

Amygdala versus Posterior Cingulate Cortex rt-fMRI Neurofeedback for PTSD: Interim Therapeutic and Mechanistic Findings from a Multi-Session RCT

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Introduction

PTSD is associated with altered interactions among large-scale intrinsic connectivity networks, including the salience network (SN), default mode network (DMN), and central executive network (CEN). Real-time fMRI neurofeedback (rt-fMRI-NFB) provides a spatially specific approach for modulating clinically relevant hub regions within these networks. The amygdala, a SN hub involved in threat and emotion processing, has traditionally been targeted in rt-fMRI-NFB studies of PTSD due to its hyperactivity in this population. Amygdala downregulation protocols have reported clinically meaningful PTSD symptom severity reductions alongside prefrontal/CEN regulatory engagement [1-3]. More recently, the posterior cingulate cortex (PCC) has emerged as a promising DMN-focused target for treating PTSD [4]. As a central DMN hub implicated in self-referential processing, the PCC contributes to trauma reliving in PTSD and shows hyperactivity to trauma-related cues. In a single-session pilot study directly comparing PCC- and amygdala-targeted rt-fMRI-NFB, reductions in state reliving and distress were observed only in the PCC group [5]. Preliminary connectivity work suggests PCC downregulation may engage anterior DMN regions [6]. It remains untested whether PCC-targeted, multi-session regulation can produce therapeutic effects comparable to the more established amygdala approach while engaging distinct, DMN-based mechanisms. This would support SN- and DMN-based mechanisms as two distinct, viable routes to PTSD symptom relief.

In this interim active-arm report from an ongoing, larger randomized controlled trial, the first N=30 participants with PTSD completed three weekly sessions of rt-fMRI-NFB targeting either the amygdala or PCC. The primary objective is to compare PTSD symptom severity change across NFB targets. Given promising single-session evidence for PCC-targeted regulation [4,5], we hypothesize that multi-session PCC-targeted regulation will produce reductions in PTSD symptom severity comparable to the more established amygdala-targeted approach. As a secondary, mechanistic objective, we examine target engagement, whole-brain activation, and effective connectivity within target-specific circuits during regulation. Target engagement and whole-brain activation are reported here; regulation-dependent effective connectivity is currently being estimated on this same sample. We hypothesize top-down or reciprocal (rather than bottom-up) amygdala–prefrontal connectivity during amygdala-targeted regulation. For PCC-targeted regulation, given limited prior connectivity evidence, we will explore the direction of PCC–anterior DMN connectivity changes.

Methods

This randomized, two-group, double-blind trial examined rt-fMRI-NFB in adults with PTSD. Participants (N=30) aged 18–65 years with a current primary diagnosis of PTSD were randomized to receive neurofeedback from one of two target regions: the amygdala (n=15) or PCC (n=15). Participants completed three weekly rt-fMRI-NFB sessions over a three-week period on a 3 T

Siemens Biograph mMR scanner. Each neurofeedback session included three training runs in which participants attempted to downregulate their assigned target region while viewing personalized trauma-related words. The primary clinical outcomes were self-reported trait PTSD symptom severity, measured with the PTSD Checklist for DSM-5 (PCL-5) at baseline, after each neurofeedback session, and one-month follow-up, and self-reported state symptoms, measured with the Response to Script-Driven Imagery (RSDI) scale immediately following regulation while still in the scanner. Secondary, mechanistic outcomes included target-region BOLD regulation and whole-brain activation during regulation, reported here. Regulation-dependent effective connectivity within target-specific circuits will be estimated using dynamic causal modeling (DCM). Models will include amygdala and prefrontal control regions for the amygdala group, and PCC and anterior DMN hubs for the PCC group, with regulation periods modeled as modulatory inputs on candidate directed connections.

Results

Primary self-report clinical outcomes: Both groups exhibited clinically meaningful reductions in trait PTSD symptom severity on the PCL-5, with large effects in the amygdala group (effect size $d = 1.24$, $pFDR < 0.001$) and medium-to-large effects in the PCC group ($d = 0.73$, $pFDR < 0.001$). Significant group-by-timepoint interactions suggested distinct symptom trajectories across targets, with the amygdala group showing earlier improvement. In contrast, state symptoms collected in the scanner (RSDI) showed earlier improvement in the PCC group.

Secondary mechanistic outcomes: Both groups engaged their assigned targets, exhibiting reduced target-region BOLD during regulation blocks across sessions. Whole-brain direct group comparisons revealed that the PCC group displayed greater medial prefrontal cortex (mPFC) activation than the amygdala group across sessions (cluster-level $pFDR < 0.001$), consistent with preferential anterior DMN engagement. Planned DCM analyses of target-specific effective connectivity, evaluating the directional hypotheses described above, are in progress on this same sample.

Conclusions

These preliminary findings suggest that multi-session PCC-targeted rt-fMRI-NFB may offer clinical benefit comparable to the more established amygdala-targeted approach, with both groups showing clinically meaningful PTSD symptom reductions that followed distinct trajectories. Greater anterior DMN engagement during PCC-targeted regulation further suggests that amygdala and PCC neurofeedback may recruit partially distinct regulatory networks, supporting the neurobiological specificity of these target-focused interventions. These findings should be interpreted in light of the modest interim sample size ($n=15/\text{group}$). Together, these findings lend preliminary support to selectively targeting SN- or DMN-based mechanisms as viable routes to PTSD symptom relief. The ongoing DCM analyses will test this more directly.

References

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