



## Regulating posttraumatic stress disorder symptoms with neurofeedback: Regaining control of the mind

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### 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 psychophysologique 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.<sup>1</sup> The incidence of PTSD in

all public safety personnel rescue workers<sup>2</sup> 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.<sup>3</sup> Similarly, 13% of returning Canadian Armed Forces personnel are diagnosed with

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deployment-related mental disorders, including PTSD.<sup>4</sup> 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.<sup>5</sup> 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,<sup>6,7</sup> where a recent systematic review reported an average dropout rate of one in three patients among Veterans.<sup>7</sup> In community-based settings, only 56% of patients with PTSD received a minimally adequate dose of psychotherapy.<sup>8</sup> A cross-national meta-analysis study suggests that psychotherapy is reported to be successful in only about 60% of cases.<sup>9</sup> 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.<sup>10,11</sup> 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.<sup>12</sup>

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.<sup>13–15</sup> 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.<sup>16</sup> 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.<sup>17</sup>

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.<sup>1,18</sup> 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.<sup>1,18</sup> 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.<sup>1,19–22</sup>

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.<sup>13,14,16–18,23</sup> 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.<sup>1,18,19,22</sup> Neurofeedback involves a brain-computer interface that provides real-time feedback of brain activity that individuals learn to regulate using a “closed-loop” paradigm.<sup>13,14,24</sup> 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.<sup>14,18</sup> 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.<sup>18,25</sup> 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.<sup>13,14</sup> Notably, EEG neurofeedback has also recently been used to target more specific subcortical regions of the brain.<sup>26–28</sup> 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.<sup>13,14</sup> 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).<sup>13</sup>

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.<sup>13,14,18,29</sup> 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.<sup>13,14,18</sup> In support of structural changes occurring in response to neurofeedback,<sup>30,31</sup> 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.<sup>29</sup> 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.<sup>32</sup> 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.<sup>33</sup> 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),<sup>34,35</sup> cognitive dysfunction (CEN),<sup>36–38</sup> as well as dysregulated arousal/hypervigilance and chronic threat monitoring (SN).<sup>33,35,37,39–50</sup> 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.<sup>45,51</sup> Indeed, neurofeedback has been proposed as a potential avenue by which to normalize these network abnormalities in PTSD.<sup>45</sup>

Recent studies suggest covariation between alpha-wave oscillations in the brain and changes in the aforementioned ICNs<sup>52,53</sup> that are particularly implicated in PTSD.<sup>45</sup> Alpha oscillations (8–12Hz) are easily measurable with EEG and correspond to a state of resting wakefulness correlated to the DMN,<sup>54,55</sup> where patients with PTSD are known to display decreased DMN connectivity at rest in key hubs of this network.<sup>40,45,46</sup> In conjunction, PTSD patients display abnormally reduced alpha oscillations, proposed to be a global index of chronic hyperarousal.<sup>13,56–58</sup> 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<sup>13</sup> and ICN dynamics.<sup>32</sup>

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.<sup>19,20,22,59–69</sup> PTSD symptoms of hyperarousal have been correlated with negative mPFC-amygdala coupling,<sup>64</sup> where PTSD patients display reduced PFC-amygdala connectivity as compared to controls, corresponding to reduced regulation of emotion centres during the resting state.<sup>70</sup>

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.<sup>18,28,32,71,72</sup> 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).<sup>71,72</sup> 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.<sup>28,32</sup> 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.<sup>14</sup> Several studies have examined the capacity to regulate emotion processing by targeting neurofeedback of the amygdala using rt-fMRI-nfb in both healthy individuals<sup>73–78</sup> and psychiatric populations, including borderline personality disorder (BPD),<sup>79</sup> major depressive disorder,<sup>80–82</sup> and PTSD.<sup>71,72,83,84</sup>

The amygdala is a region associated with the processing and generation of emotions,<sup>85–87</sup> where dysregulated amygdala activation has been shown to be central to the development and maintenance of PTSD symptoms.<sup>19,22,46,51,67,68,88</sup> 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.<sup>19,20,22,46</sup> 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.<sup>74–76,89</sup> Neurofeedback regulation of the amygdala may offer a way to therapeutically normalize the abnormal cortico-subcortical pathways maintaining PTSD.

Nicholson et al.<sup>71</sup> 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.<sup>71</sup> Importantly, patients were also able to learn to regulate their amygdala activation on a subsequent transfer trial without neurofeedback.<sup>71</sup> Here, increased activation in the dorsolateral and ventrolateral PFC was observed in trials where patients were instructed to downregulate their amygdala.<sup>71</sup> 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.<sup>71</sup> 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.<sup>74–76,89–91</sup> 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.<sup>92</sup>

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.<sup>71</sup> 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.<sup>14,71,92,94</sup> 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.<sup>11,88,95,96</sup>

In another Canadian research study, Nicholson et al.<sup>72</sup> 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.<sup>34,40,45,46,97</sup> 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.<sup>72</sup> Critically, the literature suggests decreased recruitment and functional connectivity within CEN emotion regulation PFC regions among PTSD patients,<sup>37,38,45,98</sup> where attenuated regulatory activation in the PFC is associated with PTSD symptoms of emotion undermodulation (i.e., hyperemotionality) and amygdala hyperactivation.<sup>19,20,22</sup> 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.<sup>72</sup> In the same study, DMN recruitment related to self-referential processing and autobiographical memory was stabilized during neurofeedback runs.<sup>72</sup> Individuals with PTSD have been shown to maladaptively recruit the DMN during tasks that require cognitive control.<sup>97</sup> 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.<sup>72</sup> 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<sup>71,72</sup> 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,<sup>71,72</sup> effects similar to those observed using EEG signals for neurofeedback in patients with PTSD.<sup>28,32</sup>

## 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,<sup>28,32,99–101</sup> culminating in a recent randomized controlled trial in patients with chronic PTSD.<sup>102</sup>

Peniston and Kulkosky<sup>100</sup> 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.<sup>100</sup> Furthermore, the neurofeedback group also displayed more significant improvements on the Minnesota Multiphasic Personality Inventory (MMPI) scales, as compared to controls.<sup>99</sup> 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.<sup>32</sup> Interestingly, this neurofeedback protocol also led to

changes in ICNs highly associated with PTSD symptomatology.<sup>32,45</sup> 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.<sup>32,45</sup> 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.<sup>32</sup> Importantly, these results are supported by other alpha-based, controlled neurofeedback studies in healthy individuals, which display lasting changes in cortical plasticity post neurofeedback.<sup>103,104</sup>

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.<sup>28</sup> 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.<sup>28</sup> 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.<sup>22</sup> 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.<sup>28,105</sup>

In accordance with this model, EEG neurofeedback training of amygdala-correlated activity leads to emotion regulation improvements in soldiers during combat training.<sup>26</sup> 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.<sup>28</sup>

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.<sup>102</sup> 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.<sup>102</sup> 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.<sup>102</sup> Only a very small amount (4%) of participants in the active treatment condition reported side effects of increased flashbacks,<sup>102</sup> 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.<sup>101</sup> 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.<sup>22,102,106</sup> 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.

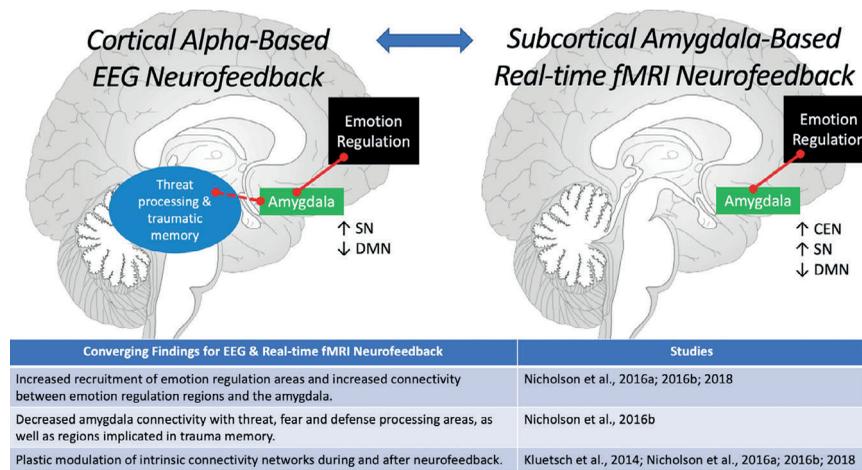
### CONVERGING EVIDENCE FOR REAL-TIME fMRI AND EEG NEUROFEEDBACK IN THE TREATMENT OF PTSD

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<sup>71,72</sup> and alpha-based EEG neurofeedback<sup>28,32</sup> 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.<sup>28,32,71,72</sup>

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.<sup>26,27</sup> Importantly, when targeting the amygdala via EEG neurofeedback, results suggest modulation of neural pathways comodulated during amygdala-based targeted rt-fMRI-nfb.<sup>26,27</sup> 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.<sup>81</sup> Specifically, the study by Zotev et al.<sup>81</sup> 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.<sup>81</sup>

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,



**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.<sup>1,19–22</sup>

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.<sup>13,18</sup> 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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