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# Real-time fMRI Neurofeedback and PTSD: Efficacy in Symptom Relief and Neural Circuit Restoration

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Real-time fMRI Neurofeedback and PTSD: efficacy in  
symptom relief and neural circuit restoration

by

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An undergraduate honors thesis submitted in partial  
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## Introduction

Posttraumatic Stress Disorder (PTSD) is a psychiatric illness that occurs in approximately 25% of people who have experienced or witnessed a traumatic event (Nicholson et al., 2018). The main diagnostic features of PTSD include repetitive, intrusive recollections of the event; avoidance of stimuli related to trauma; and hyperarousal or functional distress (American Psychiatric Association, 2000). Within these categories, further symptomatology may include vivid dreams and memories, lack of interest or care, social detachment, emotional numbness, insomnia, irritability, hypervigilance and deficits in cognitive functioning, concentration, memory and learning. Comorbid psychiatric disorders are also prevalent in PTSD with civilian populations being 5.7 times more likely to experience major depression, 15.5 times more likely to develop mania and 6 to 15 times more likely to attempt suicide (Taghva et al., 2013).

Within the United States, one in 17 people will be diagnosed with PTSD within their lifetime, while 12 million adults suffer from the disorder each year (US Department of Veteran Affairs, 2022). Of those diagnosed, 74% of patients experience symptoms that last more than six months, and 30% of patients still do not see recovery even after 10 years (Taghva et al., 2013). One reason these low recovery rates exist is because 30-50% of patients show high treatment-resistance to current therapies, leading to a high rate of treatment drop-out (Gerin et al., 2016).

The options for treatment that are available to patients diagnosed with PTSD include both pharmacological and psychological therapies. The most effective pharmacological intervention has been through the use of SSRIs, but even so, less than half the patients receiving this treatment see full remission (Gerin et al., 2016). Some psychotherapeutic interventions include trauma-focused cognitive behavioral therapy, exposure, narrative and psychodynamic therapies (Lee & Bowles, 2020), and while some of these treatments have shown moderate success in relieving PTSD symptomatology, there is still a need for neuroscientifically informed interventions for PTSD within clinical practice (Lanius et al., 2015).

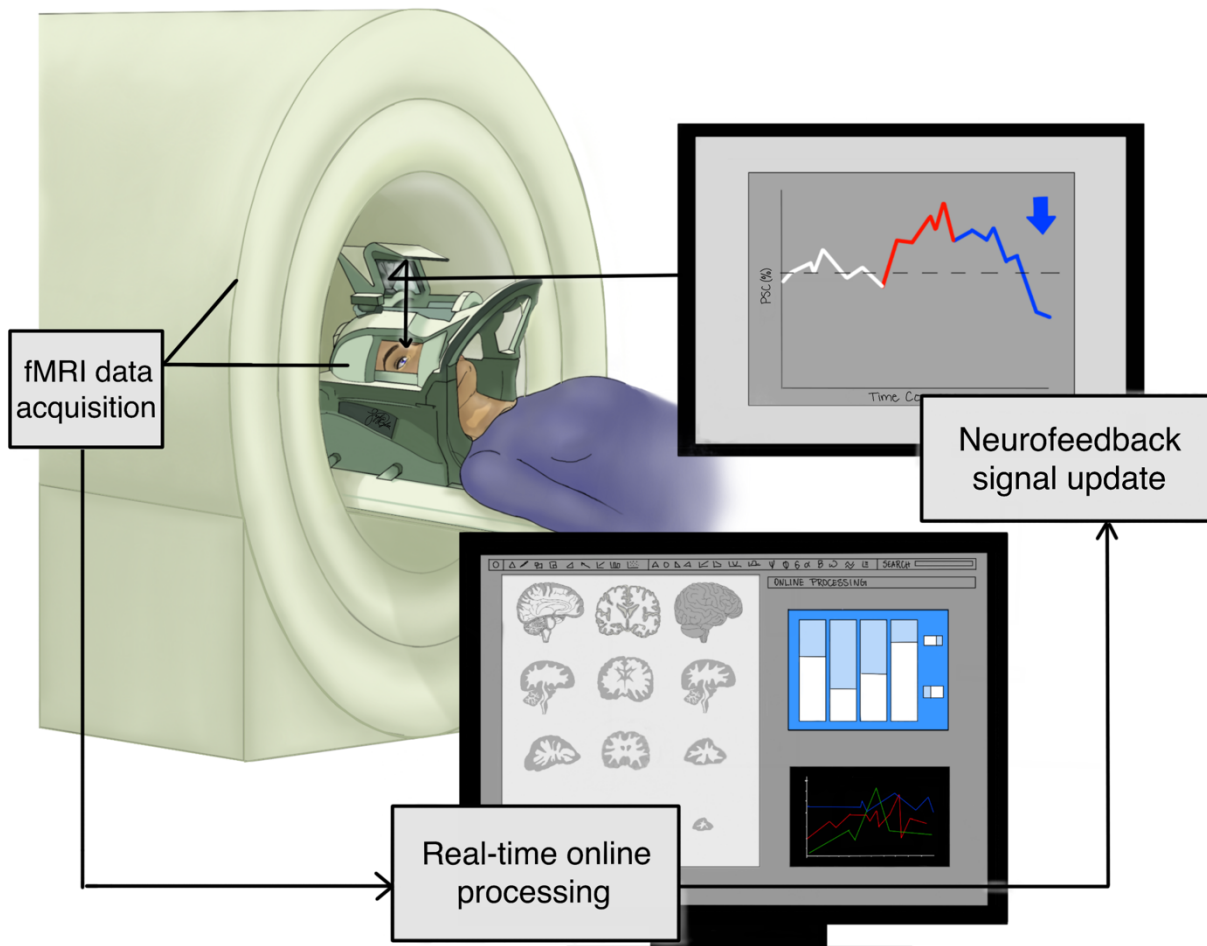
Real-time fMRI neurofeedback (rt-fMRI-NF) is being explored as one of these much needed interventions.

## *Neurofeedback*

As a tool of medical diagnosis and intervention, functional magnetic resonance imaging (fMRI) allows clinicians to see the changes in metabolic activity and blood flow within the brain that occurs due to fluctuations in neural activity. It is a noninvasive procedure and does not require a drug regimen. In neurofeedback treatments, the fMRI data is used to create a brain-computer interface that visually represents the real-time brain activity changes occurring as the participant processes the interface updates and tries to control the signal. **Figure 1** diagrams this process, an example of a “closed loop” paradigm of self-regulation (Nicholson, Ros, et al., 2020).

In this paradigm, the clinician’s role is to target ROIs that will facilitate their patient’s learning to modulate and eventually normalize aberrant connectivity patterns related to their symptomatology. The continuous process of analyzing the presented changes, using the changes as cues for emotional regulation, and seeing how the graph changes *because* of the regulation, reinforces with operant conditioning the participant’s newly trained ability to regulate their emotional response. In learning

how to exert volitional control over the activity of PTSD-associated ROIs, participants with PTSD have been shown to cause a normalizing change in their neurophysiology (Nicholson et al., 2018).



**Figure 1** | Illustration of the “Closed-Loop” paradigm. Information flows from the MRI scanner to the online-processing PC where the difference in BOLD activity from the region of interest (ROI) is calculated; the percent signal change (PSC) is then sent to the neurofeedback display monitor from which the participant can view the updated signal and use it as either a confirmation of successful regulation or as an indication that regulation is not being achieved. Whether the participant continues with the same regulatory strategy or attempts to regulate ROI activity through a different method, the change in BOLD activity as a result of the participant’s feedback integration is registered by the MRI scanner and the ‘Loop’ cycles again.<sup>1</sup>

### *fMRI vs EEG Neurofeedback*

There are two forms of neurofeedback that create the brain-computer interface: fMRI neurofeedback (fMRI-NF) and electroencephalogram neurofeedback (EEG-NF). EEG-NF has been the subject of numerous studies, the first of which was published in 1991 (Peniston, 1991), and as such, has been reviewed extensively as a treatment for psychiatric disorders.

An electroencephalogram (EEG) is a test that measures the electrical activity of the brain in alpha and/or theta waves. The signal intensity of the waves emitted by a region of the brain is used as the source of feedback in EEG-NF (Chiba et al., 2019). In fMRI-NF, it is the blood-oxygen-level-dependent (BOLD) signal from an ROI that is used as the source of feedback (as previously mentioned). Both

<sup>1</sup> Illustration by Sophia Ryker

methods of neurofeedback have been shown to cause plastic changes in neurocircuitry in patients with PTSD (Nicholson, Ros, et al., 2020).

Other than the source of feedback, the two methods differ in their spatial resolution. Electrograms from EEGs provide information on macroscopic brain activity and large scale oscillations, while an fMRI data set consists of measurements from 100,000 five cubic millimeter sections of the brain called voxels (Eck et al., 2020). The higher spatial resolution from fMRI data allows for more precise identification of ROIs and for a greater number of connectivity analyses to be conducted. This review focuses on studies conducted using rt-fMRI-NF in the treatment of PTSD because the higher spatial resolution allows for detailed analysis of the neurocircuitry changes that occur over the course of treatment.

### **Neural Profiles**

Differences in the presentation of PTSD person to person can vary drastically. Based on its diagnostic criteria in the DSM V, posttraumatic stress disorder theoretically has 636,120 different symptom presentations (Ahrenholtz et al., 2021). This then also means that the aberrant neural activity causing these symptomatic differences will have significant variation as well.

Numerous studies have been conducted that look specifically at the structural and functional differences between the brains of “normal” healthy people and those with PTSD and its subtypes (Ben-Zion et al., 2020; Esterman et al., 2020; Nicholson et al., 2019; Nicholson, Harricharan, et al., 2020). This review summarizes the various models of PTSD neurocircuitry, evidence of PTSD subtypes and the structural and functional data that support them.

### **Neurocircuitry**

Neurocircuitry refers to the connections that individual brain regions make with each other and the greater networks that are formed from these connections. Several analysis methods are used in defining the functional connections that make up the larger circuits of the human brain: bivariate analysis, multi-voxel pattern analysis, independent component analysis, recursive feature elimination and univariate analysis. Each of these uses functional MRI data to provide different insights into the neurobiological aspects of PTSD.

Bivariate analysis looks at the level of activity between two previously identified voxel clusters. It compares the level of functional connectivity occurring *between* the two clusters before and after neurofeedback.

Multi-voxel pattern analysis (MVPA) Looks at spatially distributed patterns of functional connectivity and activation by comparing the differential conditions between overlapping areas of voxel clusters. A few studies have used MVPA to identify correlations between symptom severity and aberrant connectivity in PTSD (Cisler et al., 2015; Fitzgerald et al., 2020).

Recursive feature elimination (RFE) looks at the entire brain (about 60 x 60 x 30 voxels) without *a priori* selection of ROIs. The purpose of this is to find patterns of connectivity across the brain by gradually eliminating irrelevant voxels until only those with the strongest discriminative power are left (Eck et al., 2020).

Independent component analysis (ICA) takes a large multivariate signal and extracts the individual signal data points that made up the initial large one. This is used for identifying intrinsic connectivity networks (ICNs) that are made up of functionally coupled smaller structures.

Univariate analysis looks at individual voxels or a single cluster of voxels. Each voxel is analyzed by its change in activity before and after neurofeedback; the data extracted pertains to the increase, decrease or lack of change in activity of each individual voxel or cluster. Univariate analysis is used to examine the changes in functional activity in structures implicated in PTSD psychopathology.

### **Neural Profiles and Neurofeedback**

Neurofeedback is primarily based upon the knowledge of structures within the brain and how they function, but different models of PTSD neurocircuitry emphasize different components of brain activity (Andrewes & Jenkins, 2019; Chamberlin, 2019; Patel et al., 2012). Two fMRI neurofeedback studies based on different models of PTSD could use the same participants and identical training paradigms, but use different methods of data analysis in order to center their results in the context of the model they chose. In this case, a univariate analysis might show that PTSD patients had high activity in the amygdala and low activity in the prefrontal cortex (PFC), but this does not mean that these structures are the sole mediators of PTSD psychopathology. The same dataset could be analyzed with ICA and reveal that the amygdala and PFC are actually part of a larger ICN that has altered inter-network functional connectivity (FC) with two other ICNs. Because of these differences, it is crucial to the development of rt-fMRI-NF, that the multiple models of PTSD neurocircuitry and psychopathology are analyzed in depth as to accurately inform future studies in their choice of ROI, training protocol and interpretation of neurofeedback efficacy.

### ***Purpose***

This paper is a review of all studies using real-time fMRI neurofeedback as a treatment or intervention for posttraumatic stress disorder. Each article is analyzed for its efficacy in the amelioration of PTSD symptoms and restoration of aberrant neurocircuitry in order to make recommendations for future research in the field.

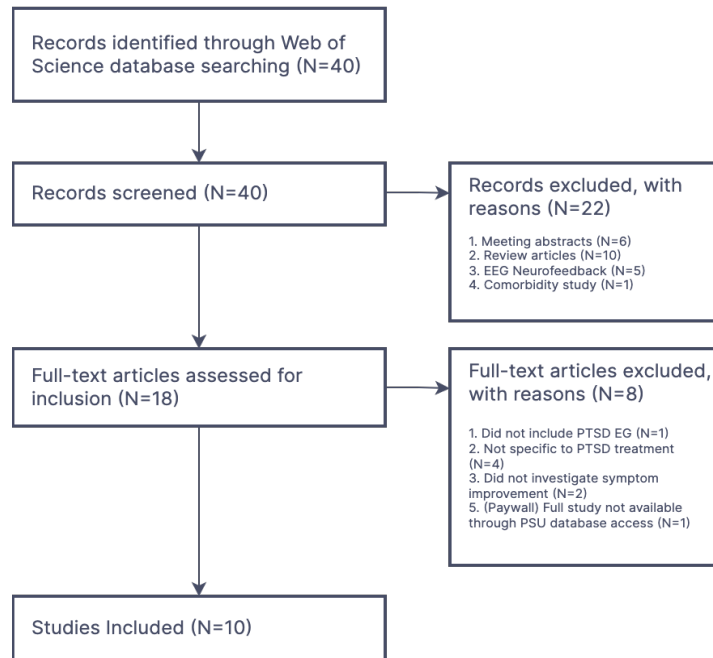
## **Methods**

### ***Literature Search and Evaluation***

*Inclusion criterion.* Only articles that investigated the use of rt-fMRI-NF as a treatment for PTSD were included. All studies reported both symptomatic and connective changes as a result of NF and could include simultaneous use of EEG measurements or comorbidity evaluations. Neurofeedback signals had to stem from fMRI online processing and specific evaluations on PTSD without comorbidity had to be present.

*Literature Identification.* The keywords used for database searching included “PTSD,” “posttraumatic stress disorder,” “fMRI,” “functional magnetic resonance imaging,” and “neurofeedback.” Boolean operators were used with these key words to refine results found in the Web of Science database. The search for “PTSD” produced 41,770 reports, “fMRI” produced 76,685 reports, and “neurofeedback” produced 2,960 reports; the Boolean phrase of [(“PTSD” OR “Posttraumatic stress disorder”) AND (“fMRI” OR “functional magnetic resonance imaging”) AND (“neurofeedback”)] however, produced forty reports, including only those that mentioned at least one of either term in each group.

*Screening for inclusion.* From this set of forty reports, review articles and meeting abstracts were excluded (**Figure 2**). Screening for inclusion was then based on title alone; articles investigating EEG neurofeedback were excluded, as were articles specifically investigating comorbidity between PTSD and another axis one disorder. These exclusion criteria narrowed the number of reports to eighteen.



**Figure 2** | Literature search and exclusion process.

## Data Extraction and Analysis

For each article, information was categorized into three main topics: demographics, protocol, and analysis. Demographics information was further broken down into control groups (CG), experimental groups (EG), sex, specifiers, diagnosis, diagnostic measures, symptom assessments and other questionnaires. Protocol information was subdivided into therapeutic strategies, ROI, feedback frequency, regulatory strategies, emotional stimuli, stimulus presentation, practice (PR) and transfer runs (TR). Lastly, analysis information was divided into analysis models, symptom improvements, regulation success and areas of increased or decreased connectivity. Quantitative data for NF sessions and NF runs per session were reported along with protocol information, and sample size and age were reported with demographics. All coding was inductive and done manually.

The content analysis was done initially within each main topic. Further patterns were analyzed based on ROI and therapeutic strategy.

## Results

### Demographics

The included studies investigating rt-fMRI-NF as a treatment for PTSD were all published between 2016 and 2022 (see **Table 1**). The first three published articles were proof-of-concept (POC) studies and did not include CGs, but all subsequent research included either a ‘healthy’ control (HC)

population or a control condition of sham neurofeedback—an ROI in a brain region not associated with emotion regulation. Excluding the first POC study that only had three participants and no control, the average number of people in either CG or an experimental group (EG) was fourteen. The mean age of all participants was 40 ( $\pm 7$ ) years and 63% of the studies included both male and female participants; the remaining 37% included only men.

Each study had at least one group (EG and/or CG) with a medical diagnosis of PTSD. Some studies also included a ‘trauma-exposed’ control group comprised of people who had experienced a traumatic event, and had subsequently been clinically evaluated and *not* diagnosed with PTSD. Another control population, as previously mentioned, was the HC or the ‘non-trauma-exposed control’. Five studies further narrowed the populations they investigated by only including combat veterans (Gerin et al., 2016; Misaki et al., 2018b; Zotev et al., 2018), or patients who developed PTSD after exposure to a single traumatic event (Zweerings et al., 2018, 2020).

While most participants had received a clinical diagnosis prior to the start of a study, diagnostic tests, surveys and symptom measurements were also done or supervised by the researchers in order to assess PTSD severity and the change in scale scores over the course of the study. The most commonly used diagnostic measures were the Clinician Administered PTSD Scale (CAPS), the PTSD Checklist—Military version (PCL-M), and the Structural Clinical Interview for DSM-IV (SCID). The two measures that were used in studies conducted in Germany were the Essener Trauma-Inventar-traumasymptomatik (ETI-TS, the German version of CAPS) and an ICD-10 diagnosis (the International Classification of Diseases, tenth edition) (Zweerings et al., 2018, 2020). The CAPS, PCL-M, and ETI-TS are numerical scales.

Symptom severity was assessed with numerous surveys. Depressive symptoms were evaluated with either the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HDRS); anxiety was assessed with the State-Trait Anxiety Inventory (STAI), Hamilton Anxiety Scale (HAM-A), or Hamilton Anxiety Rating Scale (HARS); the Response to Script Driven Imagery (RSDI) scale produced measures on four symptom subscales: dissociation, hyperarousal, avoidance and reliving. Several other assessments included the Multiscale Dissociation Inventory (MDI), Combat Exposure Scale (CES), Childhood Trauma Questionnaire (CTQ), the Impact of Event scale—Revised (IES-R), the German version of the Extended Positive and Negative Affect Scale (PANAS-X) and the Self-Assessment Manikin (SAM) scale.

### *Neurofeedback Training Protocol*

Within the eight initial data-collecting studies, six different training protocols were used within the same general methodological path (**Figure 3**). All training protocol characteristics are listed in **Table 2**.

The therapeutic strategies implemented by the initial studies were put into three main categories: emotion induction and regulation training (EIRT), positive emotion enhancement training (PEET) and Cognitive Reappraisal training (CRT). Four studies implemented EIRT using symptom provocation methods as the emotional stimulus (Gerin et al., 2016; Nicholson et al., 2017, 2018, 2022). These included the reading of personalized trauma scripts, display of personalized trauma (or stress) words, or display of general trauma-related images. In each of these studies participants were instructed to downregulate the feedback signal, derived from either the bilateral



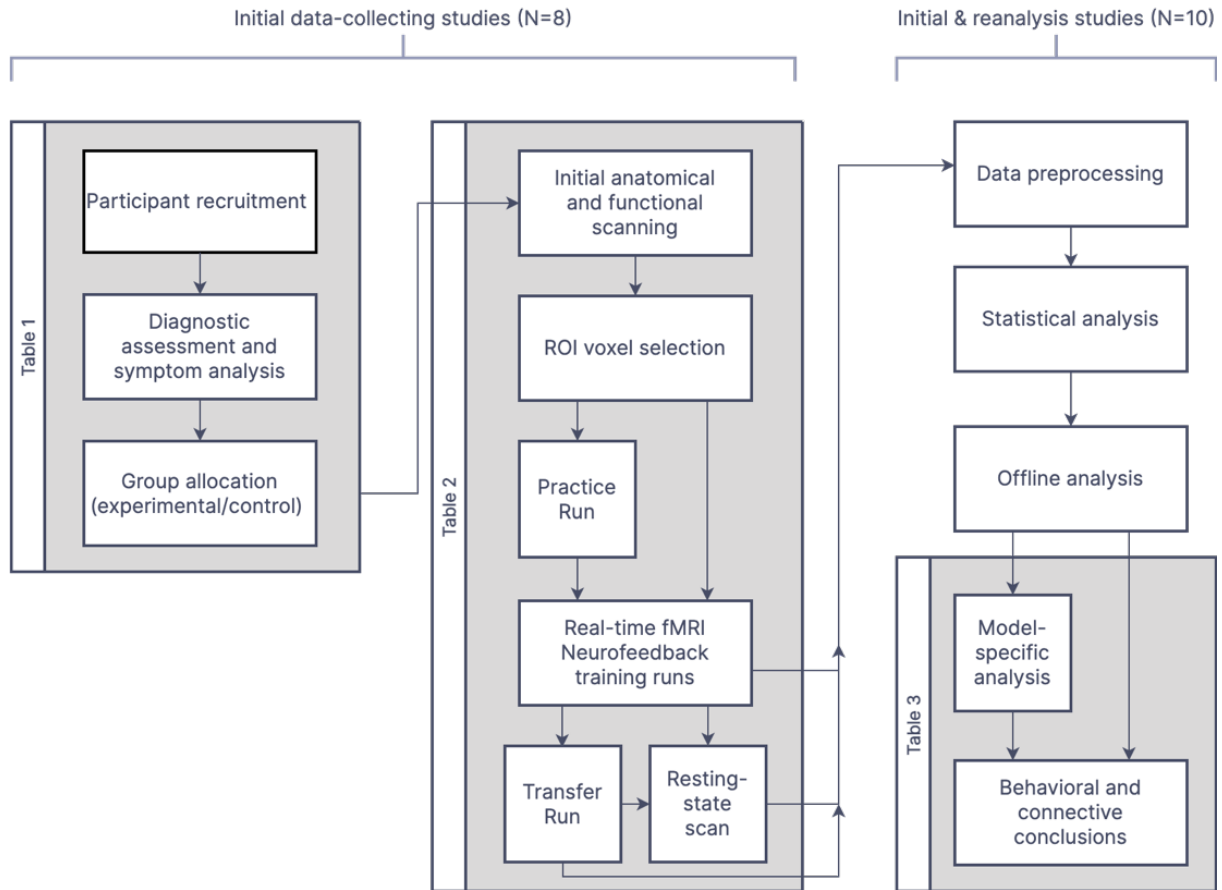
amygdala (B-AMG) (Gerin et al., 2016; Nicholson et al., 2017, 2018) or the posterior cingulate cortex (PCC)(Nicholson et al., 2022). The same protocol was used for two of these studies (Nicholson et al., 2017, 2018). A fifth study used symptom provocation as well, but implemented CRT as the therapeutic strategy (Zweerings et al., 2020). Participants in this study were instructed to upregulate the feedback signal derived from the left lateral prefrontal cortex (L-lPFC).

**Table 1** | Demographics

Study	Group	Sample (Sex)	Age ( $\pm$ SD)	Specifiers	Diagnosis	Diagnostic Measures	Symptom Assessments	Other tests and questionnaires
Gerin - 2016	EG	3 (M)	41 ( $\pm$ 3)	Combat Trauma	PTSD	CAPS, SCID	BDI, STAI	CES
Misaki - 2018	EG	16 (M)	30 ( $\pm$ 6)	Combat Veterans with PTSD	PTSD	CAPS, PCL-M	MADRS, HAM-A	--
	CG	6 (M)	31 ( $\pm$ 9)	Combat Veterans with PTSD	PTSD	CAPS, PCL-M	MADRS, HAM-A	--
	CG	11 (M)	36 ( $\pm$ 1)	Combat Veterans without PTSD	Healthy	CAPS, PCL-M	MADRS, HAM-A	--
Nicholson - 2017	EG	10 (MF)	47 ( $\pm$ 7)	--	PTSD	CAPS, SCID	BDI, MDI, RSDI	CTQ
Nicholson - 2018	EG	14 (MF)	48 ( $\pm$ 10)	--	PTSD	CAPS, SCID	BDI, MDI, RSDI	CTQ
Nicholson - 2022	EG	14 (MF)	50 ( $\pm$ 5)	--	PTSD	CAPS, SCID	BDI, MDI, RSDI, DERS	CTQ
	CG	15 (MF)	38 ( $\pm$ 13)	--	Healthy	CAPS, SCID	BDI, MDI, RSDI, DERS	CTQ
Zotев - 2018	EG	15 (M)	31 ( $\pm$ 5)	Combat Trauma	PTSD	CAPS, PCL-M	HDRS, MADRS	--
	CG	8 (M)	37 ( $\pm$ 8)	Combat Trauma	PTSD	CAPS, PCL-M	HDRS, MADRS	--
Zweerings - 2018	EG	9 (MF)	42 ( $\pm$ 14)	PTSD after single traumatic event	PTSD	ICD-10 nosis	IES-R, PANAS-X	--
	CG	9 (MF)	41 ( $\pm$ 13)	--	Healthy	--	PANAS-X	--
Zweerings - 2020	EG	20 (MF)	46 ( $\pm$ 12)	PTSD after single traumatic event	PTSD	ETI-TS, SCID	HADS, PANAS, SAM	WST, digit-span task, TCQ-R
	CG	21 (MF)	44 ( $\pm$ 11)	--	Healthy	--	HADS, PANAS, SAM	WST, digit-span task, TCQ-R

*The demographics of each original research article including their diagnosis (relative to PTSD), the tests used for diagnostic confirmation and those used to measure symptom severity.* EG: experimental group; CG: control group; CG\*: sham neurofeedback used as control condition; HC: healthy control; M: male; F: female; CAPS: Clinician Administered PTSD Scale for DSM-IV; PCL-M: PTSD Checklist – Military version; SCID: Structured Clinical Interview for DSM-IV; ICD-10: International Classification of Diseases—version 10; ETI-TS: Essener Trauma-Inventar-traumasymptomatik (German version of CAPS); BDI: Beck Depression Inventory; STAI: State-Trait Anxiety Inventory; MADRS: Montgomery-Åsberg Depression Rating Scale; MDI: Multiscale Dissociation Inventory; PANAS-X: German version of the Extended Positive and Negative Affect Scale; RSDI: Response to Script Driven Imagery Scale; SAM: Self-Assessment Manikin; DERS: Difficulty in Emotion Regulation Scale; HAM-A: Hamilton Anxiety Scale; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; CES: Combat Exposure Scale; CTQ: Childhood Trauma Questionnaire; IES-R: Impact of Event Scale – Revised; TCQ-R: Thought Control Questionnaire (German version); WST: Wortschatztest (German verbal intelligence test).

The remaining three studies implemented PEET, using autobiographical positive memory recall (APMR) as the emotional stimulus (Misaki et al., 2018b; Zotev et al., 2018; Zweerings et al., 2018). Two of these studies instructed participants to upregulate the feedback signal, the ROI for which was either the left horizontal segment of the intraparietal sulcus (L-HIPS) for the CG or the left amygdala (L-AMG) for the EG; these studies were conducted by the same research group and the same protocol was used for both (Misaki et al., 2018b; Zotev et al., 2018). The third study also instructed participants to upregulate the feedback signal, this time derived from the anterior cingulate cortex (ACC)(Zweerings et al., 2018).



**Figure 3** | Flow chart of the general methodological path followed by the reviewed studies.

For seven of the studies, feedback from the ROI was updated continuously (with a two to four second lag) for the participant to use throughout the task/condition. One study however (Zweerings et al., 2020), provided only intermittent feedback in between conditions. This took the form of a two digit number that indicated the percent signal change (PSC) that occurred within the ROI over the previous condition.

The schedules followed by each study fell into two categories; one entailed three sessions (visits) with at least three neurofeedback runs per session, and the other included only one session with two to three rt-fMRI-NF runs. In seven of the studies, participants were given a ‘practice’ or trial run in the MRI scanner directly preceding the first NF run and in six of the studies, participants did an extra run directly after the last NF run. In these transfer runs (TR), the participants went through all the

same regulatory and task-based conditions as the NF runs but did not receive feedback. In another study (Zweerings et al., 2020), only half of the participants got a transfer run due to the crossover design that had a randomized group do four rt-fMRI runs, one with NF and the next without or one without NF and the next with (i.e. NF-NoNF-NF-*NoNF* vs. NoNF-NF-NoNF-NF).

**Table 2** | Neurofeedback Protocol

Study	Group	Therapeutic Strategy	ROI	Feedback frequency	Regulatory strategies	Emotional Stimulus	Stimulus Presentation	Runs/ Session	NF Sessions	PR	TR
Gerin - 2016	EG	EIRT	↓B-AMG	Continuous	Not provided	Personalized trauma script	Aural	5-6	3	N	N
Misaki - 2018	EG & HC	PEET	↑L-AMG	Continuous	Provided	APMR	Self-generated	3	3	Y	Y
	CG*	PEET	↑L-HIPS	Continuous	Provided	APMR	Self-generated	3	3	Y	Y
Nicholson - 2017	EG	EIRT	↓B-AMG	Continuous	Not provided	Symptom provocation	Visual	3	1	Y	Y
Nicholson - 2018	EG	EIRT	↓B-AMG	Continuous	Not provided	Symptom provocation	Visual	3	1	Y	Y
Nicholson - 2022	EG & HC	EIRT	↓PCC	Continuous	Not provided	Symptom provocation	Visual	3	1	Y	Y
Zotev - 2018	EG	PEET	↑L-AMG	Continuous	Provided	APMR	Self-generated	3	3	Y	Y
	CG*	PEET	↑L-HIPS	Continuous	Provided	APMR	Self-generated	3	3	Y	Y
Zweerings - 2018	EG & HC	PEET	↑ACC	Continuous	Provided	APMR	Self-generated	3	3	Y	Y
Zweerings - 2020	EG & HC	CRT	↑L-IPFC	Intermittent	Provided	Symptom provocation	Visual	2	1	Y	Y**

*The neurofeedback training protocol for each original research article. Studies with different protocols for the control and experimental groups have two rows. EIRT: Emotion induction and regulation training; PEET: Positive emotion enhancement training; CRT: Cognitive reappraisal training; AMG: amygdala; HIPS: horizontal segment of the intraparietal sulcus; PCC: posterior cingulate cortex; ACC: anterior cingulate cortex; PFC: prefrontal cortex; APMR: Autobiographical positive memory recall; N: no; Y: yes; \*\*crossover study that caused half of each group to receive a transfer run, and the other half an extra practice run; B-: bilateral; L-: Left; l: lateral; PR: practice run; TR: transfer run.*

## Behavior and Connectivity Findings

Once the MRI data collection was complete, images were preprocessed and often transformed into template brain spaces. The initial statistical analyses were performed along with offline image processing which included basic General Linear Modeling (GLM) of within- and between-group activation patterns. Some studies stopped analysis at this point while others continued on to model specific analyses (**Figure 3**). The two most common analysis methods included linear regression and seed-based functional connectivity analysis; others included Structural Equation Model Mapping (SEMM), general Psychophysiological Interaction (gPPI) analysis, Dynamic Causal Modeling (DCM), Independent Component Analysis (ICA) and Principal Component Analysis (PCA). Each article reported successful ROI regulation in participants with PTSD and all but one reported some sort of symptom improvement after rt-fMRI-NF intervention (**Table 3**).

**Table 3** | Behavior and connectivity findings

Study	Therapeutic Strategy	Analysis Model	Symptom improvement	Areas of Increased Connectivity	Areas of Decreased Connectivity	Successful ROI Regulation
Misaki - 2018	PEET	Longitudinal MDMR	↓ PCL-M, CAPS (total, sub-D, sub-C), MADRS, HAM-A	(rsFC)↑ SMA—dACC; PCun—L-dlPFC; L-AMG—vIPFC		Y
Misaki - 2019*		SEMM	↓ CAPS, PCL-M, MADRS		(reg>view)↓ dmPFC, MCC, PCun, R-SPL, R-I, R-cerebellum culmen	Y
Misaki - 2021**		Linear model analysis	↓ CAPS, MADRS	↑ hippocampal volume (L-CA1 head subfield)		Y
Zotev - 2018		Seed-based functional connectivity	↓ CAPS (overall, sub-C, sub-D); ↓HDRS	(reg>view)↑ L-AMG – [L-dlPFC; L-IOFC; and R-AMG/PHG]	(reg>view)↓ L-AMG—[Lingual gyrus; R-PCC; and R-angular gyrus]	Y
Zweerings - 2018		Linear regression	↓ IES-R (total and intrusive symptoms)	(reg>base)↑ ACC, L-PFC		Y
Gerin – 2016	EIRT	Seed-based functional connectivity	↓ PCL-M & CAPS	(rsFC)↑ AMG - OFC/vACC	(rsFC)↓ B-AMG—[AI, PHC, PCun, dACC]	Y
Nicholson - 2017		gPPI, DCM	↓ CAPS	(reg>view)↑ vIPFC, dlPFC, dmPFC	(reg>view)↓ B-AMG	Y
Nicholson - 2018		ICA, PCA	No changes in symptomatology observed	(rest & reg)↑ L-CEN recruitment; (reg>view)↑ SN recruitment	(reg>view)↓ B-AMG	Y
Nicholson - 2022		Linear regression, MLC	↓ RSDI (distress symptoms and reliving symptoms), DERS, CAPS		(reg>view)↓ PCC/PCun; dmPFC; L-postcentral gyrus; R-temporal pole; R-STG; MCC; L-AMG/hippocampus	Y
Zweerings - 2020	CRT	Whole brain GLM	↓ PANAS (negative affect) and ETI (intrusion and avoidance symptoms)	(reg>view)↑ L-dlPFC, SMA, L-IFG, cerebellum	(reg>view)↓ B-AMG	Y

The analysis models used for each initial data-collecting and reanalysis study, along with the observed changes in symptoms and connectivity in participants with PTSD. The shaded rows indicate the first study listed using a particular therapeutic strategy. ↓ = a decrease in diagnostic score or connectivity; ↑ = an increase in diagnostic score or connectivity; CAPS sub-D: CAPS criterion D subscale, hyperarousal symptoms; CAPS sub-C: CAPS criterion C subscale, avoidance symptoms; MDMR: Multivariate Distance Matrix Regression; MCL: machine learning classification; (reg>view): change was greater during regulation conditions compared to view conditions; base: baseline measure before NF; (rest & reg): change the same during regulation and rest conditions; rsFC: resting state functional connectivity; L-: left; R-: right; OFC: orbitofrontal cortex; MCC: mid cingulate cortex; SMA: supplementary motor area; PCun: precuneus; PHG: parahippocampal gyrus; PHC: parahippocampal cortex; SN: salience network; CEN: central executive network; STG: superior temporal gyrus; SPL: superior parietal lobe; AI: anterior insula; v: ventral; d: dorsal; m: medial; \*Reanalysis of Zotev-2018 data; \*\*Reanalysis of Misaki-2018 data.

### Symptom and Severity Changes

Enhanced FC between the AMG and PFC (OFC, dlPFC, dmPFC, vACC) was positively correlated with the degree of CAPS score change in five studies (Gerin et al., 2016; Misaki et al., 2018b; Nicholson et al., 2017, 2022; Zotev et al., 2018; Zweerings et al., 2020). A greater reduction in CAPS score was also associated with increased FC between the PCun and L-dlPFC (Misaki et al., 2018b), ACC upregulation (Zweerings et al., 2018), and decreased FC of the L-AMG with both the R-PCC and R-angular gyrus (Zotev et al., 2018). Higher activation in the AI during view conditions (emotion induction without active regulation) was not positively correlated with improved CAPS scores, and was actually associated with a lesser improvement in symptomatology (Nicholson et al., 2022).

### Amygdala Downregulation

The studies investigating AMG downregulation reported several similar changes including increased PFC activity and connectivity with the AMG, paired with decreased activity within the B-AMG in general. Gerin et al. (2016) reported changes in resting-state functional connectivity (rsFC) for structures in regard to the ROI (B-AMG). These included increased rsFC with the OFC and vACC, decreased rsFC with the AI, PHC, PCun, and dACC, and decreased rsFC between the L/R-AMG. Nicholson et al. (2018) reported successful B-AMG downregulation during the *regulate* condition (active regulation of NF signal) for all NF and transfer runs, with increasing success over each consecutive run. Participants also showed increased activation of the dlPFC during *regulate* as compared to *view* during the NF sessions. The results from the ICA and PCA analysis indicated that four components with medium to high correlations to predefined template network masks were identified from the participants' activation patterns; these included the DMN, SN, L-CEN and R-CEN. The DMN component included the B-vmPFC, IOFC, dmPFC, IFG, R-hippocampus, B-caudate and ACC. The SN component included the B-dACC, B-insula, periaqueductal gray, cerebellum (lobule V, VI), STG, MTG and MFG. Both the L-CEN and R-CEN included the superior and middle B-dlPFC, the superior and inferior parietal lobes, STG, MTG, cuneus, precuneus, PCC, thalamus, and caudate. The L-CEN also included the supramarginal gyrus, angular gyrus, B-insula, hippocampus, B-AMG, L-cerebellar region (crus 1 and VIIIB) and L-dmPFC. The R-CEN included the R-dmPFC, L-cerebellar region and R-insula. Activity within these components indicated higher overall recruitment of the L-CEN during NF compared to the R-CEN despite poor initial recruitment, and the inactivity of both CEN components during *rest* conditions (no emotional stimulus or regulation). Further, as L-CEN activity increased over NF runs, AMG activity decreased. The DMN component initially exhibited low activity during *rest*, but increased in activity level during *rest* over NF runs. Overall, the L-CEN increased significantly over the NF and transfer runs during *rest* and *regulate*, the R-CEN was most active during the *neutral* condition (natural response to neutral stimulus), the DMN increased over the NF *rest* conditions and the SN had the highest activity during the *regulate* and *view* conditions (Nicholson et al., 2018).

Nicholson et al. (2017) also reported successful ROI downregulation over the course of NF and transfer runs. This lower activation was associated with the increased activation in the dlPFC and vlPFC. An increase in task-based FC was observed to be greater during *regulate* as compared to *view* between the AMG and the dlPFC and dmPFC. Significant correlations between symptom severity and areas of activation were noted: specifically, a negative correlation between dissociative symptoms and activation in the PFC, rostral ACC (rACC), and insula, and a positive correlation between PTSD symptom severity and the degree of AMG downregulation during NF. On the final NF run as compared to the first run, stronger activation of the dlPFC and vlPFC was observed during *regulate*. The gPPI analysis identified increases in task-based FC as a result of NF (*regulate*>*view*) between the L-AMG and L-dmPFC/dACC, L-AMG and R-dlPFC and between the R-AMG and R-dmPFC. For these relationships found by the gPPI, the DCM analysis indicated a medium to strong distinction for a model that included network input to the PFC, modulation of connectivity from the AMG to PFC via the regulation condition, and modulation of connectivity from the PFC to the AMG also via *regulate* (Figure 4) (Nicholson et al., 2017).

### **PCC Downregulation**

Successful downregulation of the PCC was achieved during all NF runs and TR. For the EG, decreases in FC were observed in the PCC/PCun, B-dmPFC, L-postcentral gyrus, R-temporal pole, MCC, L-AMG, L-hippocampus, and R-STG during *regulate* as compared to *view*. For the HC, decreases in the PCC/PCun, B-postcentral gyrus, R-MTG, L-STG and R-dlPFC were observed (*regulate*>*view*). Correlations between symptom measures and activity were also observed. Positive correlations between CAPS total and L-AI activity and between DERS score and R-AI activity were noted during the *view* condition. Negative correlations between CAPS and R-dlPFC activity and between DERS and R-dlPFC activity were noted during the *regulate* condition. In other words, higher activation in the AI during view was associated with a smaller decrease in CAPS and DERS scores (i.e. higher scores relative to other end scores, though not higher than the initial symptom severity); and higher dlPFC activation during regulate was associated with greater decreases in CAPS and DERS scores (i.e. much lower scores relative to others' and relative to initial scores). A decrease in reliving and distress symptoms were also observed (Nicholson et al., 2022).

### **L-IPFC Upregulation**

Successful regulation of the L-IPFC was observed during NF. During CRT, the EG showed increased activation during *regulate* in the L-precentral gyrus and occipital regions; the HC showed increased activation of the IFG, thalamus and caudate nucleus.

A decrease in AMG activity was also observed for the EG and a stronger AMG attenuation was correlated with a stronger reduction in PTSD symptoms and negative affect. Overall, the changes in symptomatology were significant for intrusive and avoidance subscales of ETI, the total ETI score and for the PANAS negative and positive affect scores. Further, 50% of the EG showed clinically meaningful changes in symptom measurements. In a follow up interview four weeks after training, 75% of PTSD patients said they had used the CRT techniques in their daily life with beneficial effects and 95% said that they'd experienced control over their brain state during rt-fMRI-NF (Zweerings et al., 2020).

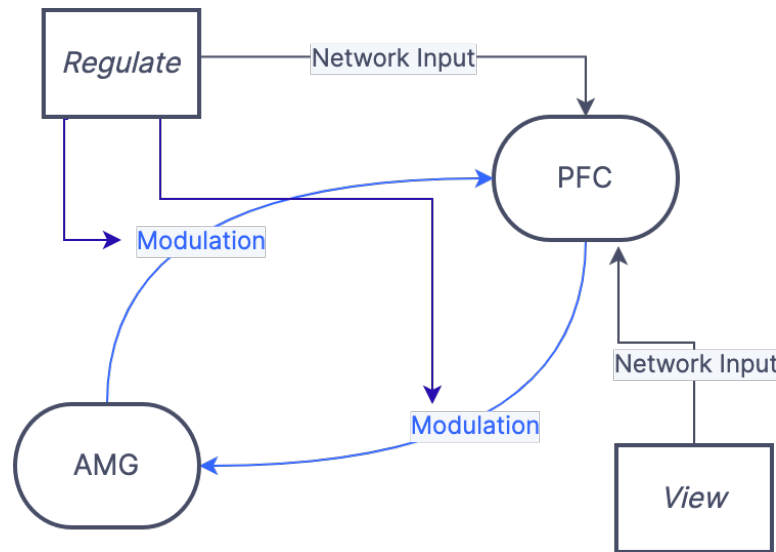
### **L-AMG Upregulation**

Zotev et al. (2018) reported a reduction in CAPS score that negatively correlated with enhanced ROI connectivity with R-AMG/PHG, L-IOFC, and L-dlPFC during the regulation task. In other words, as connectivity between these structures and the ROI increased, a greater drop in CAPS score was observed. Positive correlations between CAPS score change and change in connectivity were also observed for connections between the ROI and the lingual gyrus, R-PCC and R-angular gyrus during the regulation task. It was also noted that patients with higher initial severity scores demonstrated increased L-AMG FC with the L-IOFC, B-dlPFC and L-precentral gyrus during the first NF session. Overall, 80% of the EG participants saw a clinically meaningful reduction in CAPS score, while 38% of the CG saw such a drop (Zotev et al., 2018).

Misaki et al., (2019) reanalyzed the previous data set with SEMM and found that low activation in the dmPFC and R-MCC were associated with greater reduction in PCL-M scores. Low activation in the PCun, R-SPL, R-I and R-cerebellum culmen were also associated with symptom reduction, though these regions were only significantly associated when the ROI activity was low as well. This study also provided further data on symptom improvements as seen in Zotev et al. (2018): both decreases

in CAPS and MADRS scores were highly significant ( $p < 0.005$ ) and the drop in PCL-M scores was moderately significant ( $P < 0.05$ ) (Misaki et al., 2019).

Another study reported increased rsFC between the L-AMG and vIPFC, SMA and dACC, and between the PCun and L-dIPFC after rt-fMRI-NF. The connectivity increase between the SMA and dACC was significantly associated with the observed decrease in PCL-M scores for only the PTSD EG. A significant association between symptom decrease and connectivity increase was also seen for the CAPS sub-D score and the PCun/L-dIPFC connection (Misaki et al., 2018b). The reanalysis of this data set found a significant increase in hippocampal volume in the CA1 head region (Misaki et al., 2021).



**Figure 4** | Diagram of the DCM model found to best fit the relationships identified by the gPPI analysis performed by Nicholson et al. (2017).

### ACC Upregulation

Successful upregulation of the ACC was achieved in the NF runs and was significantly apparent in the TR (Zweerings et al., 2018). While the HC showed a higher learning rate than the EG, the EG learning rate was still significant. Both groups showed increased activation of the L-IFG, R-STG, L-STG, and L-IPL during NF compared to baseline; the EG showed increased activity in the frontopolar cortex compared to the HC. After rt-fMRI-NF, the EG showed a decrease in IES-R intrusive symptoms (Zweerings et al., 2018).

### Pre-Intervention Aberrations

Several studies reported initial structural and connective abnormalities in patients with PTSD; these included lower FC between the ROI (L-AMG) and the B-IOFC, B-dIPFC, R-mOFC, medial frontal polar cortex, vIPFC, SFG, MTG, ACC and B-insula during the practice run (Zotev et al., 2018). Lower rsFC between the L-AMG and vIPFC, SMA and dACC, PCun and L-dIPFC were also observed (Misaki et al., 2018), along with lower hippocampal volume in the CA1 head region (Misaki et al., 2021).

## Discussion

In order to properly frame the findings of this review, an explanation of the different models of PTSD neurocircuitry is first required. This is followed by an in depth look at the results found within each therapeutic strategy group, and concluded with recommendations for future rt-fMRI-NF studies for PTSD.

### *Models of PTSD*

#### **Traditional Model**

The traditional neurocircuitry model of PTSD generally stipulates that the AMG and hippocampus are hyperactive, and that medial PFC regions are hypoactive (Nicholson, Ros, et al., 2020; Patel et al., 2012). The AMG/hippocampal connection plays a role in consolidating emotional memories, but their hyperactivity in PTSD may amplify the intrusive nature of traumatic memories for people with PTSD (Chamberlin, 2019; Patel et al., 2012). The hypoconnectivity of the prefrontal regions with the AMG may also result in decreased top-down regulation that allows for further AMG hyperactivity, hyperarousal and emotion under-modulation (Nicholson, Ros, et al., 2020).

#### **Triple Network Model**

The Triple Network Model (TNM) of psychopathology is based on the idea that large-scale brain systems rely on specific intra- and inter-network connections in order to function properly. It proposes that the cognitive and affective symptoms of a psychiatric condition may stem from the aberrant connections within and between the Central Executive Network (CEN), the Salience Network (SN) and the Default Mode Network (DMN). Further, different configurations of altered connectivity within these networks may be a root cause of the vast array of psychopathologies that humans can suffer from (Menon, 2011; Patel et al., 2012). In other words, one can go from seeing too many wires that can cross in too many different ways, to looking at the connections between these three networks and how their patterns of aberrant connectivity form different constellations of symptomatology.

The patterns of ICN activity attributed to PTSD include a hyperactive SN, hypoactive CEN, and improper recruitment of DMN structures by the other networks.

#### *DMN*

The default mode network contains the PCC, mPFC, PCun, MCC and IPL (**Figure 5**) (Ahrenholtz et al., 2021; Chamberlin, 2019; Nicholson et al., 2018; Patel et al., 2012); the MTL and PHC are often included in the DMN as well (Akiki et al., 2017). While mainly active during rest, it is a key part of self-referential processing, future-oriented thinking, emotion regulation and social cognition (Koch et al., 2016; Nicholson et al., 2018; Patel et al., 2012). Altered self-referential processing is a common symptom in PTSD and has been linked to altered connectivity and recruitment of the DMN (Bluhm et al., 2009; Daniels et al., 2010).

#### *SN*

The salience network is centered around the dACC, AI, and AMG (**Figure 5**) and plays a role in the detection of internal and externally salient stimuli in order to direct attention and behavior (Chamberlin, 2019; Misaki et al., 2018a; Nicholson et al., 2018; Patel et al., 2012). This is

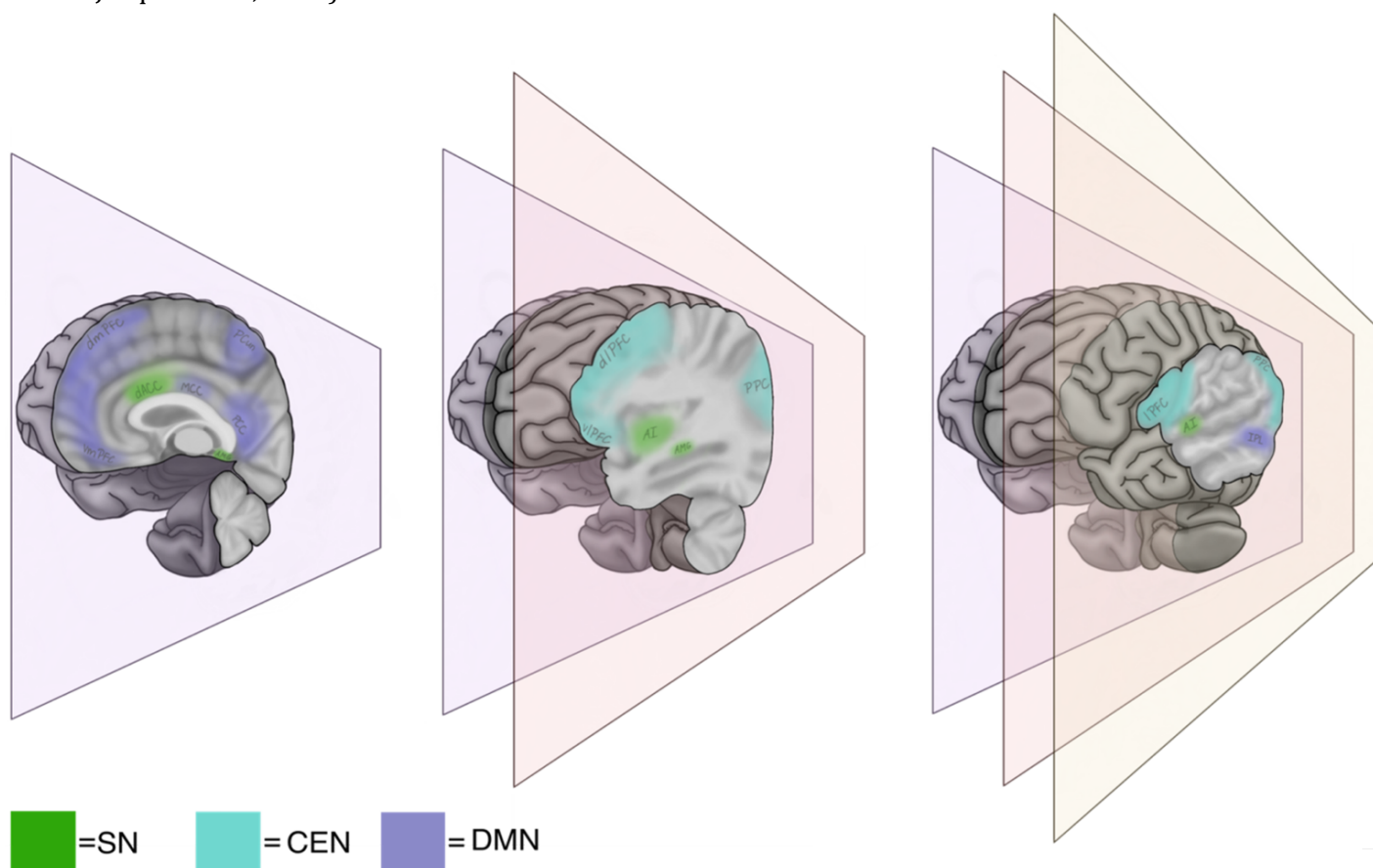


accomplished by facilitating the switch between the DMN and CEN based on the task at hand (Chamberlin, 2019; Daniels et al., 2010; Koch et al., 2016; Patel et al., 2012).

The SN also functions in interoceptive processing, autonomic regulation and reward processing (Akiki et al., 2017; Chamberlin, 2019; Cisler et al., 2014; Daniels et al., 2010; Lanius et al., 2015; Rabellino et al., 2015). Dysregulation in arousal and interoceptive processing are commonly reported symptoms in PTSD along with disrupted FC of the AI with the AMG and other SN regions (Akiki et al., 2017; Chamberlin, 2019; Cisler et al., 2013, 2014; Daniels et al., 2010; Hayes et al., 2012; Lanius et al., 2015; Misaki et al., 2018a; Rabellino et al., 2015; Rabinak et al., 2011; Sripada et al., 2012). Hyperactive symptoms are also associated with increased AMG and SN activity. This may be due to the allocation of more cognitive resources to the simultaneous monitoring of multiple stimuli; as a result, patients often show hypervigilance and difficulty focusing (Hayes et al., 2012).

### *CEN*

The central executive network is primarily based within the dlPFC, but also includes other frontoparietal and cerebellar structures (Figure 5) (Akiki et al., 2017; Chamberlin, 2019; Nicholson et al., 2018). The main functions of the CEN are related to the cognitive control of thought, emotion, working memory and behavior (Nicholson et al., 2018). In PTSD, cognitive dysfunction symptoms are often linked to the decreased recruitment of the CEN (Cisler et al., 2013; Russman Block et al., 2017; St. Jacques et al., 2013).



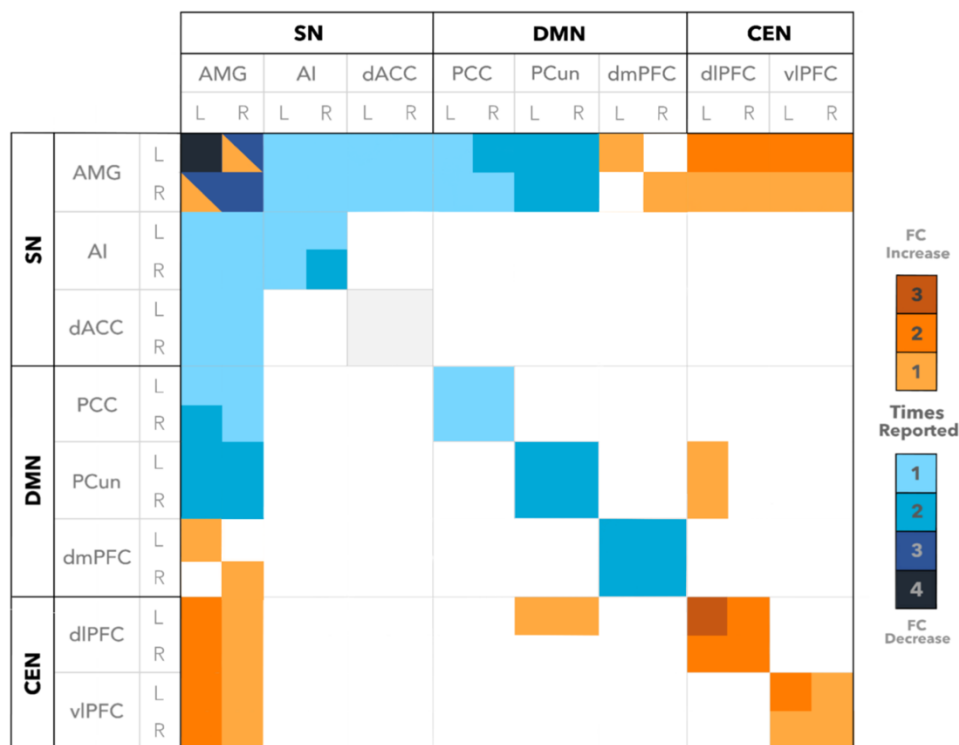
**Figure 5** | Illustration of the general ICN regions within the brain. <sup>2</sup>

<sup>2</sup> Illustration by Sophia Ryker

## The Network Balance Model of Trauma and Resolution (NBMTR)

The NBMTR is based on the TNM and the fluctuating dynamics between the three large-scale ICNs. The ideal function if each ICN is not constant but varies based on the task at hand; the broad shifts from CEN dominance to DMN dominance teeter-totters on the axis of the SN. While the SN scans for salient information in the internal and external environment, the stimulus that eventually captures one's attention determines which other network will take the dominant role in attending to the task-based needs. If, however, the SN is hyperactive, it is no longer a sturdy axis over which the CEN and DMN can smoothly transfer weight, it is more like a water balloon—making the CEN and DMN shift wildly in all directions as they try to regain balance. It is this prolonged compensation in the presence of a hyperactive SN that may give rise to the structural changes seen in PTSD (Chamberlin, 2019).

The presently reviewed studies demonstrate that aberrant connections within the DMN, SN, CEN, and all the many in between, are not permanently out of proper commission though; the adaptive potential of the human brain and body is what caused the presentation of PTSD, and it is also a way to understand and help improve it. The NBMTR posits that spontaneous resolution of dysfunctional connectivity may be achieved through psychophysiological therapy.



**Figure 6** | The frequency of connectivity changes seen after rt-fMRI-NF. Blue squares represent a reported decrease in FC while the orange squares represent a reported increase. Each darker shade of either color indicates that another study reported the same change in FC. The changes in functional activity of a single region is given along the diagonal where each structure intersects with itself on the opposite axis. Diagonal bisection of a square indicates that opposite reports were given for the same structure interaction (AMG upregulation vs downregulation).

## The Big Picture

The traditional model of PTSD centers connectivity aberrations around the hyperactive AMG and hypoactive PFC. The TNM looks at ICN interactions for psychological disorders. The NBMTR implicates dysregulated ICN dynamics in the structural changes seen in PTSD, proposing that re-balancing network dynamics is the key to spontaneous resolution.

These three models each play a significant role in the understanding of PTSD neurocircuitry by analyzing the different ways in which regions of the brain interact with each other in different times, functions and disorders. No single model is fully accurate on its own and requires the others to fill in the gaps. In order to further understand the neurobiological underpinnings of PTSD, changes in connectivity and activity can be viewed through these different lenses.

### *Connectivity Correlations*

Within the reviewed studies, several connectivity observations were made repeatedly within PTSD participants. Seven of the original data sets reported at least one subsection of the PFC increased in activity over the course of NF training (Gerin et al., 2016; Misaki et al., 2018b; Nicholson et al., 2017, 2022; Zotev et al., 2018; Zweerings et al., 2018, 2020); specific increases in FC between the AMG and PFC regions were noted in three studies (Gerin et al., 2016; Misaki et al., 2018b; Zotev et al., 2018), and a general decrease in AMG activity (reg>view) was reported in four *other* studies (Nicholson et al., 2017, 2018, 2022; Zweerings et al., 2020). Each of these findings suggests a normalization in the aberrant activity implicated in the traditional model of PTSD.

Interesting similarities also arose between two studies that employed entirely different NF protocols. Among the observations made by Nicholson et al., (2022), decreased PCun, dmPFC and MCC activity were reported (reg>view); these same areas also demonstrated decreased activity in the reanalysis of Zotev et al., (2018) done by Misaki et al., (2019). The reanalysis noted that the lower activity in the dmPFC and MCC were mediating factors on symptom improvement during regulation, and that the lower PCun activity was a moderating factor. Each of these structures is either a core structure of the DMN or very closely related to DMN functions (Koch et al., 2016; Kohn et al., 2014). Their noted decreases during both EIRT with PCC downregulation and APMR with AMG upregulation therefore suggests that appropriate switching to CEN control (NBMTR) can be achieved through different methods of rt-fMRI-NF.

Another similar observation made by studies with different NF protocols came from Zotev et al., (2018) and Nicholson et al., (2017). Despite targeting the upregulation vs the downregulation of the AMG, both reported that patients with higher *initial* symptom severity were able to regulate the AMG to a greater degree. This could be due to patients with more severe symptoms having a more severely dysregulated AMG. In this case, regulation to normal activity levels would show up as a greater amplitude of feedback change.

The frequency of connectivity and activity changes between key nodes of each ICN can be seen in **Figure 6**. Increases in connectivity between the AMG and CEN, and in CEN activity in general, shows that changes towards a more balanced relationship were achieved through neurofeedback training. The increased FC between the AMG and dmPFC (DMN region) is consistent with normalized activity as well due to the role of the dmPFC in emotion regulation. This increase, along with the CEN/AMG increase, indicates that PFC top-down regulation over the AMG during emotion regulation tasks was enhanced. The decreased FC and activity of the other DMN regions also indicates normalized connections, as the PCun and PCC work more in episodic memory retrieval, self-referential thought, and visuo-spatial imagery (Cavanna & Trimble, 2006). Hyperactivity in the PCC and PCun is often reported in PTSD, so this decreased connectivity also represents a normalizing change.

The SN/SN interactions (Figure 6) show the most reported decreases in FC and activity. As previously mentioned, the SN is hyperactive in PTSD and so these decreases represent crucial

normalizing changes within the balance of ICN activity. Of note, the bisected R/L-AMG interaction, while seemingly an outlier, represents the activity change reported by one of the studies targeting the upregulation of the AMG during PEET, and therefore does not represent an increase in aberrant activity.

## **Therapeutic Strategy**

### *PEET*

During NF targeting the upregulation of the L-AMG with APMR, a reduction in PTSD severity was observed in association with enhanced L-AMG FC with the R-AMG, L-IOFC, and L-dlPFC during regulation (Zotev et al., 2018). The L-IOFC and L-dlPFC are both structures involved with executive function and emotion regulation (CEN), and this enhanced connectivity occurred along with an increased ability of patients to regulate the NF signal—and therefore, their emotional state.

Positive correlations between a reduction in CAPS score and reduction in connectivity were observed between the AMG and R-PCC and between the AMG and R-angular gyrus also during regulation (Zotev et al., 2018). The R-PCC and R-angular gyrus are structures typically associated with the DMN, and their decreased connectivity with the L-AMG suggests that successful network switching by the SN occurred; this may have allowed CEN activity to increase, and DMN activity to decrease, therefore enhancing appropriate adaptation to the cognitive demand of the task. Further, this successful network switching is a possible marker of normalizing changes towards more balanced ICN interactions.

Also for this data set, a subsequent reanalysis with SEMM revealed that the dmPFC and MCC had significant path coefficients for mediating effects on PCL-M change (Misaki et al., 2019). Low activation in these DMN areas during regulation was associated with greater symptom improvement. Low activation in the PCun, R-SPL, R-I and R-cerebellum culmen was also associated with greater symptom improvement, but only when the NF signal (from the ROI) was also low; these areas had significant path coefficients for a moderation effect on the brain-symptom change path. These findings show that broad patterns of activation are involved in NF training, and that the relative co-activation of other regions could be a crucial area of study for understanding the mechanisms of symptom improvement in PTSD (Misaki et al., 2019).

Misaki et al. (2018b), expanded on their previous connectome wide investigation of PTSD resting state FC (Misaki et al., 2018a). With participants drawn from the same sample, two groups consisted of veterans with PTSD (PTSD-exp, PTSD-ctrl) and the third consisted of veterans without PTSD (VC); both the PTSD-exp and VC received NF from the L-AMG, while the PTSD-ctrl received NF from the L-HIPS. A demographic group included in the initial study and not in the NF study was the NC (non-trauma-exposed control), but comparisons were made to the NC rsFC data in the NF study (Misaki et al., 2018a). An initial hypoconnectivity between the L-AMG and vlPFC as compared to the NC was regained after NF training for the PTSD-exp group and not for the PTSD-ctrl (Misaki et al., 2018a, 2018b). The hypoconnectivity between the PFC and AMG that is often reported in PTSD seemed to move towards a normalized level of FC as a result of L-AMG upregulation during APMR. This also further supports the Traditional Model of PTSD and demonstrates that these dysfunctional connections can be improved through rt-fMRI-NF.

A critical observation made by Misaki et al. (2018b) was that the enhanced L-AMG/vlPFC connection was *not* associated with symptom change, but that changes in connectivity between the

SMA and dACC, and between the PCun and L-dlPFC were significantly associated with improved PCL-M and CAPS sub-D scores respectively. This reinforces the idea that the effects of NF training are not limited to the ROI and that other, mediating connections may be a key mechanism of PTSD symptom improvement.

Due to the SMA's reported role in emotion regulation, and the dACC's role in emotion expression and reappraisal, the increased FC between the SMA and dACC may indicate improved emotion representation and acceptance, leading also to improved patient views on their symptom state (Bonini et al., 2014; Buhle et al., 2014; Ellard et al., 2017; Etkin et al., 2011; Frank et al., 2014; Kohn et al., 2014; Misaki et al., 2018b). The increase in PCun/L-dlPFC FC was only observed in patients with hyperarousal symptom reduction in both the PTSD-exp and PTSD-ctrl, though the reduction in hyperarousal symptoms was only significant for the PTSD-exp group (Figure 6). The PCun, functioning in memory retrieval and mental imagery, is usually indicated as being hyperactive in PTSD, but often is reported as such in response to emotion induction (trauma related photos, for example); Misaki et al. therefore suggested that the hyperactive PCun activity might only be related to negative memories, or that the enhanced connection to the L-dlPFC resulted in increased prefrontal control over the PCun (Misaki et al., 2018b).

A subsequent analysis of this data analyzed the change in hippocampal volume after rt-fMRI-NF (Misaki et al., 2021). Though no change in volume was associated with symptom change, an increase in the L-CA1 head region was observed for PTSD participants who received feedback from the L-AMG. Because of the role of the CA1 region in autobiographical memory recall, and the increase only occurring in PTSD-exp, the APMR strategy targeting the L-AMG may have directly resulted in the selective CA1 volume increase (Misaki et al., 2021).

The final APMR study targeted ACC upregulation and included a PTSD patient EG and HC (Zweerings et al., 2018). The ACC is considered a critical part of emotion regulation, goal-directed behavior and attention, and is often reported to have decreased FC in PTSD (Kohn et al., 2014; Shenhav et al., 2013). In this study, both groups saw a significant ACC activity increase during NF runs and the TR, but the rate of learning to regulate ACC activity was much higher in the HC. The lower, though still positive learning slope of PTSD patients supports the idea that decreased ACC activity may play a role in decreased cognitive control, leading to difficulties in self-regulatory behavior (Zweerings et al., 2018). The noted increased activity in the L-PFC in PTSD patients however suggests that other regulatory structures were being recruited in the effort to regulate ACC activity; this may have enhanced the patients' ability to upregulate the NF signal and therefore, their rate of learning. The improvements in intrusive symptoms was positively correlated with the degree to which the ACC was upregulated which supports the traditional model of PTSD; with the increased activity in the PFC and ACC, the hypoactive regulatory structures common to PTSD saw a change towards normalized activity levels that were associated with improvements in PTSD symptomatology.

In all, PEET provides strong evidence towards the efficacy of rt-fMRI-NF in the treatment of PTSD. Each study reported improvements in symptomatology and reported changes between the larger ICNs, the structures implicated in dysfunctional neurocircuitry or both.

### *EIRT*

Three of the four EIRT studies, did not include a control group or condition and therefore, findings must be taken as supporting but not confirmatory (Gerin et al., 2016; Nicholson et al., 2017, 2018). These were also the only studies that investigated AMG downregulation, and two of three saw changes in symptomatology; one of which only had three participants and a flexible methodology (Gerin et al., 2016; Nicholson et al., 2017). The reason these studies did not have a CG and had a relatively small number of participants was due to their POC nature.

Both Gerin et al., (2016) and Nicholson et al., (2017) found increased FC in the PFC and decreased FC in the AMG and SN; this aligns with the traditional model of PTSD in that the hypoactive PFC and hyperactive AMG both demonstrated normalizing changes towards a more balanced relationship (Figure 4). Correlations between CAPS improvement and AMG downregulation were also noted, but the small sample sizes of these studies reduces the statistical significance of these findings in comparison with others.

Specific to (Nicholson et al., 2017) was a decrease in dissociative symptoms that was associated with an increase in rostral ACC, PFC and insula activity. While still not confirmatory evidence, it is interesting because of the regulatory role and typically diminished activity of the rACC and PFC in emotional conflict resolution, and the insula's role in interoceptive processing (Offringa et al., 2013). Activity increases in these regions could be representative of increased emotion resolution and a patient that is more in touch with their bodily experience—things traditionally lacking with dissociative symptoms.

The third study that used EIRT reported that no significant changes in symptomatology were observed (Nicholson et al., 2018). The target of this study was also the AMG and the connectivity changes throughout NF training were analyzed in terms of MLC ICN components. In other words, the task-based activity observed in participants during a practice run, was run through a machine-learning classifier that then picked out emerging patterns and matched them to the most similar preprogrammed ICN mask (a general voxel-wise map of each ICN made from previously compiled neuroimaging data). The structures with associated task-based activity were grouped together.

This component identification was done prior to NF training and consequently included the aberrant ICN interactions that are thought to underlie significant chunks of PTSD symptomatology. The L-CEN component that was identified included the PCC, PCun and hippocampus—structures typically belonging to the DMN—along with the AMG and insula, SN associated areas. The reported L-CEN activity increase over the course of the study therefore does not actually reflect a normalizing change in ICN interactions. Most of the findings of this study reveal more about the dysfunctional neurocircuitry of PTSD than the effects of NF, but even so, provides unique information on structure recruitment in PTSD. The idea that PTSD patients inappropriately recruit DMN regions during cognitively demanding tasks, for example, can be supported by the inclusion of the PCC, PCun and hippocampus in the L-CEN: the component implicated in explicit cognitive emotion regulation (Daniels et al., 2010; Nicholson et al., 2018).

While the MLC analysis did not provide much information on the efficacy of rt-fMRI-NF, it did show that AMG downregulation was achieved to a greater degree over each subsequent NF run and that dlPFC activity increased during regulation. In future studies, the MLC should also be performed during a final NF run or TR, in order to see how NF training changed task-dependent and structurally specific recruitment of ICNs.

The fourth EIRT study included both a HC and EG (Nicholson et al., 2022). Both PTSD patients and healthy controls were able to downregulate the PCC during NF and TR, and a significant decrease in reliving symptoms were shown for each group, but a significant decrease in distress symptoms was only seen for the EG. Participants with PTSD demonstrated within-group decreases in activity for the post-central gyrus, dmPFC, MCC, PCC, PCun, AMG, hippocampus and STG during regulation; in other words, reduced DMN and SN recruitment were seen which indicates a more balanced relationship between the large-scale networks was achieved through PCC downregulation.

Some other interesting findings regarding DERS and CAPS scores included a positive correlation with AI and cerebellar activity and a negative correlation with dlPFC activity. This means that participants with higher DERS/CAPS scores had higher activation within the AI and Cerebellum (lobule IV/Crus I), and participants with lower scores (HC) had higher activation in the R-dlPFC (Nicholson et al., 2022). These findings are consistent with the aberrant network recruitment proposed by the TNM for PTSD, with hyperactive SN areas and hypoactive CEN areas being associated with symptom severity.

Overall, the research done regarding the downregulation of the amygdala during EIRT did not provide substantial evidence for its efficacy in the treatment of PTSD, but did provide useful information regarding circuitry dynamics before and during NF (Gerin et al., 2016; Nicholson et al., 2017, 2018). Previous studies have indicated that AMG downregulation enhances PFC activity, and this was supported by each of the studies targeting the AMG for NF downregulation (Nicholson, Ros, et al., 2020; Patel et al., 2012). The use of EIRT in PCC downregulation produced more convincing evidence for its efficacy in PTSD treatment and is a promising foundation for future research (Nicholson et al., 2022).

### *CRT*

The single study that implemented CRT found a clinically meaningful change in symptoms scores (ETI-TS) for 50% of the patients four weeks after training, which was accompanied by significant improvements in positive and negative affect (Zweerings et al., 2020). Though few connectivity changes were reported, an increase in PFC and decrease in AMG activity was noted, indicating improved FC within the structures implicated in the Traditional Model of PTSD. This and the clinically meaningful change in ETI scores is further substantiated by the follow-up patient reports a month after training: 95% of PTSD patients said they experienced control over the NF signal, 75% said they successfully used the CR strategies in their daily life and all but one patient said that the training was helpful (Zweerings et al., 2020). The larger sample size of this study adds even more significance to these findings in comparison to the other reviewed articles.

### *Strategy Overview*

In all, the majority of the rt-fMRI-NF studies reported improved symptomatology in PTSD patients, but those that provided the strongest evidence towards its efficacy as a treatment were the CRT and PEET studies (Misaki et al., 2018b, 2019; Zotev et al., 2018; Zweerings et al., 2018, 2020). In direct comparison, PEET with AMG upregulation resulted in more diverse symptom improvements than EIRT with AMG downregulation, but it was not possible to statistically analyze the differences in score change between the two methods as Zweerings et al., (2018, & 2020) used symptom scales

that were not based on the same numerical gradient. A problem arose for statistical analysis with Nicholson et al. (2017, 2018, & 2022) as well, as only pre-NF symptom scores were provided.

Also for EIRT, the lack of CG for 75% of the studies made it difficult to determine whether connectivity and symptom changes were due to the specific ROI, the mode of emotion induction, or the number of training sessions (Gerin et al., 2016; Nicholson et al., 2017, 2018). The exception to this came from the EIRT study that targeted PCC downregulation (Nicholson et al., 2022). This study did provide significant evidence for PTSD specific symptom changes in correlation to NC changes after NF and introduced the first use of the PCC as an ROI for PTSD NF training. Critically, the efficacy of AMG downregulation was not found to be substantial in comparison to other ROIs despite its hyperactivity being one of the most reported neural aberrations in PTSD (Nicholson, Ros, et al., 2020).

It is important to note that the amount of data available on the outcomes of different NF protocols is very limited and as such, the efficacy of one method over the other cannot be determined outright. There are however, several study characteristics that have shown more promise than others.

### *Future Directions for the study of rt-fMRI-NF*

With the development of the Consensus on the reporting and experimental design of clinical and cognitive-behavioral neurofeedback studies (CRED-nf checklist) in 2020, several big-picture study characteristics should become more prevalent in rt-fMRI-NF research (Ros et al., 2020). These include sample sizes with larger statistical power, the use of control groups or conditions, implementing double-blind experimental designs, and standardized reporting on feedback specifications and outcome measures. Based on this review however, several recommendations specific to the use of rt-fMRI-NF in the treatment of PTSD can be made.

#### *Schedule*

Three of the studies reviewed in this paper implemented a three-run, one-session NF design that reported changes in symptomatology and neurocircuitry after a single day of NF training (Table 2). Four studies implemented a three-run, three-session NF design with two further follow-up visits that allowed for the analysis of longer term changes. The final study implemented a two-run, one-session design, but had a follow up visit with PTSD patients a month later to re-examine symptom severity and perceived efficacy. Out of these three timelines, the three-run, three-visit timeline had the most significant symptom/connectivity correlations. This is likely due to the greater amount of time spent practicing emotion regulation techniques.

It is reasonable to expect that people will require more than a single day to learn to play the piano, and it is reasonable to expect that PTSD patients will require more than a single training session to learn to regulate their aberrant emotional circuits. This extended timeline also make sense as a large portion of PTSD symptomatology stems from difficulties in cognitive tasks, memory and attention (Hayes et al., 2012).

Based on this review, the recommended schedule for rt-fMRI-NF in the treatment of PTSD is three NF runs per session, at least three sessions and a follow-up period that covers several months. With the increased amount of training, it is likely that greater improvements in symptomatology and connectivity will be observed; the long-term effects of NF can then be analyzed with the extended follow-up period.



### *ROI and Therapeutic Strategy*

The EG ROIs used in the reviewed studies include the AMG, PCC, ACC, and L-IPFC (Table 2), with the strongest results coming from the studies that targeted AMG and L-IPFC upregulation and PCC downregulation. Each of these used a different therapeutic strategy (PEET, CRT and EIRT respectively), but even so, demonstrated similar connectivity changes of increased FC with IPFC regions (Misaki et al., 2018b; Zotev et al., 2018; Zweerings et al., 2020), decreased AMG FC (Misaki et al., 2018b; Nicholson et al., 2022; Zotev et al., 2018; Zweerings et al., 2020), and lower MCC, dmPFC and PCun activity (Misaki et al., 2019; Nicholson et al., 2022). The common connectivity themes and associated symptom reductions show that these three ROIs, when regulated in their respective directions, recruit similar wide-spread brain regions involved in the neurobiological fabric of PTSD.

Future research investigating AMG upregulation with PEET should further explore its efficacy in symptom improvement following the experimental design of Zotev et al., (2018) and Misaki et al. (2018), but with larger sample sizes. For future studies using L-IPFC upregulation with CRT, the work of Zweerings et al., (2020) should be expanded upon by increasing the number of NF sessions; the highly positive results from just a single session of CRT NF suggest that even more significant changes in symptomatology could be achieved with a greater number of sessions. Future investigations into PCC downregulation with EIRT should also increase the number of training sessions used in Nicholson et al. (2022).

It is recommended that future studies expand the research into AMG upregulation with PEET, L-IPFC upregulation with CRT, and PCC downregulation with EIRT. These should also be conducted with larger sample sizes and the previously recommended schedule.

### *Clinical measures*

Every rt-fMRI-NF study dealing with PTSD should use the CAPS scale (total and subscales) to assess initial vs final symptom severity (in English speaking countries). For studies conducted in Germany, the ETI-TS should be used. Other symptom measures can be used as well, but the pre and post NF scores for either CAPS or ETI should be given for each dataset as they can be used for any population and cover different subscales of symptoms, allowing for the analysis of more nuanced symptomatic changes. This would also allow for direct inter-study comparison of symptom improvements and would enhance the productivity of research into rt-fMRI-NF and PTSD.

## **Conclusion**

This review investigated the efficacy of rt-fMRI-NF as a treatment for PTSD and found evidence that this non-invasive, neurobiologically informed intervention can result in normalized functional connectivity and improved symptomatology. The most successful therapeutic strategy and ROI pairings were positive emotion enhancement with AMG upregulation, emotion induction and regulation with PCC downregulation, and cognitive reappraisal with L-IPFC upregulation. Consistent reports of increased activity in prefrontal regions and decreased activity in the AMG showed that the aberrant connectivity defined by the Traditional Model of PTSD can be improved with rt-fMRI-NF. Supporting evidence for the Triple Network Model was also frequently reported, with regulatory conditions showing enhanced activity in the central executive regions and diminished activity in the default mode network. These activity changes represent improved CEN-DMN task-based switching—a crucial function of the large-scale neural networks that is all too often dysregulated in PTSD.

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