlapping symptoms, often with shared comorbidity across disorders.[36,37] Consequently, patient groups are biologically heterogenous and misdiagnosis, or overdiagnosis, are common.[38] As a result, currently accepted diagnostic criteria do not delineate illnesses with high biological specificity, and genetic, neuroimaging and other biological alterations, frequently cross diagnostic boundaries.[39,40] Hence, the ability to align broad-based disease domains with biological marker discovery is particularly challenging.[41]

New discoveries and advanced technologies are transforming the understanding of mental health and represent a hopeful sign the approaches and models that have sustained the field for over 40 years are yielding to a wealth of new data and forecasting the emergence of a renewed and more powerful scientific paradigm.[32,42] Application of genomics, proteomics, and other innovations in neuroscience to develop biological signatures will be an important part of the solution to improve the precision and validity of psychiatric diagnosis.[43–45] As an example, a dissociative subtype of PTSD was included in the DSM-5 criteria based largely on functional neuroimaging results.[46]

Research Domain Criteria (RDoC) and biomarker discovery

In an effort to improve diagnosis and treatment, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project in 2008. It is a classification system for mental health conditions that can be linked to dysfunctional biological pathways based on dimensions of observable behaviour and neurobiological measures.[47] This evidence-based initiative seeks to integrate neuroscientific findings with research in psychopathology to delineate neurocircuitry.[48] RDoC dimensions cover a range of features, from normal to abnormal functioning, to target and identify phenotypes and biomarkers for mental health disorders.[34] These dimensions were created to establish a novel, biologically-informed psychiatric nosology, that combines standardized and validated methods to produce molecular, behavioural, and neurobiological profiles of disorders for improved classification.[49,50]

Adopting an RDoC approach offers opportunities for biomarker identification and development.[51–54] Detecting specific biological signatures, such as mutations identified by genetic screening, abnormal proteins discovered in bodily fluids, or structural and functional features of the brain displayed on neuroimaging, may enable researchers and clinicians to identify those at risk of developing a disorder, contribute to more accurate diagnosis when symptoms alone are ambiguous, and/or help to predict responses to specific treatments.[55–58] By exploring the causes of mental health conditions, and how they can inform interventions to modulate neural pathways, the circuit-based RDoC offers a more practical account of disorders than symptom-based systems.[49,50] Ultimately, this will promote the translational process so that treatment targets are precisely aligned to dysfunctional internal mechanisms relevant to clinical manifestations.[59,60]

APPLICATION OF BIOMARKERS IN MENTAL HEALTH

Biomarkers are measures indicative of a specific disorder, its severity or treatment response.[43,61] They are used widely in many areas of medicine, but biomarker development for mental health disorders has lagged behind.[62,63] Thus, an urgent goal of psychiatric research is to identify suitable biomarkers.[44]

Need for biological markers in mental disorders

There is currently an unmet clinical need for molecular or other biomarkers in studies of major mental health disorders to improve diagnosis and treatment options.[43,64,65] Compared to non-psychiatric conditions, understanding of the pathophysiology of most mental health disorders is limited.[66–68] To date, several biomarkers have been studied for various psychiatric conditions, but their clinical application is still in the early stages.[69,70] Identification of such biomarkers has not yet borne fruit, due in large measure to the fact that these disorders are classified based on established diagnostic concepts.[45,69]

Also, the identification of biomarkers for a disease that has been categorized based on symptoms may not be useful in the clinic if such classifications are inaccurate and confound symptoms across co-occurring disorders.[71,72] Innovative approaches are required for the identification of biomarkers that can be used to classify at-risk patients and those who will likely deteriorate to more severe mental states.[73] Successful identification of biomarkers will advance the field of psychiatry toward the goal of biological tests for improved diagnosis, symptom management, and treatment response.[74,75] Many researchers and clinicians now support of the idea of deconstructing traditional diagnoses in favour of more empirical methods, such as classification through the use of biomarker panels.[76,77] This is not intended as a replacement for existing systems, but as an adjunct to conventional methods.

Definition and classification of biomarkers

Biomarkers are critical to the rational development of medical diagnostics and therapeutics, but substantial confusion persists regarding basic definitions and concepts involved in their use in research and clinical practice.[78,79] Clarification of the definitions of different biomarker classes and a better understanding of their appropriate application could yield substantial benefits to mental health.[25] In 1998, the National Institutes of Health (NIH) Biomarkers Definitions Working Group established a broad definition of a biomarker (Box 1) as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention."[80(p.91)] Subsequently, the Food and Drug Administration (FDA) and the NIH – in their co-published *BEST* (*Biomarkers, EndpointS, and other Tools*) *Resource* – extended the definition to include "measurable characteristics that reflect molecular, histologic, radiographic, or physiologic processes" as types of biomarkers.[81(p.4)]

In this regard, potential biomarkers may be classified into several general categories (Figure 1) based on their specific, measurable characteristics.[81–83]

1. **Susceptibility/Risk** biomarkers indicate the potential for developing a disease in an asymptomatic individual. For example, breast cancer (BRCA1/2) gene mutations predicting antecedent predisposition to breast cancer, and elevated low-density

BOX 1. THE IDEAL BIOMARKER FOR MENTAL HEALTH

Biomarkers are physical characteristics that can be measured or evaluated as an indication of a normal biological process, a disease, or response to a drug. From a practical standpoint, a biomarker would specifically and sensitively reflect a disease state that could be used to diagnose a condition, predict the natural outcome for an individual with this condition, predict whether the individual will benefit from specific treatment or how aggressively to treat them, and assess an individual's response to treatment.

Following are the characteristics of an ideal biomarker:

- It is specifically associated with a disease state and differentiates between similar physiological conditions;
- It can be identified using standard biological tissues, such as serum, saliva, or urine;
- It should be detectable by rapid, simple, accurate, and inexpensive detection methods;
- It should have a measurable baseline and predictable expression level under potential conditions.

In a psychiatric context, biomarkers could be used to predict the development of not only mental disorders, but also personality or behavioural traits, and emotional or cognitive capacity; they could also be used to inform treatment decisions.

Following are some examples of potential biomarkers:

- Specific patterns of neural activity in particular brain regions, detected by neuroimaging, such as fMRI, MEG, PET;
- Specific protein signatures in blood or other tissues;
- Specific gene sequences or single-nucleotide polymorphisms;
- Specific endophenotypes (intermediate traits in causality between genes and diseases), such as biochemical, neurophysiological, or neuropsychological features.

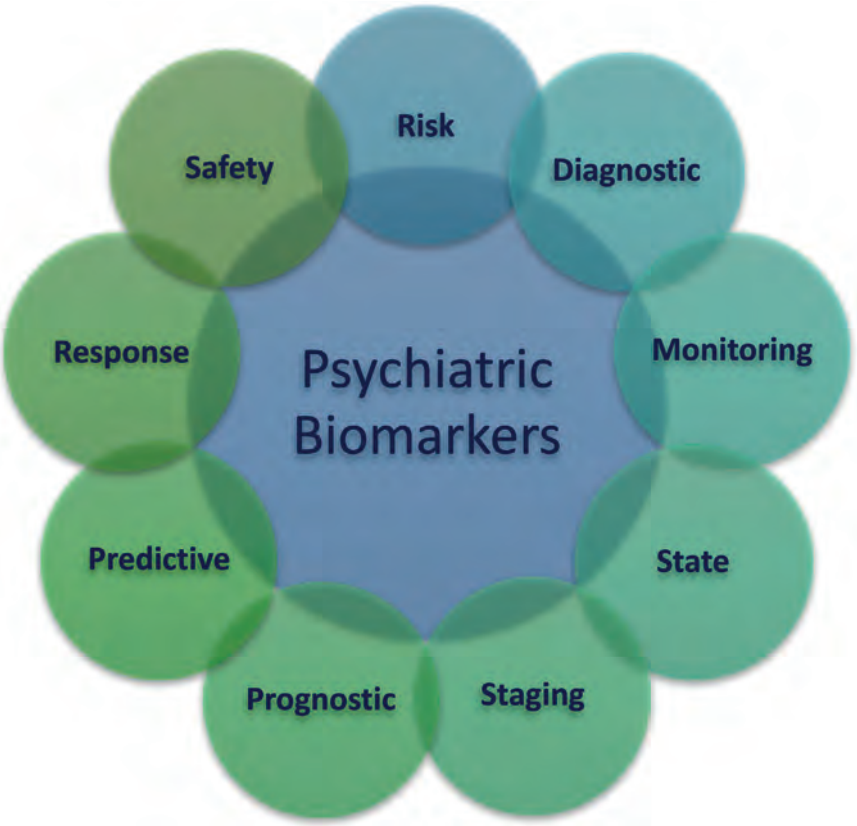

Figure 1. Psychiatric biomarkers

lipoprotein (LDL) cholesterol for risk of coronary artery disease.

2. **Diagnostic** or trait markers identify individuals with the disease or a subset, ideally with no overlap between disorders. For example, cardiac troponin and creatine phosphokinase for diagnosis of myocardial infarction, or neurofibrillary tangles in Alzheimer's disease.
3. **Monitoring** markers can be measured serially to assess changes in disease status. Examples include hepatitis C virus ribonucleic acid (HCV-RNA), or CD4 T-cell counts in HIV infection to evaluate disease status.
4. **State** markers reflect the status or clinical severity of a particular disease process, which delineates the present acuity of an individual disease episode. An example would be reduced brain-derived neurotrophic factor (BDNF) in MDD.
5. **Staging** markers reflect the categorization of an individual's stage of illness or disease severity. An example would be increased natriuretic peptide for congestive heart failure.
6. **Prognostic** markers identify the likelihood of a clinical event or the probable future course of an illness. Examples would include increasing prostate-specific antigen (PSA) for cancer progression, or C-reactive protein (CRP) for unstable angina with recurrent coronary events.
7. **Predictive** markers identify individuals who are likely to experience a favourable/unfavourable effect from a specific intervention. For example, epidermal growth factor receptor (EGFR) mutations forecast the potential for a patient with lung cancer to respond to anti-EGFR therapy.
8. **Response** biomarkers show that a biological reaction has occurred in an individual when marker levels change in response to a therapeutic intervention. An example would be using hemoglobin A1c (HbA1c) for evaluating antihyperglycemic agents in diabetes.
9. **Safety** biomarkers indicate the presence or extent of toxicity as an adverse event related to an intervention. An example would be liver aminotransferases to indicate potential hepatoxicity.

Molecular biomarkers generally refer to biochemical mediators, which can be measured in various biological samples (e.g., tissue, plasma, serum, saliva, spinal fluid,

urine, stools); they include nucleic acids-based markers (i.e., RNA, DNA, gene mutations or polymorphisms), peptides, proteins, lipids metabolites, and other small biomolecules.[84,85] Biomarkers may also be classified based upon technological characteristics, such as imaging or radiographic biomarkers (e.g., computed tomography [CT], magnetoencephalography [MEG], magnetic resonance imaging [MRI], positron emission tomography [PET]).[86,87] Biomarkers rely on available technology, and as more is understood about the biological correlates of psychiatric disorders, the classification of markers across these categories can shift.[82,86]

TECHNOLOGIES FOR BIOMARKER DISCOVERY AND DEVELOPMENT

Methods of biomarker discovery in mental health continue to evolve as new and more powerful analytical technologies are established to screen the products of human cells and tissues.[88,89] The past decade has witnessed impressive advances in the field of large-scale and high-throughput biology, which has contributed significantly to a period of new technology development.[90,91]

Role of *'omic* technologies in mental health

In the post-human genome era, the emergence of large-scale *'omic* detection platforms and high-throughput technologies – based upon the acquisition of broad encompassing datasets from a single sample to identify biomarkers of disease and elucidate novel functional or pathological mechanisms – has revolutionized biomedical research.[92] These new biomolecular techniques stimulate recent progress in biomarker discovery, with the ability to uncover relevant markers quickly and without detailed insight into disease mechanisms.

The advent of multi-omics approaches and technologies (see Table 1), used initially to define the universal detection of genes (*genomics* – studies the whole genome) and global mRNA expression (transcriptomics – examines levels of all transcripts within a cell), has rapidly expanded in the last few decades to include studies of proteins (*proteomics* – studies a large subset of proteins present in a cell or tissue), reversible DNA modifications (*epigenomics* – DNA methylation or histone acetylation), metabolites (*metabolomics* – analyzes the complete set of low molecular weight amino acids, organic acids, lipids, sugars), and microbiota (*microbiomics* – surveys the microbial community and its genes in a person) are now incorporated into routine biological methods.[93–95] Ever-evolving omics techniques, employing systems biology approaches by which large numbers of individual molecules can be easily interrogated without *a priori* assumptions, are effective in the generation of new hypotheses and the identification of putative biomarkers in a *post hoc* manner following often serendipitous discovery from system-wide data mining.[96,97] If validated, such hypotheses and biomarkers may influence psychiatric care, which will help propel mental health into the era of precision medicine.[98]

Properties of a biological system are not only defined by the simple addition of elementary functions but also emerge from interactions between features at each level of biological structure (i.e., molecules, organelles, cells, tissues, organs). Systems biology and multi-omics methods accept that complex systems behaviour are better understood if considered as a whole.[99] The ability to have an immediate global molecular view of an individual, compared to probing a single gene or a few components of a cell-signalling pathway, has fundamentally shifted the research paradigm.

Key technologies for biomarker detection

Much progress has been made in the field of biomarker detection technologies.[91] Originally, scientists relied on traditional laboratory research tools, such as gel electrophoresis and immuno-histochemistry, to identify altered gene and/or protein expression.[100] Today, a wide range of techniques are used for the detection of biomarkers, and a number of assays are already available.[101] The principal omics-based tools and techniques used for comprehensive high-throughput biomarker detection and discovery are summarized in Table 1. Automated DNA sequencers enabled the sequencing of genomes; microarray and mass spectrometry permit global transcriptional profiling and lead to large-scale proteomic and metabolomics analysis.[102] These modern omics-based technologies are capable of performing parallel – rather than serial – analyses and can help to identify distinguishing patterns and multiple markers instead of just a single marker. Such strategies represent a central component in the search for novel biomarkers,[103] and these advances have facilitated the rapid expansion of diagnostic methods in routine clinical practice.[92,104] The ultimate goal behind the clinical use of biomarkers is to develop sensitive, reliable, specific, and cost-effective tools for early diagnosis and monitoring of mental health disorders.[105]

The rapid expansion of diagnostic tools, based on developments in multi-omics technologies, can be fundamental for the development of personalized medicine.[106,107] This paradigm rests on recent technological progress that allows much larger volumes of

Table 1. Summary of principal technologies for high-throughput biomarker detection[90,91,158]

Data type	Main platforms and applications
Genomic, transcriptomic	Genome-wide association (GWAS) methods
(DNA, RNA)	• Whole genome cDNA oligonucleotide microarrays, whole genome sequencing (WGS), and whole exome sequencing (WES)
	• Serial analysis of gene expression (SAGE)
	• Next-generation sequencing (NGS): transcriptome sequencing (RNA-Seq), chromatin immunoprecipitation sequencing (ChIPSeq)
	• Gene expression profiling based on alternate RNA splicing
	Individual sequences
	• Real-time (RT)-polymerase chain reaction (PCR)
	• Competitive RT-PCR
	• RNA protection assay
	Analysis of single-cell gene expression
Epigenomic, epigenetic	DNA methylation profiling
	• Methylation at cytosine-based sequences (CpG)
	• Quantitative single-nucleotide polymorphism (methyl-SNP) analysis
	• Histone endonuclease-linked detection of methylation (HELMET)
	Histone modification profiling acetylation, methylation, phosphorylation
	Non-coding (nc) RNA profiling: long ncRNA and micro (mi)RNA
	PCR and nanostring
Proteomic	Two-dimensional (2D) gel electrophoresis (GE) and difference GE (DIGE)
(proteins, peptides)	Mass spectrometry (MS)
	• Liquid chromatography-tandem mass spectrometric (LC-MS/MS)
	• Matrix-assisted laser desorption/ionization (MALDI), time-of-flight MALDI (MALDI-TOF)
	• Quantitative tandem MS
	• Imaging MS
	Immunoassay
	• Enzyme linked immunosorbent assay (ELISA); multiplex arrays
Metabolomic, lipidomic, glycomic	MS-based kits
(metabolites, lipids, carbohydrates)	LC-MS
	Urinary profiling by capillary electrophoresis
	Nuclear magnetic resonance (NMR)
	Oligosaccharide arrays; lipidomic technologies
Microbiomics	Shotgun metagenomics of the "core microbiome," NGS of total DNA: from targeted 16S or QIIME (quantitative insights into microbial ecology)
(bacteria, fungi, viruses)	

accumulating data to be analyzed.[108] Omics approaches are resource-intensive, analytically demanding and require the use of sophisticated statistical and modelling to analyze datasets comprising hundreds to thousands of variables in order to minimize false discovery results.[109] Although these methods are continually evolving, there is still a need for novel approaches to big data analysis, especially with regard to improved network-oriented models that can incorporate multiple data types to fully integrate the complexity of biology in health and disease.[110,111]

Biomarker development

The process of biomarker development comprises five main phases (Figure 2): (1) **Biomarker Discovery**, which

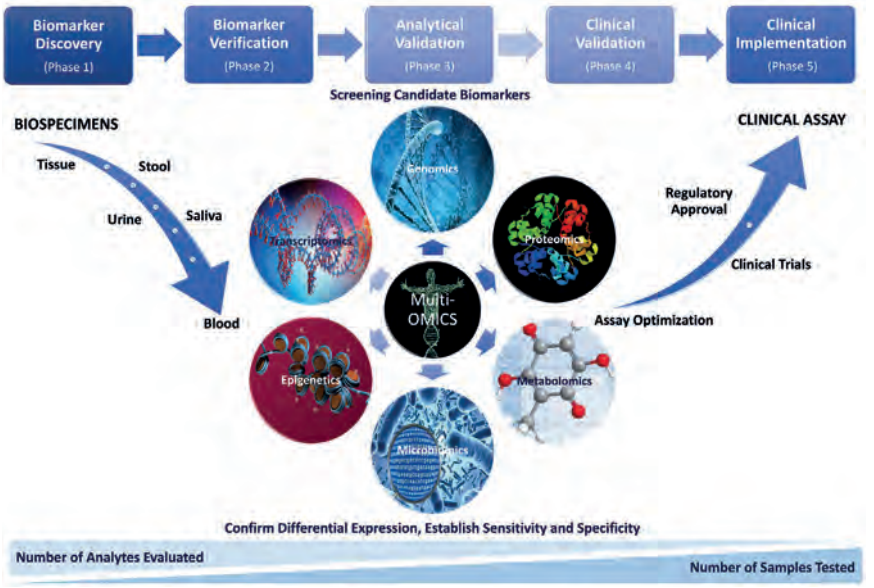

Figure 2. Omics-based biomarker development phases

includes exploratory study to identify potentially useful biomarkers; (2) **Biomarker Verification**, during which the assay is developed and verified to confirm differential expression of candidate biomarkers; (3) **Analytical Validation**, which is performed for optimization of sensitive and specific, reproducible, high-throughput assays; (4) **Clinical Validation**, which assesses the utility of a candidate biomarker for distinguishing between people with and without a specific disorder in larger research cohorts, or to detect preclinical disease in prospective screening studies; (5) **Clinical Implementation**, which establishes regulatory approvals for successfully translating research on biomarker development from the lab to the bedside with high-throughput, multiplexed, low-cost diagnostic assays or clinical tests.

The first step on the path to biomarker discovery is the identification of a candidate marker of disease or its manifestations.[112] To be useful, biomarkers must have at least a moderate level of sensitivity, specificity, and predictive value.[113] Subsequently, the reproducibility of findings in other studies across different populations will test the actual effectiveness of this biomarker. The development of biomarkers requires rigorous clinical validation studies and feasibility and accessibility in particular clinical situations.[114] Biospecimens may derive from cell lines, animal models, or blood samples from patients enrolled in ongoing clinical trials or archived samples from completed studies or biobanks.[115–117] Along with the identification of candidate biomarkers, this step may provide potential therapeutic targets and knowledge on molecular mechanisms by which biomarkers may contribute to the pathological state.[118]

Sample handling is a critical component to be considered in studies aimed at biomarker discovery.[45,119] It is essential to follow standardized protocols during sample collection, storage, and processing, as well as to use validated and well-calibrated analytical methods to achieve robust and reproducible analyses.[115,120] A crucial aspect of the discovery phase is the confirmation of the findings using an independent sample set. The high-throughput nature of omics technologies is well-suited for biomarker discovery since it allows a detailed characterization of biospecimens.[111] But, poor reproducibility and a high number of false positives makes it necessary to undertake both analytical and clinical validation to confirm or reject the suitability of a candidate biomarker in diagnosing or predicting the disease of interest.[121,122]

HOW BIOMARKERS MAY BE USED IN MENTAL HEALTH

Increasing efforts have been made to classify mental health disorders on the basis of objective biomarkers,[25,113] claiming that such markers can clarify the etiology and mechanisms of disorders, confirm a diagnosis, identify at-risk individuals, determine the severity of illness, or predict the clinical course of the disorder.[123] Some authors also suggest that the use of biomarkers might lead to personalized psychiatric treatments and inform the type, timing, and course of interventions to be used, as well as monitoring clinical response to them.[43,124]

Aiding in diagnosis

A logical initial step in biomarker development would be to investigate an association between biomarkers and a specific diagnostic category.[125] This would require identifying biomarkers that can discriminate one diagnostic category from another, as well as separating patients from so-called healthy controls. It would be a breakthrough if a biomarker, or set of biomarkers, were shown to be specifically related to one or more diagnostic categories.

Treatment response prediction

Biomarkers could be used for predicting the response of patients following treatment with specific psychiatric medications.[44] This approach could predict efficacy, potential adverse events, or both.[126] Patients could be divided into sub-groups of likely responders and non-responders and at-risk or not at-risk of developing side effects, respectively.[127] Examples of biomarkers that could be used for this include those derived from imaging techniques, serum assays, genetic profiling, physiological measures, histopathological findings or psychological tests.[43] There are already some commercially available examples of genomic biomarker tests that predict the responses of patients receiving a certain drug based on how quickly that drug is metabolized within the body.[128]

Identifying the staging of psychiatric conditions

There has been a recent focus more on the dynamic nature of psychiatric conditions, as occurs in other disorders.[129] This is particularly true if the origins of a particular psychiatric condition are neurodevelopmental, as this implies an illness trajectory. For example, biological classification of the heterogeneity of PTSD, using a staging approach of disease, has been proposed.[83] A primary rationale for staging is to emphasize the likelihood that distinct therapeutic approaches need to be used, according to the degree of biological progression of the disorder. Similarly, four stages of schizophrenia have been hypothesized: (1) risk, (2) prodromal symptoms, (3) psychosis, and (4) chronic disability. Risk is the stage before detectable deficits occur and the prodromal phase of schizophrenia is now known to be a valid second stage, which occurs before the onset of full-blown psychosis.[129]

Types of biomarkers identified in mental disorders

Converging results from neuroimaging, neuroscience, genetic association studies and measurements of peripheral blood biomarkers, have suggested the presence of several biological themes in the broad context of PTSD and other psychiatric diseases, such as MDD and bipolar disorder.[130–132] Studies suggest that PTSD is likely a systemic illness, affecting not only the brain but the entire body.[133] Therefore, disease markers likely span multiple biological domains, including genes, proteins, cells, tissues, and organism-level physiological alterations.[134] Some of the recurring themes include the identification of biomarkers associated with neuroendocrine hormonal alterations (e.g., cortisol or catecholamines), and dysregulated immune and inflammatory responses (i.e., cytokines, chemokines, growth factors).[135–140] While PTSD and MDD are currently diagnosed based solely on classic psychological and behavioural symptoms, mounting evidence has highlighted a link between these disorders and alterations in immune and inflammatory systems.[141–144]

Epidemiological studies have established that PTSD is associated with significantly higher rates of physical comorbidities in which immune dysregulation is involved, such as metabolic syndrome, cardiovascular disease, and autoimmune diseases. In line with this, a number of blood biomarker studies have reported that, relative to healthy controls, individuals with PTSD exhibit significantly elevated levels of pro-inflammatory markers, such as interleukin (IL)-1β, IL-6, TNF-α, and CRP.[141,143] Likewise, reduced blood levels of BDNF are associated with the pathophysiology of MDD, a useful biomarker for the state of MDD and its treatment response.[145]

Various lines of animal and human research suggest inflammation is not only related to PTSD but may also play an important role in its pathogenesis and pathophysiology.[146] Given the current lack of treatment options for PTSD and major depression, possibilities of new therapeutic approaches using pharmacological and non-pharmacological interventions that have anti-inflammatory effects may be appropriate.[147,148] Despite the growing attention given to the inflammatory pathobiology of PTSD, a great deal remains to be clarified, including more detailed mechanisms of inflammation, the potential usefulness of inflammatory markers as diagnostic/prognostic aides, and efficacy of novel treatment strategies targeting inflammation.[146,149]

The promise of systems biology, big data, and precision medicine in mental health

Precision medicine takes into account the specific characteristics of a patient to personalize prevention, diagnosis,

and treatment.[98] Apart from the relevant clinical and epidemiological information, precision medicine relies extensively on information provided by multiple omics fields. Advances in data science have made it possible to develop specialized tools to collect, store, and analyze vast high-dimensional biological datasets.[150] Developments in bioinformatics, network analytics, and sophisticated machine learning algorithms for the integration of big data from multi-omic datasets have the potential to identify individual markers of interest, or to derive signatures or patterns of many markers, to uncover biological networks that may not have been identifiable using traditional approaches.[151,152] Big data resources for research have attracted increasing interest across health care, but applications in mental health have remained relatively limited to date.[153]

Applying big data analytics is key for tackling the many challenges outlined surrounding heterogeneity, biomarker variability, detecting optimal markers and propelling the mental health field toward translational research.[153,154] Substantial new data has been generated, and there is renewed interest in discovering novel biomarkers for use in patient care and drug development.[100] The goal of these discovery methods is to identify genetic variations or mutations, as well as changes in gene or protein expression or activity that can be linked to a disease state or a response to medical intervention.[155] This has provided new insights into the genetics of mental health and is increasingly being used in drug discovery and assessment of efficacy.[156] In the future, systems biology, big data analytics, along with pharmacogenomics (i.e., the intersection of genomics and pharmacology) may enable the development of innovative approaches in mental health that will be predictive, preventive, and personalized.[106,157]

FUTURE PROSPECTS

Biotechnological advancements have opened a new frontier for mental health research and individualized care. Emerging technological tools and techniques are increasingly used for the diagnosis and treatment of mental health disorders in both civilian and military medical settings, where it may be argued they could improve the accessibility, effectiveness and affordability of individualized care. In particular, the application of multi-omics and imaging technologies enable researchers to probe the underlying biological basis for mental health and disease. This knowledge has the potential to translate into more effective therapeutics.

Technology is advancing the search for new blood-based biomarkers, which have taken centre stage in the development of molecular medicine, to unlock new insights into disease progression and inform clinical research. From proteomics to epigenetic screening, biomarkers and advanced data analytics powered by machine learning are among the most promising technological innovations transforming the military and civilian health care sectors. To date, several biomarkers have been studied for various mental health disorders. Still, given the complexity of these disorders, further research is needed to define a comprehensive panel of biomarkers derived from different platforms to precisely reflect disease-related alterations and improve confirmatory diagnosis and early treatment interventions.

Military medicine is unique, in that clinical care is intimately linked to the imperatives of individual well-being and operational readiness, operational effectiveness, and force sustainability. Military clinicians and commanders must contend with the consequences of poor mental health, while advancing to the strategic goal of preserving manpower and reducing the debilitating impact of psychiatric disorders. This may be achieved in part by implementing high-quality surveillance and screening programs to detect factors that predispose individuals to mental health disorders, providing early intervention strategies for acute war-related syndromes, and treating long-term psychiatric disability after deployment. Likewise, developing reliable and reproducible biomarkers promises a predictor of disease and/or of recovery. Reducing the prediction dilemma for military leaders, clinicians and, indeed, the front-line soldiers that rely on subjective experience alone, will constitute a major leap forward in military health care. Such objective testing would aid in ensuring soldier and unit readiness remains high, while also permitting CAF and NATO forces to recognize the risks and requirements of these specialized populations, and ultimately, to better care for their members.

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REVIEW

Uncovering the heterogeneity of posttraumatic stress disorder: Towards a personalized medicine approach for military members and Veterans

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ABSTRACT

Introduction: Recently, there has been substantial interest in exploring the heterogeneity of posttraumatic stress disorder (PTSD) on a neurobiological level, as individuals with PTSD, including military members and Veterans, vary in their presentation of symptoms. **Methods**: Critically, a dissociative subtype of PTSD (PTSD+DS) has been defined, where a large body of evidence suggests that the unique presentation of symptoms among PTSD+DS patients is associated with aberrant neurobiological underpinnings. **Results:** PTSD+DS is often characterized by emotion overmodulation, with increased top-down activation from emotion regulation areas, which is associated with emotional detachment, depersonalization, and derealization. This is in stark contrast to the symptoms commonly observed in individuals with PTSD, who exhibit emotion undermodulation, which involves decreased top-down regulation of hyperactive emotion generation areas and is associated with vivid re-experiencing of trauma memories and hyperarousal. **Discussion:** This article examines a clinical case example that clearly illustrates this heterogeneous presentation of PTSD symptomatology and psychopathology. It discusses the implications this evidence base holds for a neurobiologically-informed, personalized medicine approach to treatment for military members and Veterans.

Keywords: depersonalization, derealization, dissociative subtype of PTSD, emotional overmodulation, emotional undermodulation, military members, NATO, personalized medicine, PTSD, Veterans

RÉSUMÉ

Introduction : Récemment, on remarque un intérêt marqué pour l'exploration de l'hétérogénéité neurobiologique du syndrome de stress post-traumatique (SSPT), car la présentation des symptômes des personnes ayant un SSPT est variable, y compris chez les militaires et les vétérans. **Méthodologie :** Sur le plan critique et selon la définition d'un sous-type dissociatif du SSPT (SSPT+SD), un important ensemble de preuves indique que la présentation unique des symptômes chez les patients ayant un SSPT+SD dépend de fondements neurobiologiques aberrants. **Résultats :** Le SSPT+SD se caractérise souvent par une surmodulation émotionnelle, comportant une activation descendante accrue des zones de régulation émotionnelle, lesquelles s'associent à un détachement émotionnel, à une dépersonnalisation et à une déréalisation. Cette observation tranche nettement avec les symptômes généralement observés chez les personnes ayant un SSPT, qui présentent plutôt une sous-modulation émotionnelle, rattachée à une régulation descendante accrue des zones de production émotionnelle hyperactives et provoque des réminiscences saisissantes de traumatismes et une hyperexcitation. **Discussion :** Le présent article donne l'exemple d'un cas clinique qui démontre clairement la présentation hétérogène de la symptomatologie et de la psychopathologie du SSPT. Il se penche sur les conséquences de ces éléments probants pour une approche médicale personnalisée du traitement des militaires et des vétérans, reposant sur la neurobiologie.

Mots-clés : dépersonnalisation, déréalisation, médecine personnalisée, militaires, OTAN, sous-type dissociatif du SSPT, SSPT, sous-modulation émotionnelle, surmodulation émotionnelle, vétérans

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CLINICAL PRESENTATIONS OF PTSD SYMPTOMATOLOGY

Posttraumatic stress disorder (PTSD) is a prevalent psychiatric illness that often develops following exposure to traumatic events,[1,2] including those experienced during military deployment. Critically, trauma-related experiences have been shown to have a substantial impact on the mental health of military members.[3] Of importance, PTSD is highly prevalent among Canadian Armed Forces (CAF) personnel,[4,5] where suicide prevention is major concern.[6] Indeed, over the last few years, the field of posttraumatic stress has emphasized the importance of gaining an increased understanding of the neurobiological mechanisms underlying PTSD and trauma-related disorders, in order to prevent illness, improve treatment, and provide optimal functional recovery among patients.[2,7–9]

There has been substantial interest in exploring the heterogeneity of PTSD on the neurobiological level,[2,7] where a dissociative subtype of PTSD (PTSD+DS) has recently been defined.[1] The dissociative subtype of PTSD commonly displays symptoms of emotional detachment, including depersonalization, such as out-of-body experiences, and derealization, where the physical environment appears to be unreal and dreamlike.[1] These symptoms typically occur in addition to those usually experienced by individuals suffering from PTSD, including vivid re-experiencing, avoidance of trauma-related stimuli, alterations in cognitions and mood, and hyperarousal symptoms.[1] Self-report questionnaire examples examining dissociative responses and symptomatology include: "Have there been times where you felt disconnected from your body, as if your body were not your own?" "Have there been times when your body did not feel real?" and "Have there been times when you felt like you were watching the world around you as an outsider, as if the world did not seem real?"[10]

Critically, PTSD+DS patients are often characterized by emotion overmodulation, which leads to attenuated processing within emotion generation areas and is thought to underlie aforementioned symptoms of emotional detachment, depersonalization, and derealization.[1,2,11–14] It has been suggested that PTSD+DS emotion overmodulation represents an extreme form of emotion regulation as a means to control intolerable, overwhelming affect and hyperarousal in the aftermath of trauma. This is in stark contrast to symptoms commonly observed in PTSD patients who exhibit emotion undermodulation, consisting of decreased regulation on hyperactive emotion generation areas with associated vivid re-experiencing, hyperarousal, and hypervigilance.[1,2,13,12,15] Below is a summary clinical case report that clearly illustrates this heterogeneous presentation of PTSD symptomatology and psychopathology.[16] With relevance to trauma-exposed military members and Veterans, similar clinical presentations of PTSD are also typically observed in these populations.

During a devastating car accident that involved over 100 vehicles and multiple deaths, a husband and wife (John and Sarah) were physically trapped in their car for several minutes while they awaited help from rescue workers. It was here that they witnessed a child burn to death and ultimately feared they too would die.[16] When assessed four weeks after this horrific incident, both John and Sarah met criteria for acute PTSD, with respective severity scores of 74 and 86 on the Clinician-Administered PTSD Scale.[17] Remarkably, neither husband nor wife sustained significant physical injury during the accident. Critically, John and Sarah had very different responses to this traumatic event on the subjective, psychophysiological, and neurobiological level, as well as differential responses to PTSD treatment.[16]

First, these individuals differed in terms of their peritraumatic responses to the accident. John reported extreme hyperarousal during and after the car accident and was actively involved in escaping the car by breaking the car windshield, which allowed for their escape. Shortly after the accident, John began experiencing flashbacks and nightmares, whereby these flashbacks were characterized by vivid re-experiencing of the traumatic event. John also began to exhibit significant avoidance related symptoms, such as avoiding highways, and avoiding thoughts and conversations about the accident. Furthermore, John's sleep was significantly impaired along with his concentration, rendering him unable to work. He also reported additional symptoms of hyperarousal such as increased startle responses and irritability. By contrast, Sarah reported being in shock during and after the accident, and experienced significant tonic immobility during the life-threatening event; this included an inability to move or take action while trapped in the car watching the child burn to death. Although Sarah similarly reported experiencing flashbacks and nightmares after the event, these re-living experiences mostly involved emotional detachment, including feeling "numb" and "frozen."

As John did, Sarah avoided driving as well as reading news articles about the accident and was highly irritable and easily angered. Interestingly, Sarah experienced much greater peritraumatic dissociation, whereas John had virtually none. Furthermore, Sarah's sleep was also significantly impaired, in which she was unable to work during this time due to cognitive and concentration impairments.

In the aftermath of this highly traumatic experience, unique symptoms, as well as neurobiological and physiological correlates, were also observed when comparing John and Sarah during a script-driven imagery paradigm.[16] Here, script-driven imagery was used as a method to provoke PTSD symptoms and induce a state of re-experiencing in both patients.[16,18,19] Although both reported re-living the traumatic experience during symptom provocation, only John experienced intense anxiety, arousal, and escape-focused cognitions with a dramatic increase in heart rate. John's pathological responses to the traumatic reminders strongly resembles the traditionally described hyperarousal response to script-driven imagery in PTSD.[15,16,20] By contrast, Sarah reported being emotionally detached and disconnected from her body, with additional symptoms of tonic immobility similar to those she experienced during the time of trauma. Furthermore, Sarah displayed no significant change in heart rate during the symptom provocation paradigm. In terms of clinical changes to PTSD symptoms, after six months of exposure-based therapy for PTSD, John no longer met criteria for PTSD, while Sarah still had clinically significant symptoms of PTSD. Interestingly, both individuals had unique neural activation within several areas of the brain related to emotion regulation, sensory processing, consciousness, awareness, and depersonalization/derealization,[16] suggesting that differential responses to trauma may result from heterogenous neurobiological mechanisms.

In general, this case example highlights the unique subjective experience of trauma, as well as differential symptom manifestation and response to treatment among certain individuals. Furthermore, this clinical case begins to introduce the concept that individual differences in symptom presentation are associated with distinct neurobiological mechanisms in the brain. Indeed, emerging evidence supports the differential neurobiological basis of PTSD and its dissociative subtype, which has important implications for the treatment of PTSD in the military and Veteran population.

THE NEUROBIOLOGICAL BASIS OF PTSD HETEROGENEITY: PTSD VERSUS PTSD+DS

Neuroimaging studies during the last two decades have shown drastic differences in brain activation patterns when comparing PTSD, PTSD+DS and healthy individuals.[2,7,13,14,15] These findings include studies from patients with PTSD stemming from military-related trauma. Interestingly, this is true for a number of functional MRI (fMRI) modalities, such as neural activation and functional connectivity during both symptom provocation and resting state. Below is a summary of the key neurobiological differences with regard to PTSD and PTSD+DS, which may underlie the unique presentation of symptoms in each group.

Emotion modulation within PTSD and its dissociative subtype

Among individuals with PTSD, the brain has been found to be characterized by neural patterns of emotion undermodulation, which correspond to decreased regulation and inhibition from the medial prefrontal cortex (mPFC) and associated hyperresponsiveness within emotion centres such as the amygdala, insula, and midbrain/reptilian brain regions.[2,8,9,12,13,15,21–30] A recent study has shown that during the resting state, patients with PTSD demonstrate reduced functional integration in the central executive network involved in emotion regulation, as well as reduced PFC-amygdala connectivity, as compared to controls, together illustrating emotion undermodulation in PTSD, with reduced regulation on the emotion-generating limbic system.[31] This neural signature of PTSD is related to the clinical presentation of hyperarousal, vivid re-experiencing, and hypervigilance (Figure 1).[2,7,8,14,15,18,32,33] In reference to the clinical case report above,[16] these characteristic phenomena and symptoms were more observed in patient John.

By contrast, patients with PTSD+DS are characterized by emotion overmodulation, which is related to increased top-down regulatory activation from the mPFC, resulting in hypoactivation in emotion generation centres, such as the amygdala, insula, and midbra in.[2,7,8,13,15,18,21,34,35] These neural correlates are related to dissociative symptoms of depersonalization and derealization, as well as increased emotional numbing and detachment (Figure 1),[13–15,18,36] characteristic phenomena and symptoms observed in Sarah in the example above. Studies have shown repeatedly that symptoms of depersonalization and derealization are associated

with increased mPFC activation and decreased amygdala activation.[2,13,14,15,20,35,37] Taken together, the emotion modulation hypothesis suggests the balance between emotion regulation and emotion generation that produce optimal arousal in humans is disrupted in PTSD and PTSD+DS, due to decreased — as opposed to increased — emotion modulation in each patient group, respectively (Figure 2).[2,15,21]

Interestingly, these patterns of neural under and overmodulation in PTSD and PTSD+DS have been

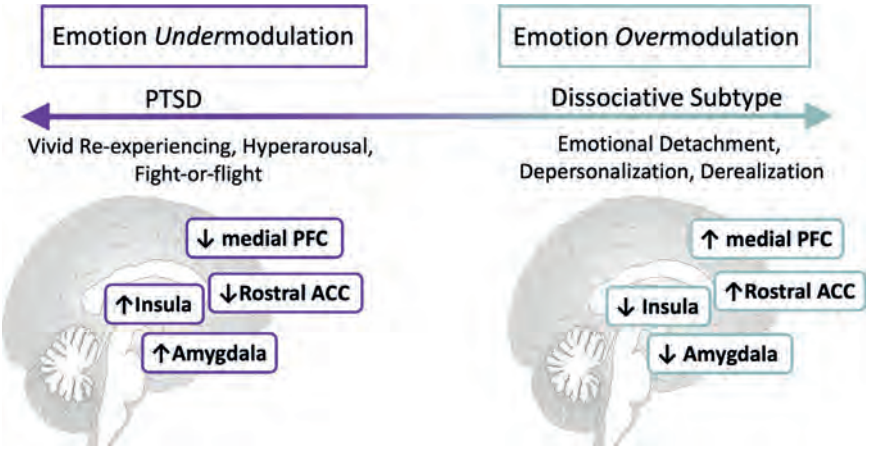

Figure 1. Emotion modulation model of PTSD

Emotional undermodulation is related to decreased regulation from prefrontal brain regions such as the medial prefrontal cortex (mPFC) and the rostral anterior cingulate cortex (ACC). This is associated with hyperactivity in limbic regions, such as amygdala and insula, and the clinical presentation of traumatic memory re-experiencing and hyperarousal symptoms in PTSD. Emotion overmodulation is related to a neural pattern of increased regulation from the mPFC and ACC, associated with decreased responsivity within limbic regions (amygdala and insula). Emotion overmodulation delineates the dissociative subtype of PTSD, in which patients typically experience symptoms of emotional detachment, including depersonalization and derealization symptoms.

PTSD = posttraumatic stress disorder; mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex

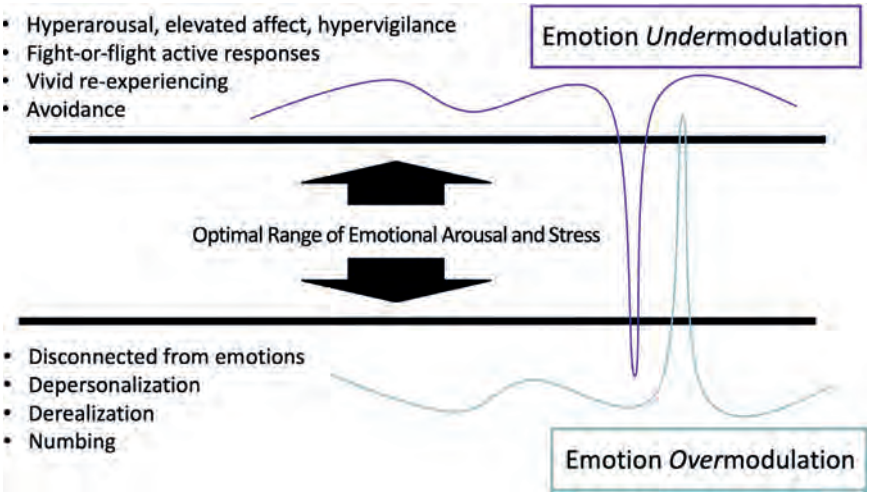

Figure 2. The emotion modulation hypothesis

The emotion modulation hypothesis suggests that the balance between emotion regulation and emotion generation that produces optimal arousal and stress responding in humans is in fact disrupted in patients with PTSD. Patients with PTSD typically display emotion undermodulation, which leads to exacerbated arousal and stress responding, whereas PTSD+DS patients exhibit emotion overmodulation, which leads to a dampening of arousal and stress responding. In relation, PTSD is characterized by elevated symptoms of hyperarousal, vivid re-experience, hypervigilance, intense affect, avoidance of trauma-related stimuli and active fight-or-flight responding. By contrast, PTSD+DS is more characterized by predominately symptoms of dissociation such as depersonalization and derealization, as well as emotional numbing and disconnectedness.

PTSD = posttraumatic stress disorder; PTSD+DS = dissociative subtype PTSD

observed in the brain both during symptom provocation and during the resting state.[2,13,14,15,20,36] This suggests that patients with PTSD have potentiated neural pathways for threat, fear, and emotional processing that may indicate exacerbated defensive posturing during rest.[12,13] Hence, it has been suggested that the neurobiological basis of the resting state is distinctly unique in patients with PTSD when compared to healthy individuals.[12,13]

Moreover, unique patterns of directed connectivity among cortical and subcortical structures during the resting state have also been demonstrated with dynamic causal modelling analyses.[21] This computational method allows one to infer the direction of connectivity or information flow within the brain based on neuroimaging data.[21,38] Here, PTSD patients showed a pattern of predominantly bottom-up information flow from emotion generation and threat processing areas (amygdala and periaqueductal gray) to executive regulation areas (vmPFC).[21] This pattern of connectivity, from emotion generation/threat processing areas up toward executive regulation regions, may further support models of emotion undermodulation, whereby subcortical areas are driving fear and emotional responses in patients with PTSD. By contrast, among PTSD+DS patients, directed connectivity models revealed predominantly top-down information flow from executive regulation areas (vmPFC) to emotion generation and threat processing areas (amygdala and periaqueductal gray).[21] This pattern of neural connectivity, from executive emotion regulation regions down toward emotion generation/threat processing areas, is suggestive of emotion overmodulation in PTSD+DS, which may lead to a dampening of emotions and affect with symptoms of depersonalization and derealization in this group.

This strong contrast in the direction of information flow between emotion regulation and emotion generation/threat processing areas may be an underlying neural mechanism responsible for the unique presentation of symptoms observed in patients John and Sarah from the clinical case report (Figure 3).[16] John may have more bottom-up processing from innate fear and emotion generation areas, leading to symptoms of intense arousal and hypervigilance, with stress-induced increases in

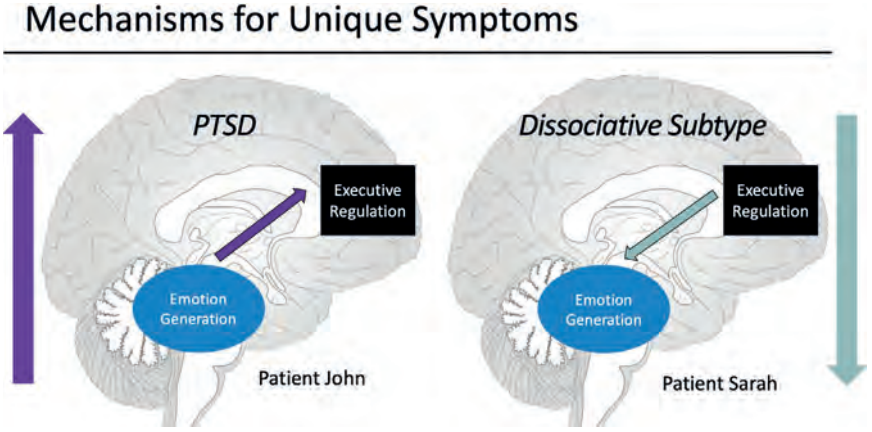

Figure 3. Directionality of connectivity within key brain regions implicated in emotional responding among individuals with PTSD and the dissociative subtype of PTSD[22]

PTSD is characterized by predominantly bottom-up connectivity from emotion generation and threat processing areas (amygdala and periaqueductal gray) to emotion regulation and executive functioning areas (ventromedial prefrontal cortex). In contrast, the dissociative subtype of PTSD is characterized by predominantly top-down connectivity from emotion regulation and executive functioning areas (ventromedial prefrontal cortex) to emotion generation areas (amygdala and periaqueductal gray). This strong contrast in the direction of information flow between emotion regulation and emotion generation/threat processing areas may be an underlying neural mechanism responsible for the unique presentation of symptoms overserved in patients John and Sarah in the summary clinical case report.[17] Here, John may have more bottom-up processing from innate fear and emotion generation areas leading to symptoms of intense arousal and hypervigilance with stress-induced increases in heart rate. Conversely, Sarah may have more top-down processing from emotion regulation regions, thereby inhibiting activation in emotion generation areas leading to emotional detachment, tonic immobility, and dissociative symptoms.[17,22]

PTSD = posttraumatic stress disorder

heart rate. By contrast, Sarah may have more top-down processing from emotion regulation regions, thereby inhibiting activation in emotion generation areas, leading to emotional detachment, tonic immobility, and significantly higher peritraumatic dissociation symptoms.[16,21] Taken together, these findings suggest unique underlying neurobiological mechanisms responsible for the manifestation of contrasting symptom profiles among PTSD patients, thereby highlighting the importance of a tailored treatment approach for military members and Veterans in order to target these specific mechanisms.

Interestingly, differential patterns of functional connectivity during the resting state have also been documented across the brain when comparing PTSD, PTSD+DS, and healthy controls.[12,21,36,39–43] Notably, these areas include not only regions involved in fear learning and responding, such as the amygdala,[44] but also include regions of the brain that span across the neural axis. Broadly, these areas include insula subregions responsible for interoceptive processing of bodily condition,[39] amygdala complexes involved in the execution of fear responses and the cortical integration of emotions,[36] the superior colliculus related to visual detection of threat stimuli,[43] the thalamus which is a multi-sensory integration hub within the brain,[42] the bed nucleus of the stria terminalis involved in anticipatory and sustained reactivity to threat,[41] and the periaqueductal gray, a brain stem structure involved in defensive responding to threat (PAG).[12] In particular, supporting evidence for the emotion modulation model of PTSD has been demonstrated when examining the functional connectivity patterns of the cerebellum during the resting state.[40] Consistent with emotion overmodulation, PTSD+DS was associated with increased functional connectivity of the cognitive posterior cerebellum with prefrontal cortex areas related to emotion regulation as compared to PTSD.[40] By contrast, and in support of emotion undermodulation, PTSD was associated with decreased functional connectivity between the cognitive posterior cerebellum and prefrontal cortex areas involved in emotion regulation as compared to healthy individuals.[40] These findings illustrate that aberrant functional connectivity patterns across a myriad of brain regions distinguish PTSD and PTSD+DS from healthy individuals.

In summary, there is an emerging body of evidence that demonstrates differential patterns of neural activation and connectivity when comparing PTSD patients to healthy individuals, and also when comparing PTSD and PTSD+DS patients. These findings highlight the complexity of the neural mechanisms underlying and maintaining symptoms of PTSD with regard to a multitude of brain regions spanning from the cortex to brain stem. With reference to the clinical case report, this suggests that a more personalized approach to psychiatric medicine is of critical importance when treating heterogeneous presentations of PTSD, as there are differential neural circuits that maintain unique PTSD psychopathology. As such, there is an urgent need to develop both novel treatment interventions that target specifically this aberrant neural circuitry within PTSD and PTSD+DS, as well as to further identify objective neural biomarkers that can classify PTSD heterogeneity. This is particularly relevant for the personalized treatment of PTSD in the military and Veteran population. Indeed, it has been suggested that dissemination models must develop beyond one-size-fits-all conceptualizations of treatment if they are to sufficiently reflect the complexity of PTSD in the Veteran population.[45]

CLASSIFYING PTSD AND PTSD+DS: THE CLINICAL SIGNIFICANCE OF ARTIFICIAL INTELLIGENCE

As outlined previously, it has been shown that patients with PTSD and PTSD+DS demonstrate unique neurobiological correlates that are associated with their contrasting symptom profiles. Interestingly, contemporary neuroimaging computational methods have been utilized to further characterize and differentiate these two groups. Once such method consists of neuroimaging artificial intelligence (AI), whereby machine learning is utilized with fMRI data in order to predict a PTSD diagnosis and symptom presentation.

Neuroimaging machine learning applications learn spatially distributed patterns from fMRI data in order to make clinical predictions. These methods can generate models based on complex sources of information that provide a powerful avenue to leverage technology to evaluate risk factors, identify illness subtypes, classify patients and predict responses to treatment.[46] Importantly, machine learning computations for fMRI are sensitive enough to make inferences at the single-subject level that would otherwise not be possible using classical univariate fMRI group comparisons.[47–49] In other words, machine learning models can be generalized to individual patients to make clinical predictions; a capacity with critical implications for clinical diagnosis, treatment, and prediction of psychiatric prognosis.

Recently, a growing number of studies have applied machine learning methods to neuroimaging data in order to predict and characterize PTSD.[13,50–57] Indeed, it has been shown that machine learning algorithms were able to accurately classify PTSD, PTSD+DS, and healthy controls using whole brain resting-state activation with 91.63% accuracy (Figure 4).

Further examination of resting-state activation patterns that were used in the machine learning analysis revealed that patients with PTSD displayed increased neural activation in the amygdala, globus pallidus, and motor/somatosensory regions of the cerebellum – areas related to emotion reactivity and fight-or-flight motor responses – whereas in patients with PTSD+DS, activation was higher in emotion regulation regions of the prefrontal cortex and areas of the cerebellum involved in executive functioning[13] (Figure 5). Additionally, in the same study, amygdala complex functional connectivity maps were able to classify PTSD, PTSD+DS and healthy controls with 85% accuracy,[13] further demonstrating the importance of functional connections with emotion generation regions in differentiating the three groups.

Critically, identifying objective neural classifiers that can categorize PTSD heterogeneity may help to select treatments for PTSD versus PTSD+DS. Importantly, in addition to separating PTSD and PTSD+DS patients from healthy controls, machine learning algorithms also have the power to predict response to treatment among various subtypes of PTSD patients. With reference to the clinical case report,[16] a more personalized medicine approach is critical, given the distinct neural patterns, symptom presentations and differential responses to exposure therapy observed in patients John and Sarah. Indeed, it would be highly beneficial if machine learning tools could be used to predict post-trauma symptom presentation, in addition to the trajectory of PTSD development, individual response to treatment, and pre-trauma risk factors. Taken together, recent findings in neuroimaging machine learning[13] suggest that AI is capable of discriminating between PTSD and PTSD+DS, and may, in the future, be capable of predicting individual differences in response to treatment and PTSD prognosis based on complex sources of neural dynamics.

INTERIM CONCLUSIONS AND FUTURE DIRECTIONS FOR EXPLORATION

The evidence presented in this review suggests that it is of critical importance to develop models to better understand the neurobiological basis of PTSD heterogeneity to prevent illness and suicide, improve treatment of the disorder, and provide optimal functional recovery among patients. The clinical case report presented

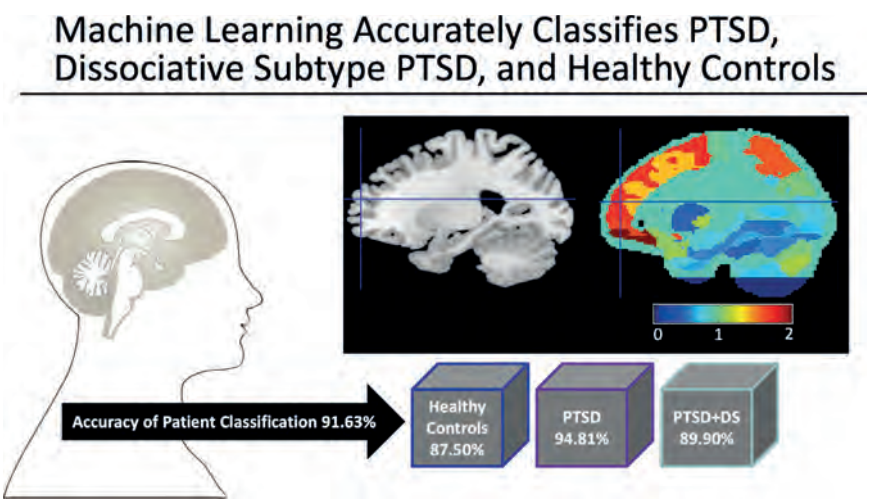

Figure 4. Machine learning classification analysis predicting diagnosis of PTSD, dissociative subtype PTSD and healthy individuals[13]

Machine learning algorithms were able to accurately classify PTSD, PTSD+DS, and healthy controls using whole brain resting-state activation with 91.63% accuracy. A visual depiction of the weights used by the decision function of the machine to classify the three groups is displayed in the top right corner of the image for visualization purposes. Predictive class values for each group were: healthy individuals 87.50%, PTSD 94.81%, and PTSD+DS 89.90%.

PTSD = posttraumatic stress disorder; PTSD+DS = dissociative subtype PTSD

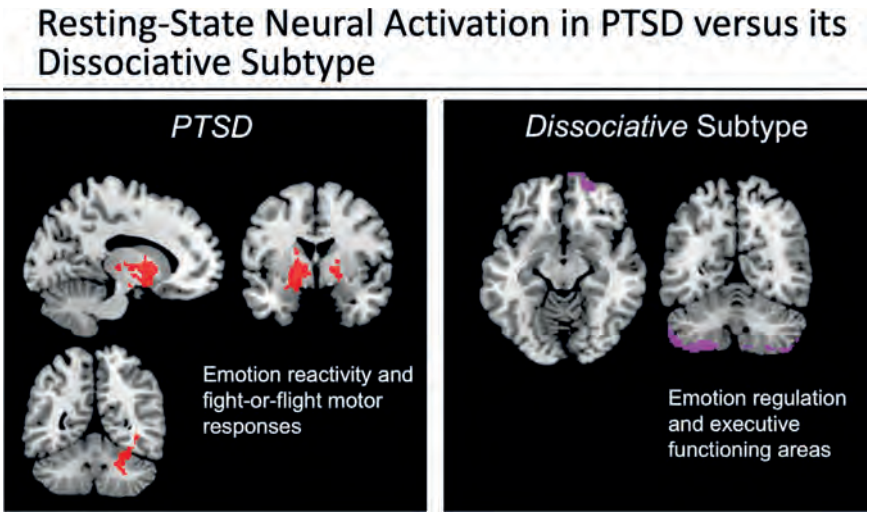

Figure 5. Resting-state activation differences in patients with PTSD as compared to PTSD+DS

Patients with PTSD were found to display increased neural activation within the amygdala, globus pallidus, and motor/somatosensory regions of the cerebellum (areas related to emotion reactivity and fight-or-flight motor responses), whereas in patients with PTSD+DS, activation was higher in emotion regulation regions of the prefrontal cortex and areas of the cerebellum involved in executive functioning.[13]

PTSD = posttraumatic stress disorder; PTSD+DS = dissociative subtype PTSD

highlights the unique subjective experience of trauma, as well as differential symptom manifestation and response to treatment in individuals. Furthermore, the clinical example compliments empirical findings that demonstrate associations between individual differences in symptom presentation and distinct neurobiological mechanisms in the brain, specifically between PTSD and PTSD+DS patients.

Emerging evidence supports the differential neurobiological basis of PTSD and PTSD+DS. In the future, however, it will be critical to study further additional subtypes of PTSD, as multiple factors may contribute to heterogeneity in PTSD, including, but not limited to, peritraumatic dissociation, moral injury, childhood trauma and adversity, and psychiatric comorbidity.[58–63] For example, a recent study found that a specific subtype of victims who report higher degrees of peritraumatic dissociation during and immediately after trauma were more vulnerable to developing PTSD, and should therefore be prioritized to receive psychological interventions for this reason.[60] Moral injury, guilt, and shame have been shown to relate to adverse mental health outcomes, particularly during the onset of PTSD among CAF personnel, which may also contribute to the prognosis of the disorder and development of specific symptoms.[59,64] Therefore, further exploration of these factors, and their relation to PTSD development after trauma, is warranted.

It is proposed the field of psychiatry would also benefit significantly from developing objective biomarkers that could both classify heterogeneous patient populations presenting with unique symptoms, as well as predict individual responses to treatment, in order to facilitate a more personalized treatment approach to medicine among military members and Veterans. Indeed, based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*), there are 636,120 ways in which to present with PTSD.[1] It is therefore critical that modern neuroimaging analyses, such as AI and machine learning methods, be utilized to develop technologies that can facilitate optimal treatment of heterogenous presentations of PTSD. In turn, future clinical implementation of these cutting-edge tools may not only allow for earlier and more accurate PTSD subtype classification, but may also revolutionize the field of personalized medicine by pairing patients with optimal treatments, and predicting individual responses to such interventions.

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