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

Benjamin T. Dunkley[a,b,c], Rakesh Jetly[d], Elizabeth W. Pang[b,e] and Margot J. Taylor[a,b,f]

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,

a Department of Diagnostic Imaging, The Hospital for Sick Children (SickKids), Toronto
b Neurosciences & Mental Health, The Hospital for Sick Children (SickKids) Research Institute, Toronto
c Department of Medical Imaging, University of Toronto, Toronto
d Department of National Defence, Canadian Forces Health Services Group, Department of National Defence, Ottawa
e Division of Neurology, The Hospital for Sick Children (SickKids), Toronto
f Department of Psychology, University of Toronto, Toronto

Correspondence should be addressed to Benjamin Dunkley at ben.dunkley@sickkids.ca

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

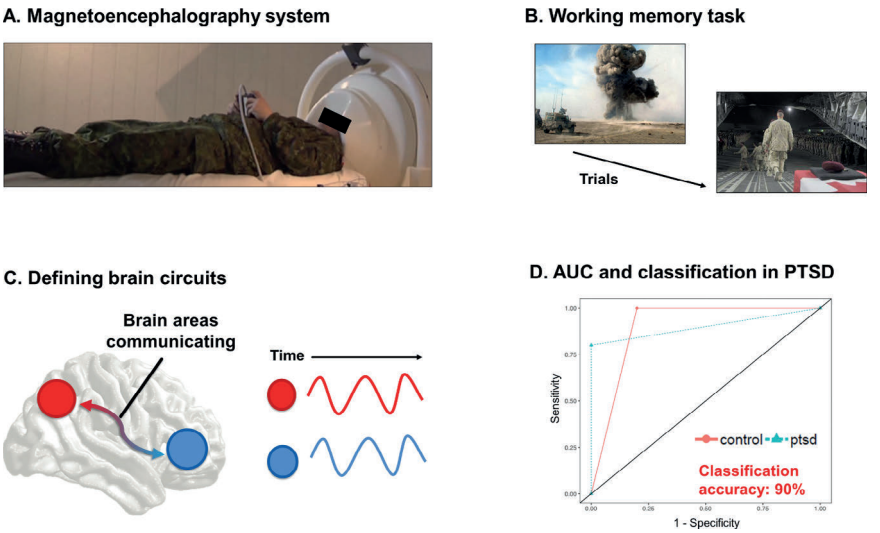

Figure 1. **(A)** Magnetoencephalography system. MEG can be used for non-invasive biomarker identification of mental health challenges in armed forces members and Veterans. The MEG system measures brain function, is completely non-invasive, quiet, non-claustrophobic, fast, and better tolerated than other 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.

REFERENCES

1. Abdul-Hamid WK, Hughes JH. Nothing new under the sun: post-traumatic stress disorders in the ancient world? Early Sci Med. 2014;19(6):549–57. https://doi.org/10.1163/15733823-00196p02. Medline:25577928
2. Boulos D, Zamorski MA. Deployment-related mental disorders among Canadian Forces personnel deployed in support of the mission in Afghanistan, 2001–2008. CMAJ. 2013;185(11):E545–52. https://doi.org/10.1503/cmaj.122120. Medline:23820441
3. American Psychatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Arlington, VA: American Psychiatric Association; 2000.
4. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602. https://doi.org/10.1001/archpsyc.62.6.593. Medline:15939837
5. Zamorski MA, Bennett RE, Rusu C, et al. Prevalence of past-year mental disorders in the Canadian Armed Forces, 2002–2013. Can J Psychiatry. 2016;61(1):26S–35S. https://doi.org/10.1177/0706743716628854. Medline:27270739
6. Garber BG, Rusu C, Zamorski MA. Deployment-related mild traumatic brain injury, mental health problems, and post-concussive symptoms in Canadian Armed Forces personnel. BMC Psychiatry. 2014;14(1):325. https://doi.org/10.1186/preaccept-4758297971370968.
7. Richardson LK, Frueh BC, Acierno R. Prevalence estimates of combat-related post-traumatic stress disorder:

critical review. Aust N Z J Psychiatry. 2010;44(1):4–19. https://doi.org/10.3109/00048670903393597. Medline:20073563
8. Patel R, Spreng RN, Shin LM, et al. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 2012;36(9):2130–42. https://doi.org/10.1016/j.neubiorev.2012.06.003. Medline:22766141
9. Senneseth M, Alsaker K, Natvig GK. Health-related quality of life and post-traumatic stress disorder symptoms in accident and emergency attenders suffering from psychosocial crises: a longitudinal study. J Adv Nurs. 2012;68(2):402–13. https://doi.org/10.1111/j.1365-2648.2011.05752.x. Medline:21740459
10. Giacco D, Matanov A, Priebe S. Symptoms and subjective quality of life in post-traumatic stress disorder: a longitudinal study. PLoS One. 2013;8(4):e60991. https://doi.org/10.1371/journal.pone.0060991. Medline:23585868
11. Steenkamp MM, Litz BT. One-size-fits-all approach to PTSD in the VA not supported by the evidence. Am Psychol. 2014;69(7):706–7. https://doi.org/10.1037/a0037360. Medline:25265298
12. Fenster RJ, Lebois LAM, Ressler KJ, et al. Brain circuit dysfunction in post-traumatic stress disorder: from mouse to man. Nat Rev Neurosci. 2018;19(9):535–51. https://doi.org/10.1038/s41583-018-0039-7. Medline:30054570
13. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research-past, present, and future. Biol Psychiatry 2006;60(4):376–82. https://doi.org/10.1016/j.biopsych.2006.06.004. Medline:16919525
14. Hämäläinen M, Hari R, Ilmoniemi RJ, et al. Magnetoencephalography theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys. 1993;65(2):413–97. https://doi.org/10.1103/revmodphys.65.413.
15. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci. 2005;9(10):474–80. https://doi.org/10.1016/j.tics.2005.08.011. Medline:16150631
16. Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed. 1997;10(4–5):165–70. https://doi.org/10.1002/(sici)1099-1492(199706/08)10:4/5%3C165::aid-nbm454%3E3.0.co;2-7.
17. Buzsáki G, Watson BO. Brain rhythms and neural syntax: implications for efficient coding of cognitive content and neuropsychiatric disease. Dialogues Clin Neurosci. 2012;14(4):345–67. https://doi.org/10.1093/oso/9780190905385.003.0006.
18. Engel AK, Gerloff C, Hilgetag CC, et al. Intrinsic coupling modes: multiscale interactions in ongoing brain activity. Neuron. 2013;80(4):867–86. https://doi.org/10.1016/j.neuron.2013.09.038. Medline:24267648
19. Mišić B, Fatima Z, Askren MK, et al. The functional connectivity landscape of the human brain. PLoS One. 2014;9(10):e111007. https://doi.org/10.1371/journal.pone.0111007. Medline:25350370
20. Ray WJ, Odenwald M, Neuner F, et al. Decoupling neural networks from reality: dissociative experiences in torture victims are reflected in abnormal brain waves in left frontal cortex. Psychol Sci. 2006;17(10):825–9. https://doi.org/10.1111/j.1467-9280.2006.01788.x. Medline:17100779
21. Badura-Brack AS, Becker KM, McDermott TJ, et al. Decreased somatosensory activity to non-threatening touch in combat Veterans with posttraumatic stress disorder. Psychiatry Res. 2015;233(2):194–200. https://doi.org/10.1016/j.pscychresns.2015.06.012. Medline:26184460
22. Catani C, Adenauer H, Keil J, et al. Pattern of cortical activation during processing of aversive stimuli in traumatized survivors of war and torture. Eur Arch Psychiatry Clin Neurosci. 2009;259(6):340–51. https://doi.org/10.1007/s00406-009-0006-4. Medline:19360450
23. McDermott TJ, Badura-Brack AS, Becker KM, et al. Attention training improves aberrant neural dynamics during working memory processing in Veterans with PTSD. Cogn Affect Behav Neurosci. 2016;16(6):1140–9. https://doi.org/10.3758/s13415-016-0459-7. Medline:27722837
24. Brunetti M, Marzetti L, Sepede G, et al. Resilience and cross-network connectivity: a neural model for post-trauma survival. Prog Neuropsychopharmacol Biol Psychiatry. 2017;77:110–19. https://doi.org/10.1016/j.pnpbp.2017.04.010. Medline:28408294
25. Dunkley BT, Doesburg SM, Sedge PA, et al. Resting-state hippocampal connectivity correlates with symptom severity in post-traumatic stress disorder. Neuroimage Clin. 2014;5:377–84. https://doi.org/10.1016/j.nicl.2014.07.017. Medline:25180157
26. Dunkley BT, Doesburg SM, Jetly R, et al. Characterising intra- and inter-intrinsic network synchrony in combat-related post-traumatic stress disorder. Psychiatry Res. 2015;234(2):172–81. https://doi.org/10.1016/j.pscychresns.2015.09.002. Medline:26422117
27. Dunkley BT, Sedge PA, Doesburg SM, et al. Theta, mental flexibility, and post-traumatic stress disorder: connecting in the parietal cortex. PLoS One. 2015;10(4):e0123541. https://doi.org/10.1371/journal.pone.0123541. Medline:25909654

28. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. Neuroimage. 2010;53(4):1197–207. https://doi.org/10.1016/j.neuroimage.2010.06.041. Medline:20600983
29. McDermott T, Badura-Brack AS, Becker KM, et al. Attention training improves aberrant neural dynamics during working memory processing in Veterans with PTSD. Cogn Affect Behav Neurosci. 2016;16(6):1140–9. https://doi.org/10.3758/s13415-016-0459-7. Medline:27722837
30. Badura-Brack AS, McDermott TJ, Becker KM, et al. Attention training modulates resting-state neurophysiological abnormalities in posttraumatic stress disorder. Psychiatry Res Neuroimaging. 2018;271:135–41. https://doi.org/10.1016/j.pscychresns.2017.11.008. Medline:29174765
31. Badura-Brack AS, McDermott TJ, Heinrichs-Graham E, et al. Veterans with PTSD demonstrate amygdala hyperactivity while viewing threatening faces: a MEG study. Biol Psychol. 2018;132:228–32. https://doi.org/10.1016/j.biopsycho.2018.01.005. Medline:29309826
32. Zheng J, Stevenson RF, Mander BA, et al. Multiplexing of theta and alpha rhythms in the amygdala-hippocampal circuit supports pattern separation of emotional information. Neuron. 2019;102(4):887–98.e5. https://doi.org/10.1016/j.neuron.2019.03.025. Medline:30979537
33. McDermott TJ, Badura-Brack AS, Becker KM, et al. Attention training improves aberrant neural dynamics during working memory processing in Veterans with PTSD. Cogn Affect Behav Neurosci. 2016;16(6):1140–9. https://doi.org/10.3758/s13415-016-0459-7. Medline:27722837
34. Dunkley BT, Pang EW, Sedge PA, et al. Alpha hypersynchrony and atypical memory processes in soldiers with post-traumatic stress disorder. J Neuroimag Psychiatry Neurol. 2016;1(2):54–63. https://doi.org/10.17756/jnpn.2016-007.
35. Dunkley BT, Wong SM, Jetly R, et al. Post-traumatic stress disorder and chronic hyperconnectivity in emotional processing. Neuroimage Clin. 2018;20:197–204. https://doi.org/10.1016/j.nicl.2018.07.007. Medline:30094169
36. Misic B, Dunkley BT, Sedge PA, et al. Post-traumatic stress constrains the dynamic repertoire of neural activity. J Neurosci. 2016;36(2):419–31.
37. Rowland JA, Stapleton-Kotloski JR, Alberto GE, et al. Contrasting effects of posttraumatic stress disorder and mild traumatic brain injury on the whole-brain resting-state network: a magnetoencephalography study. Brain Connect. 2017;7(1):45–57. https://doi.org/10.1089/brain.2015.0406. Medline:28006976
38. Downar J, Daskalakis ZJ. New targets for rTMS in depression: a review of convergent evidence. Brain Stimul. 2013;6(3):231–40. https://doi.org/10.1016/j.brs.2012.08.006. Medline:22975030
39. Philip NS, Barredo J, van 't Wout-Frank M, et al. Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. Biol Psychiatry. 2018;83(3):263–72. https://doi.org/10.1016/j.biopsych.2017.07.021. Medline:28886760
40. Sokhadze EM, Lamina EV, Casanova EL, et al. Exploratory study of rTMS neuromodulation effects on electrocortical functional measures of performance in an oddball test and behavioral symptoms in autism. Front Syst Neurosci. 2018;12:20. https://doi.org/10.3389/fnsys.2018.00020. Medline:29892214
41. Isserles M, Shalev AY, Roth Y, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder: a pilot study. Brain Stimul. 2013;6(3):377–83. https://doi.org/10.1016/j.brs.2012.07.008. Medline:22921765
42. Pallanti S, Bernardi S. Neurobiology of repeated transcranial magnetic stimulation in the treatment of anxiety: a critical review. Int Clin Psychopharmacol. 2009;24(4):163–73. https://doi.org/10.1097/yic.0b013e32832c2639. Medline:19455047
43. Karsen EF, Watts BV, Holtzheimer PE. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. Brain Stimul. 2014;7(2):151–7. https://doi.org/10.1016/j.brs.2013.10.006. Medline:24486424
44. Summers JJ, Kagerer FA, Garry MI, et al. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: a TMS study. J Neurol Sci. 2007;252(1):76–82. https://doi.org/10.1016/j.jns.2006.10.011. Medline:17134723
45. Vakorin VA, Doesburg SM, da Costa L, et al. Detecting mild traumatic brain injury using resting state magnetoencephalographic connectivity. PLoS Comput Biol. 2016;12(12):e1004914. https://doi.org/10.1371/journal.pcbi.1004914. Medline:27906973
46. Boto E, Holmes N, Leggett J, et al. Moving magnetoencephalography towards real-world applications with a wearable system. Nature. 2018;555(7698):657–61. https://doi.org/10.1038/nature26147. Medline:29562238

AUTHOR INFORMATION

Ben Dunkley, PhD, is an imaging scientist at The Hospital for Sick Children (SickKids) and an Assistant Professor at the University of Toronto. He studies brain functions underlying everyday cognitive processes, such as memory,

attention, and emotion, and how these processes are impacted by neurological and psychiatric conditions such as concussion and PTSD.

Rakesh Jetly, MD, FRCPC, is Senior Psychiatrist and Mental Health Advisor, Canadian Armed Forces, Ottawa. He is an Associate Professor of Psychiatry at Dalhousie University and at the University of Ottawa. He is also the Chair for Military Mental Health with the Royal's Institute of Mental Health Research in Ottawa. He is committed to evolving mental health research by investigating the biological underpinnings of mental health disease, by incorporating technology to modernize treatment and diagnostic modalities, and by finding strategies to advance precision medicine.

Elizabeth Pang, PhD, is a neurophysiologist and Director of the Evoked Potentials and MEG Functional Mapping Labs in the Division of Neurology at The Hospital for Sick Children (SickKids) in Toronto. She is also a Senior Associate Scientist in Neurosciences and Mental Health at the SickKids Research Institute.

Margot Taylor, PhD, is a Scientist in Diagnostic Imaging and Director of Functional Neuroimaging at The Hospital for Sick Children (SickKids) in Toronto. Her research focuses on the use of fMRI, MRI, and MEG to understand the neural bases of cognitive development and difficulties, including emotion, Theory of Mind, and working memory, from childhood into adulthood.

COMPETING INTERESTS

None declared.

This article has been peer-reviewed.

CONTRIBUTORS

All authors conceived, researched, drafted, and approved the final version submitted for publication.

FUNDING

None declared.