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Study protocol for a multi-session randomized sham-controlled trial of PCC- and amygdala-targeted neurofeedback for the treatment of PTSD

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Abstract

Background Post-traumatic stress disorder (PTSD) is marked by distressing and often chronic symptoms, including the reliving and re-experiencing of trauma memories, avoidance, negative alterations in cognition and mood, heightened arousal and reactivity, and dissociation. Current psychotherapies and pharmacotherapies may yield suboptimal results for many individuals with PTSD, underscoring the need for new approaches. Recent neuroimaging research highlights functional disruptions in brainstem, cerebellar, limbic, and cortical networks underlying PTSD. Real-time functional magnetic resonance imaging neurofeedback (rt-fMRI-NFB) is an emerging intervention that has directly targeted limbic (i.e., the amygdala) and cortical (i.e., the posterior cingulate [PCC]) regions and has shown promising initial findings in PTSD. However, key research gaps remain, such as the need for rigorous randomized controlled trials (RCTs) to establish clinical efficacy and neurophysiological specificity, determine optimal brain targets, and evaluate dose-response relationships.

Methods This double-blind, multi-session RCT investigates whether targeting distinct brain regions via rt-fMRI-NFB yields differential therapeutic effects in individuals with PTSD ($n = 72$). Participants will be randomly assigned to PCC-targeted rt-fMRI-NFB, amygdala-targeted rt-fMRI-NFB, or a sham-control group. Each participant will complete three rt-fMRI-NFB sessions over three weeks, with clinical assessments at baseline, after each session, and at a one-month follow-up. The sham group will receive a 'yoked' feedback signal from a random participant in one of the experimental groups. The primary outcome is PTSD symptom severity, measured using the PTSD Checklist for DSM-5 (PCL-5). Secondary outcomes include depressive symptoms, emotion regulation difficulties, dissociation, anxiety, interoceptive awareness, sleep quality, and state PTSD symptoms during trauma provocation. Neural outcomes will

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also be examined, focusing on brain activation and connectivity patterns. Additionally, qualitative interviews and actigraphy will assess participants' subjective experiences and track sleep and physical activity patterns.

Discussion This trial aims to address critical research gaps by evaluating the therapeutic potential of rt-fMRI-NFB targeting the PCC and amygdala in PTSD. By employing a wide range of data collection methods, this study will provide valuable insights into the clinical and neural effects of rt-fMRI-NFB. This study will be the first to investigate the phenomenological dimension and physiological impacts of rt-fMRI-NFB in this population. Taken together, these findings are expected to contribute to the development of targeted neurofeedback interventions and clarify the therapeutic mechanisms underlying rt-fMRI-NFB for PTSD.

Trial registration This study has been registered with ClinicalTrials.gov under the trial registration number NCT05456958. It was initially registered on July 13th, 2022, and most recently updated on October 9th, 2024.

Keywords Post-traumatic stress disorder, Real-time fMRI neurofeedback, Randomized controlled trial, Posterior cingulate cortex, Amygdala

Introduction

Post-traumatic stress disorder (PTSD) is a complex and often chronic mental health condition that can develop following exposure to traumatic events. It is characterized by a constellation of persistent and distressing symptoms, including the reliving and re-experiencing of traumatic events, persistent avoidance of trauma-related stimuli, negative alterations in cognition and mood, heightened arousal and reactivity, sleep disturbances (e.g., insomnia and recurrent nightmares), and dissociative symptoms [1]. A significant portion of the global population will experience traumatic events, with a substantial subset developing PTSD, underscoring its broad public health impact [2]. While psychotherapy and pharmacotherapy remain the cornerstone of PTSD treatment [3, 4], these approaches often yield suboptimal outcomes, with approximately one-half to two-thirds of patients failing to achieve full remission or discontinuing treatment prematurely [5–8]. Thus, there is an urgent need for innovative treatment modalities that effectively target the neurobiological underpinnings of PTSD and provide sustainable symptom relief.

In recent decades, functional magnetic resonance imaging (fMRI) has significantly advanced our understanding of the neurobiological mechanisms underlying PTSD. Extensive research has documented strong associations between specific symptom presentations in PTSD and functional disruptions across multiple brain regions (e.g., 9–11). In particular, hyperactivity within the amygdala—a key region involved in emotion generation and processing—has been robustly linked with PTSD symptoms both at rest and during trauma provocation [9, 10, 12–20]. PTSD is also associated with altered functional connectivity between the amygdala and other cortical and subcortical regions, including those implicated in emotion regulation and self-referential processing, such as the anterior cingulate cortex, insula, prefrontal cortex, and posterior cingulate cortex (PCC) [13, 21–26].

Although not emphasized in early models of PTSD neurocircuitry, a growing body of research has established the critical role of the PCC and default mode network (DMN) in PTSD. The PCC, a central hub of the DMN [27–31], exhibits consistent PTSD-related disruptions in functional connectivity both at rest [10, 11, 16, 20, 26, 32–36] and during executive functioning tasks [37, 38]. Graph theoretical analyses have identified functional segregation between anterior and posterior DMN hubs during rest among individuals with PTSD [33, 39–41]. Moreover, during working memory tasks, individuals with PTSD display heightened PCC connectivity with other DMN regions—contrasting with the stronger central executive and salience network engagement observed in healthy controls [37]—suggesting maladaptive DMN involvement under cognitive load. Importantly, the PCC shows marked hyperactivity in response to trauma-related cues and threatful conditions, as reported by multiple studies and meta-analyses, where many also observe links with the reliving and re-experiencing of trauma memories [42–46]. Taken together, these findings underscore the PCC and broader DMN as key contributors to PTSD pathophysiology. Indeed, functional alterations in both the amygdala and PCC—particularly hyperactivity during trauma symptom provocation—highlight their central roles in PTSD and support their selection as clinically-relevant neurofeedback targets in the present study.

Neurofeedback is a non-invasive technique whereby neural processes are measured and displayed to participants in real-time via auditory and/or visual representations, thereby enabling the self-regulation of brain states [47]. This approach has shown promise in targeting neural disruptions associated with a variety of psychiatric conditions, including PTSD, generalized anxiety disorder, major depressive disorder, and schizophrenia, among others [48–51]. In the context of PTSD specifically, several recent systematic reviews and meta-analyses have reported significant symptom improvements associated with the use of neurofeedback [52–56]. Moreover,

neurofeedback has been shown to be effective even among individuals with treatment-resistant PTSD [53, 57, 58]. Several studies have explored the use of electroencephalography-based neurofeedback (EEG-NFB) to modulate altered neural oscillations in PTSD [58–64]. A 20-week randomized controlled trial (RCT) by our group revealed that EEG-NFB led to significantly reduced symptoms, with 61.1% of participants in the experimental group no longer meeting diagnostic criteria for PTSD at a 3-month follow-up [62]. This trial also observed a normalization of aberrant connectivity within large-scale brain networks, including the DMN and salience network (SN), following EEG-NFB [62, 65]. Recent studies have also investigated real-time fMRI-based neurofeedback (rt-fMRI-NFB), which offers superior spatial resolution and the ability to capture signals from deep brain structures compared to EEG-NFB, thereby enabling the precise regulation of neural disruptions in brain regions such as the amygdala and PCC. As neurofeedback research in PTSD continues to progress, rt-fMRI-NFB studies are critical to determine optimal treatment targets and elucidate their neurophysiological specificity, thereby advancing our understanding of the mechanisms underlying neurofeedback interventions. Although several recent studies have successfully implemented rt-fMRI-NFB in PTSD populations [66–81], several critical research gaps warrant further exploration.

First, much of the existing rt-fMRI-NFB research in PTSD consists of pilot studies lacking a control group, which limits their ability to determine the neurophysiological specificity of brain activity regulation through rt-fMRI-NFB and does not account for potential placebo effects. This gap highlights the pressing need for randomized, sham-controlled trials of rt-fMRI-NFB in PTSD.

Second, there is an ongoing challenge in selecting specific brain targets among several candidate regions that are clinically relevant in the context of PTSD. Psychiatric conditions—including PTSD—involve complex neurobiological mechanisms with pathophysiological alterations spanning multiple brain regions [10, 11, 16, 32, 34, 43]. To date, most rt-fMRI-NFB studies in PTSD have focused on regulating amygdala activity, either directly or indirectly through modulation of frontal brain regions [68, 70, 72, 74, 76–79, 81]. Interestingly, only one rt-fMRI-NFB study in PTSD has examined regulation of the PCC [73]. Post-hoc comparisons between PCC- and amygdala-targeted rt-fMRI-NFB pilot studies conducted by our group showed that PCC downregulation was differentially associated with reduced reliving and distress symptoms along with concomitant decreases in PTSD-associated brain activity [67]. Additionally, accumulating evidence from previous activation and connectivity analyses of each study separately suggests that distinct neural mechanisms are associated with amygdala versus PCC downregulation. More specifically, amygdala downregulation was primarily associated with greater involvement of prefrontal cortex (PFC) emotion regulation regions (i.e., the dorsolateral PFC) [72, 74], whereas PCC downregulation was associated with the concomitant regulation of brain regions involved in emotion generation and processing (i.e., amygdala, mid-cingulate) and interoception (i.e., insula), as well as the reintegration of the functionally segregated anterior DMN (i.e., medial PFC) [66, 73]. However, no previous RCTs have directly compared the differential therapeutic and neural effects of targeting multiple clinically relevant brain regions with neurofeedback among individuals with PTSD.

Third, while several studies have implemented multiple rt-fMRI-NFB sessions for individuals with PTSD [76–78, 81], none have rigorously investigated the dose-response relationship of this intervention on PTSD symptoms. These studies often lack session-by-session comparisons of clinical outcomes, either omitting the measurement of PTSD symptoms after each session or reporting only aggregate pre- to post-treatment changes. Although Gerin et al. [81] qualitatively reported session-by-session changes in PTSD symptoms, the small sample size of only three participants precluded quantitative analysis. Despite the limited research in this area, existing findings suggest that PTSD symptoms may continue to improve across multiple rt-fMRI-NFB sessions. For example, a study by Zweerings et al. [78] reported a linear increase in regulation amplitude over three sessions, indicating ongoing improvement in participants' regulatory abilities. Furthermore, a recent meta-analysis found a significant moderating effect of a higher number of neurofeedback training sessions on reducing PTSD symptoms, although it included both EEG- and fMRI-NFB studies [53]. Characterizing the dose-response relationship of rt-fMRI-NFB on PTSD symptoms is crucial for optimizing treatment protocols and advancing the field of clinical neurofeedback.

Fourth, despite the critical role of sleep disturbances and alterations in physical activity patterns in PTSD, no previous research has systematically examined how rt-fMRI-NFB impacts these physiological factors. Sleep disturbances and altered physical activity patterns are common in PTSD and have been associated with worse clinical outcomes [82–86]. Indeed, sleep disturbances—particularly insomnia and recurrent nightmares—are considered hallmark symptoms of PTSD, affecting up to 90% of individuals with the disorder [87, 88]. These disruptions are not only highly prevalent but often persist even after successful trauma-focused treatment, suggesting they may require targeted interventions beyond standard PTSD therapies [85]. By integrating biometric data collection, this study will provide valuable insight into the effects of rt-fMRI-NFB on sleep disturbances and

alterations in physical activity related to PTSD, thereby enhancing our understanding of its broader therapeutic effects.

Fifth, there is a notable absence of qualitative research within the rt-fMRI-NFB field, particularly regarding participants' subjective experiences during training and the regulation strategies that they employ to gain control over the neurofeedback signal. Importantly, incorporating a phenomenological dimension to rt-fMRI-NFB studies may offer a more comprehensive understanding of the training process, its impact on participants, and its contribution to improved clinical and neural outcomes [89]. In summary, the lack of control groups, challenges in brain target selection, limited understanding of dose-response effects, insufficient examination of physiological changes, and absence of research on participants' subjective experiences highlight the critical need for further research to develop more effective neurofeedback interventions for PTSD.

Study overview

The aim of this RCT is to evaluate the therapeutic and neural effects of multiple sessions of rt-fMRI-NFB targeting different clinically relevant brain regions in PTSD. Participants will be randomly assigned to receive three sessions of either (i) PCC-targeted rt-fMRI-NFB training, (ii) amygdala-targeted rt-fMRI-NFB training, or (iii) sham-control. Clinical assessments will be completed at baseline, following each of the three rt-fMRI-NFB sessions, and at a one-month follow-up. Building on previous pilot research, this study uses a rigorous randomized, double-blind, sham-controlled design to examine the neurophysiological specificity of rt-fMRI-NFB while accounting for potential placebo effects. This trial will investigate critical research gaps related to the optimization of neurofeedback protocols in PTSD by comparing between two clinically relevant target regions and examining dose-response relationships. Semi-structured qualitative interviews will be conducted following each rt-fMRI-NFB session to understand participants' subjective experiences during training and the regulation strategies they employ, thus providing important phenomenological insights. Throughout the study, data on sleep and physical activity patterns will be collected using wearable biometric devices, addressing the need to evaluate the broader therapeutic impacts of rt-fMRI-NFB.

We predict that participants in the experimental rt-fMRI-NFB groups (i.e., PCC and amygdala) will show greater reductions in PTSD symptoms and related clinical measures as compared to the sham-control group. Based on previous findings from our pilot studies [66, 67, 73, 74], we hypothesize that PCC downregulation will be associated with greater PTSD symptom reductions—which may be due to its broader network-level effects—and that differential neural activation and connectivity patterns will be observed for the PCC and amygdala groups. Based on existing neurofeedback research [53, 78], we predict that PTSD symptoms will progressively decrease over the course of three rt-fMRI-NFB sessions. Finally, exploratory analyses will be conducted to assess the physiological, phenomenological, and specific symptom cluster effects of rt-fMRI-NFB in both groups.

Methods

Trial design

The study will be a prospective, single-centre, randomized, three-group, double-blind trial to evaluate the efficacy of PCC- and amygdala-targeted rt-fMRI-NFB for PTSD (Fig. 1). The trial setting is the Lawson Health Research Institute, St. Joseph's Hospital, London, Ontario, in association with Western University. This

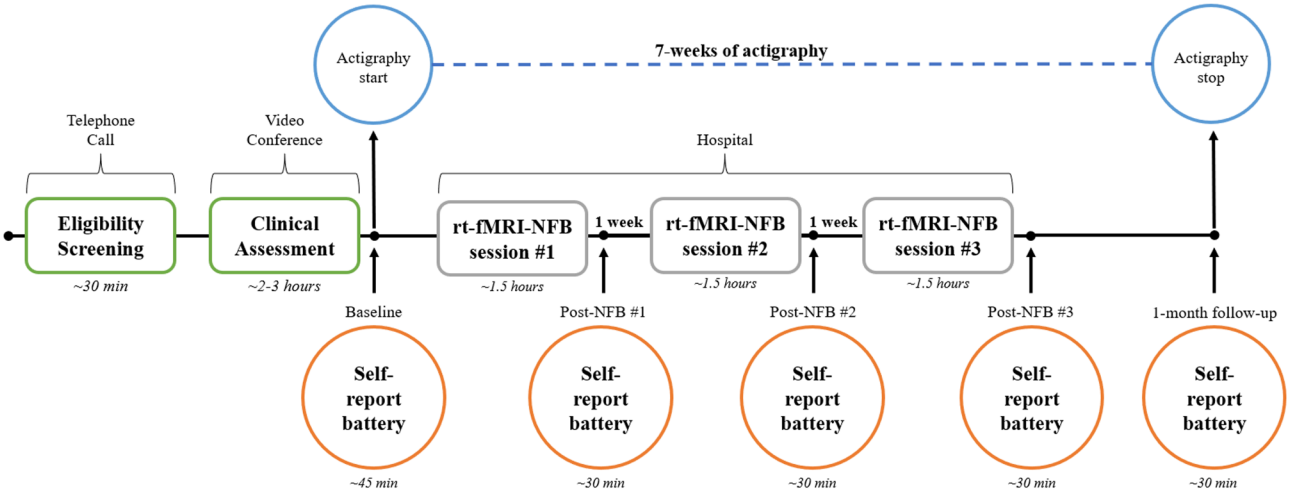

Fig. 1 Overview of the study procedure. rt-fMRI-NFB = real-time fMRI neurofeedback, min = minutes

trial protocol has been approved by the Health Sciences Research Ethics Board (HSREB) at Western University (2022-121170-73022) and the Lawson Health Research Institute (R-23-151). Written informed consent will be obtained from all study participants. This study has been registered with ClinicalTrials.gov under the trial registration number NCT05456958. It was initially registered on July 13th, 2022, and most recently updated on October 9th, 2024. We designed and prepared our study protocol in consultation with the CRED-nf checklist [90] and will include a completed version when publishing results from this trial.

Participants

Eligible participants will be adults aged 18–65 years old with a current primary diagnosis of PTSD, assessed via the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) [91]. The Mini-International Neuropsychiatric Interview (MINI) [92] will also be used to assess mental health conditions. Given the high rates of PTSD co-morbidity with major depressive disorder and anxiety disorders, participants with these comorbidities will not be excluded from the study to allow for a generalizable sample. Participants must be fluent in English and comfortable using electronic devices (e.g., laptop, tablet, smartphone). All participants must be willing and able to provide written informed consent. Participants will be excluded if they meet DSM-5 criteria for a lifetime history of bipolar disorder, psychotic disorders, obsessive-compulsive disorder, antisocial personality disorder, or current substance use or eating disorders. Participants will also be excluded for current or past pain disorders, active suicidality, a history of pervasive neurodevelopmental disorders, major medical illness that is not stabilized based on the judgment of the primary investigator, any previous head injury with loss of consciousness, a history of claustrophobia, prior engagement with neurofeedback, biofeedback, or brain stimulation therapy, and ongoing engagement in a primary trauma-focused psychotherapy treatment (e.g., cognitive behavioural therapy [CBT], eye movement desensitization and reprocessing [EMDR] therapy). Additionally, participants will be excluded if they are currently pregnant or breast-feeding, or meet any other MRI contraindications (e.g., metallic implants). Participants currently taking psychotropic medication must be on a stable dose for at least one month prior to starting the rt-fMRI-NFB trial and will be requested to maintain their medication regime without changes whenever possible. Participants will be recruited from the London, Ontario region via recruitment posters in the community (i.e., hospital and university bulletin boards, public spaces) and internet advertisements (i.e., Facebook and Kijiji). Each participant will receive $200 (CAD) monetary compensation for their involvement in the study and will be reimbursed for travel-related expenses (e.g., bus fare, parking).

Eligibility screening

Initial eligibility for the trial will be assessed via a telephone screener conducted by a study staff member following a research ethics board approved standardized script. Staff will conduct these telephone screeners from a private area to ensure participant privacy. The telephone screeners will start with a brief description of the study and then participants will be asked to provide verbal consent to answering eligibility questions to assess preliminary inclusion and exclusion criteria for the trial.

Clinical assessment

For eligible participants, an initial clinical assessment will be conducted within approximately one week of screening. During the initial clinical assessment, a graduate-level clinical psychology or neuroscience researcher—trained in trauma-informed care and PTSD assessment and supervised by licensed clinical psychologists and psychiatrists specializing in trauma—will administer the Mini-International Neuropsychiatric Interview (MINI) [92], the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [91], and the Life Events Checklist for DSM-5 (LEC-5) [93] (Table 1). The MINI will be used to evaluate the presence of psychiatric disorders, the CAPS-5 will be used to establish a primary diagnosis of PTSD and symptom severity, and the LEC-5 will provide a comprehensive trauma history. The clinical assessment will provide an opportunity for study staff to verify that participants meet all the inclusion criteria and do not meet any exclusion criteria for the trial. At the end of the clinical assessment, participants deemed eligible for the trial will be asked to select ten personalized trauma-associated words that induce emotional responses, and ten neutral words associated with neutrally-salient memories. The chosen words will be utilized for the trauma provocation paradigm during the rt-fMRI-NFB sessions. To match participants on perceived distress associated with their personalized words, they will be instructed to choose trauma-associated words that they rate as a 7 out of 10 in terms of subjective units of distress.

Clinical outcome measures

Participants will complete a battery of self-report questionnaires at five timepoints throughout the study – baseline, post-NFB #1, post-NFB #2, post-NFB #3, and one-month follow-up. These self-report questionnaires will be completed by participants via the Research Electronic Data Capture (REDCap) platform.

Table 1 Clinical assessment schedule

Assessments	Mode of delivery	Clinical assessment	Baseline	Post-NFB #1	Post-NFB #2	Post-NFB #3	1-month follow-up
Screening/Baseline							
Mini-International Neuropsychiatric Interview (MINI)	Clinician-administered	X					
Clinician-Administered PTSD Scale for DSM-5 (CAPS)	Clinician-administered	X					
Life Events Checklist for DSM-5 (LEC-5)	Self-report (REDCap)	X					
Demographic Survey	Self-report (REDCap)		X				
Childhood Trauma Questionnaire (CTQ)	Self-report (REDCap)		X				
Primary Outcome							
PTSD Checklist for DSM-5 (PCL-5)	Self-report (REDCap)		X	X	X	X	X
Secondary Outcomes							
Difficulties in Emotion Regulation Scale (DERS)	Self-report (REDCap)		X	X	X	X	X
Beck Depression Inventory (BDI)	Self-report (REDCap)		X	X	X	X	X
Multiscale Dissociation Inventory (MDI)	Self-report (REDCap)		X	X	X	X	X
Depression Anxiety Stress Scale-21 (DASS-21)	Self-report (REDCap)		X	X	X	X	X
Multidimensional Assessment of Interoceptive Awareness (MAIA)	Self-report (REDCap)		X	X	X	X	X
Insomnia Severity Index (ISI)	Self-report (REDCap)		X	X	X	X	X
During fMRI scans							
Response to Script Driven Imagery (RSDI)[1]	Self-report (Scanner)			*4x per scan*	*4x per scan*	*4x per scan*	

[1]Unlike the other secondary outcomes, which are administered between rt-fMRI-NFB sessions via REDCap, the Response to Script Driven Imagery (RSDI) is completed four times during each rt-fMRI-NFB session—immediately after each rt-fMRI-NFB run while participants remain in the scanner. NFB = neurofeedback

Primary outcome

The primary outcome measure in this trial is PTSD symptom severity as measured by the PTSD Checklist for DSM-5 (PCL-5; past week version) [94] (Table 1). The PCL-5 is a 20-item, self-report questionnaire designed to assess trait PTSD symptoms in accordance with DSM-5 diagnostic criteria within the past week. Each item is rated on a five-point scale, with higher scores indicating greater PTSD symptom severity. The PCL-5 was selected as the primary outcome measure due to its strong reliability and validity in assessing PTSD symptom severity [95] and its suitability for repeated assessments over shorter time intervals. Critically, the use of a brief, self-reported measure increases the temporal resolution of symptom change tracking following each neurofeedback session, which is essential for linking clinical effects to neural regulation dynamics and exploring dose-response relationships. While the CAPS-5 remains the gold standard for PTSD diagnosis, its length and high emotional demands on participants make it less feasible for repeated administration within a short-time period. Thus, the PCL-5 offers a more feasible approach while preserving rigorous symptom measurement over time.

Exploratory secondary outcomes

We will also examine several exploratory secondary clinical outcomes: the Beck Depression Inventory-II (BDI-II) [96], the Difficulties in Emotion Regulation Scale (DERS) [97], the Multiscale Dissociation Inventory (MDI) [98], the Depression Anxiety Stress Scale-21 (DASS-21) [99], the Multidimensional Assessment of Interoceptive Awareness (MAIA) [100], the Insomnia Severity Index (ISI) [101], and the Response to Script-Driven Imagery Scale (RSDI) [102] (Table 1). The BDI-II is a 21-item instrument measuring the severity of depression. Each item is rated on a four-point scale, with higher scores indicating greater severity of depressive symptoms. The DERS is a 36-item instrument designed to assess multiple dimensions of emotion regulation difficulties. Respondents rate items on a five-point scale, with higher scores reflecting greater difficulties in emotion regulation. The MDI is a 30-item instrument assessing dissociative symptoms across multiple dimensions. Each item is rated on a five-point scale, with higher scores indicating more severe dissociative experiences. The DASS-21 is a 21-item instrument measuring the severity of depression, anxiety, and stress. Each of the three scales contains seven items rated on a four-point scale, with higher scores reflecting greater severity of symptoms. The MAIA is a 32-item instrument assessing interoceptive awareness across eight dimensions. Items are rated on a six-point scale, with higher scores indicating greater interoceptive awareness. The ISI is a seven-item instrument assessing the severity of insomnia symptoms. Each item is rated on a five-point scale, with higher scores indicating more severe insomnia. Among the secondary outcomes, the RSDI is unique in that it will be administered directly following each rt-fMRI-NFB run while

participants remain in the scanner (rather than between rt-fMRI-NFB sessions via REDCap). The RSDI is a seven-item, self-report measure of state PTSD symptoms across the following symptom subscales: reliving, distress, physical reactions, dissociation, and emotional numbing.

Additional measures

Additional measures will be collected at baseline only. Demographic information (e.g., age, sex, gender, ethnicity, religion, socioeconomic status, educational attainment) will be gathered using a custom survey. Childhood abuse and neglect will be assessed using the Childhood Trauma Questionnaire (CTQ) [103]. The CTQ is a 28-item, self-report instrument that evaluates childhood trauma across five dimensions: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Each item is rated on a five-point scale, with higher scores indicating greater severity of childhood trauma.

rt-fMRI-NFB procedure

This study will employ a three group (PCC vs. amygdala vs. sham-control) by three session design. All participants will undergo three rt-fMRI-NFB sessions over the course of a three-week period (i.e., one session per week).

rt-fMRI-NFB sessions

Each rt-fMRI-NFB session will be structured to optimize data collection while limiting the time participants spend in the scanner, thus striking a balance between comprehensive assessment and participant comfort. Each session will include a localization scan (~three minutes), an anatomical scan (~six minutes), a pre-training resting-state scan (~six minutes), four task runs (~eight minutes each), and a post-training resting-state scan (~six minutes) (Fig. 2). The four task runs will include three neurofeedback training runs and one transfer run, with the order of the runs varying between rt-fMRI-NFB sessions to accommodate practical time constraints and ensure effective neurofeedback learning assessment. Specifically, during the first rt-fMRI-NFB session, participants will complete a pre-training transfer run (to assess baseline regulatory abilities) followed by the three neurofeedback training runs. For the second and third rt-fMRI-NFB sessions, participants will complete the three neurofeedback training runs followed by a post-training transfer run (to evaluate neurofeedback learning effects). During the transfer runs, participants will not receive any neurofeedback signal but otherwise it will be identical to the training runs. This design will allow us to measure participants' baseline regulatory capabilities without feedback and their learning progression across sessions. Other than the order of the transfer run, the tasks and timing for all three rt-fMRI-NFB sessions will be identical. After each task run, the RSDI will be administered to participants inside the scanner to assess state PTSD and dissociative symptoms.

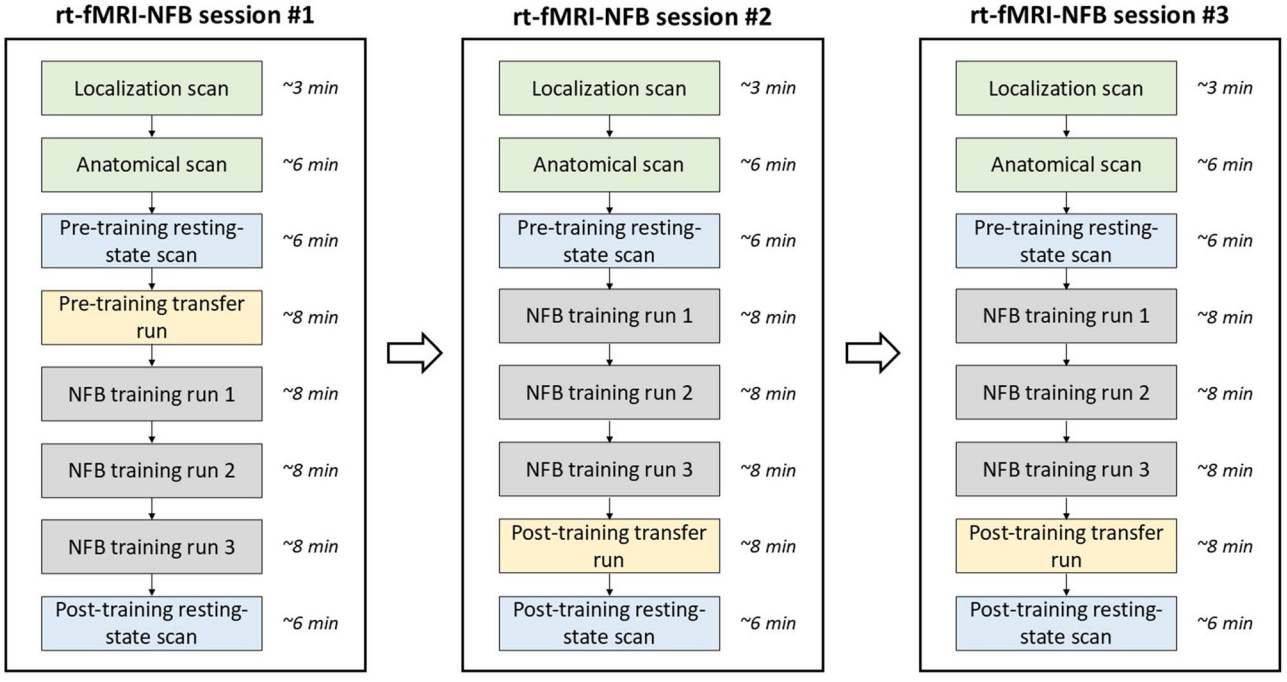

Fig. 2 Task order for rt-fMRI-NFB sessions. rt-fMRI-NFB = real-time fMRI neurofeedback, NFB = neurofeedback, min = minutes

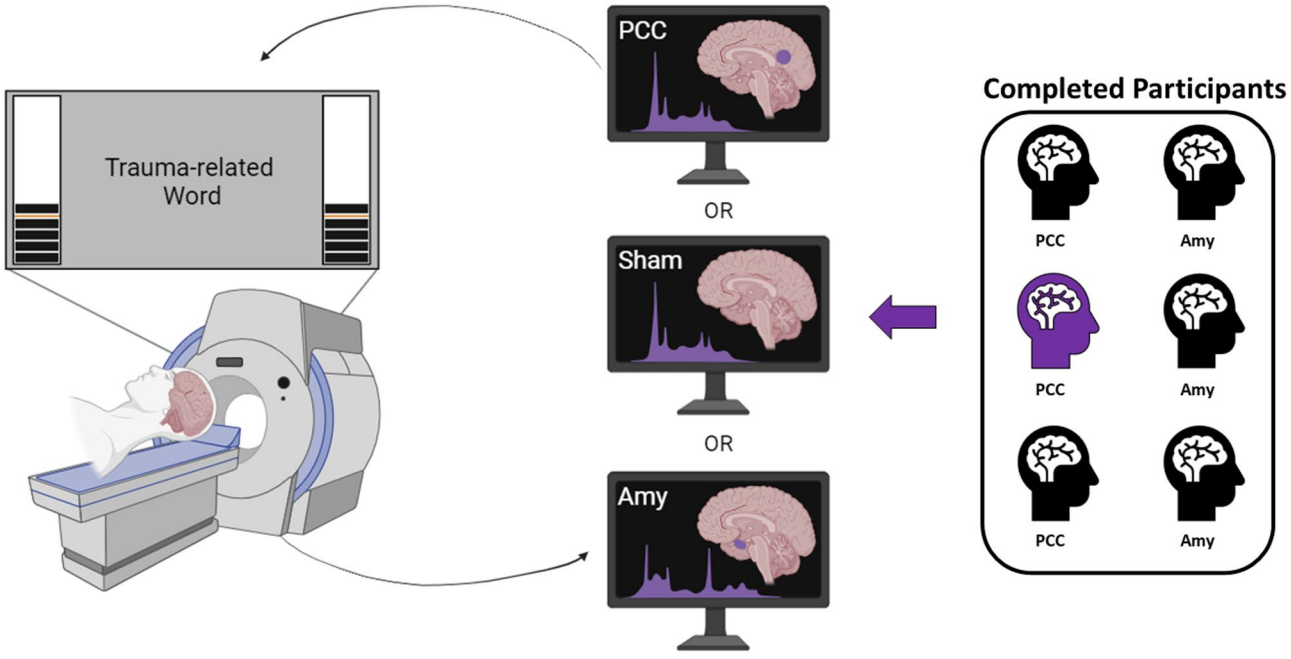

Fig. 3 Schematic of the rt-fMRI-NFB experimental set-up. The neurofeedback signal is presented as a virtual thermometer, with its level fluctuating in response to activity within the targeted neurofeedback region (PCC or amygdala). For participants in the sham-control group, the neurofeedback signal is derived from a randomly selected participant in one of the experimental groups instead of their own brain activity. Participants view this signal while undergoing a trauma provocation paradigm inside the scanner. Figure adapted with permission from Lieberman et al. [67] and Nicholson et al. (2021) [73]. PCC = posterior cingulate cortex, Amy = amygdala

rt-fMRI-NFB runs

We will employ a neurofeedback protocol consistent with those used in our previous rt-fMRI-NFB studies [66, 67, 72–74]. During the training runs, the neurofeedback signal for the two experimental groups will be based on participant's brain activity within either the amygdala or PCC, as per their randomized group assignment. All participants will be told that they will be regulating brain activity in an area related to emotion. They will not be given any specific strategies with which to regulate brain activity, rather they will be advised to learn individualized strategies that work best for themselves to control the feedback signal. Additionally, participants will be informed that the neurofeedback signal lags their brain activity by roughly 6–8 s (due to the BOLD signal delay and processing time). Each run will consist of three different conditions: (i) *regulate*, (ii) *view*, and (iii) *neutral*. Prior to the start of each condition, participants will receive an instruction that will indicate which condition will follow. In the *regulate* condition, participants will be instructed to decrease the neurofeedback signal while viewing a personalized trauma-related word. In the *view* condition, participants will view a personalized trauma-related word but will be instructed to respond naturally and not attempt to exert regulatory control over the neurofeedback signal. In the *neutral* condition, participants will view a personalized neutral word and will be instructed to respond naturally and not attempt to change the neurofeedback signal. The personalized trauma-related and neutral words will be displayed for 24 s during each condition and presented using specialized fMRI stimulus delivery software (Presentation, Neurobehavioral Systems, Albany, CA, USA). Each experimental run will consist of 15 trials (five of each condition, counterbalanced and separated by an inter-trial fixation cross). Prior to their first rt-fMRI-NFB session, participants will be randomly assigned to one of three condition sequences. These sequences will specify the order of the three experimental conditions which will vary between runs but will be identical between rt-fMRI-NFB sessions.

Neurofeedback signal

During the presentation of words in the fMRI scanner, participants will be able to view a visual feedback display in the form of a thermometer-like bar graph [66, 67, 72–74] (Fig. 3). The level of the thermometer will reflect the increase or decrease of activity in the target brain region (PCC or amygdala) relative to a baseline period shown as an orange line on the thermometer display. The level of the thermometer will be continuously updated every two seconds and shown to participants throughout the three neurofeedback training runs. Each segment of the thermometer will correspond to a 0.2% change in BOLD activation, with a maximum range of + 2.8% and − 1.2% from baseline [73, 74, 104, 105].

Sham-control group

During the rt-fMRI-NFB runs, participants in the sham-control group will receive a 'yoked' neurofeedback signal derived from a randomly selected participant in one of the experimental groups (PCC or amygdala) instead of their own brain activity. The sham-control group will include an equal number of participants matched to those in each of the PCC and amygdala groups. Additionally, an equal number of sham-control participants will be assigned to each of the three condition sequences. All other procedures and instructions will remain identical. Inclusion of this sham-control group helps to control for placebo effects, non-specific factors (e.g., feelings of nervousness or excitement), and motivation.

Qualitative interviews

After each rt-fMRI-NFB session, participants will complete a semi-structured qualitative interview with a study staff member. This interview will take place on the same day as the rt-fMRI-NFB session and will be conducted over the phone. During the interview, the participants will be asked about the regulation strategies they employed to complete the neurofeedback task and their perceived efficacy (see Supplementary material 1). Additionally, participants will be asked about their subjective experiences (e.g., motivation, valence, frustration, mind-wandering) during the neurofeedback tasks. The qualitative interviews will be recorded (via an audio recorder).

Actigraph device usage

Participants will wear a GENEActiv (Activinsights, United Kingdom) actigraph device throughout the duration of the study (i.e., one-week baseline through to one-month follow-up, for a total of seven weeks) to monitor patterns of sleep and physical activity. The GENEActive actigraph device will be worn on the non-dominant wrist and will collect continuous data at 30 Hz.

Randomization and blinding

Participants will be randomly assigned to one of the three groups—amygdala, PCC, or sham-control—in a 1:1:1 ratio. Randomization will be conducted using the Variance Minimization (VM) procedure [106] to balance groups based on five key demographic and clinical variables: (i) age, (ii) sex assigned at birth, (iii) total CAPS-5 scores, (iv) baseline PCL-5 scores, and (v) comorbid conditions (e.g., generalized anxiety disorder, major depressive disorder). In order to generate a 'yoked' neurofeedback signal for the sham-control group, randomization into this group will only occur once at least one participant has fully completed the study in each of the two experimental groups (amygdala and PCC). Participants will be blinded as to their group assignment throughout the study. Additionally, study staff responsible for conducting assessments and directly interacting with participants will remain blinded to participants' group assignments to ensure unbiased data collection. However, one study staff responsible for running the neurofeedback software will not be blinded, as they must know the group assignment to select the appropriate neurofeedback target region or sham-control setting. This staff member will not participate in any assessment activities and will have minimal interactions with participants. Additionally, the unblinded staff member will avoid sharing any details about the rt-fMRI-NFB sessions, such as participants' ability to regulate the neurofeedback signal, with other staff members to minimize the risk of unblinding.

fMRI image acquisition

All imaging will be conducted using a 3 Tesla whole-body MRI scanner (Magnetom Biograph mMR, Siemens Medical Solutions, Erlangen, Germany), equipped with a 32-channel phased array head coil to minimize head motion and enhance signal quality. The scanner that will be used for all participants is located at the Lawson Health Research Institute's Grosvenor campus (within St. Joseph's Hospital, London, Ontario, which is itself a teaching hospital affiliated with Western University). Resting-state functional whole-brain images will be acquired using a gradient echo T2*-weighted echo-planar-imaging sequence (TE = 29.4 ms, TR = 1 s, FOV = 192 × 192 mm, flip angle = 90°, in-plane resolution = 2 × 2 mm, GRAPA acceleration factor = 2, multi-band acceleration factor = 4). Each volume will consist of 64 ascending interleaved slices, angled − 20° from the AC-PC axis, with a slice thickness of 2 mm and no inter-slice gap, ensuring whole-brain coverage. Task-based functional whole-brain images (i.e., during the neurofeedback training and transfer runs) will be acquired using a gradient echo T2*-weighted echo-planar-imaging sequence (TE = 30 ms, TR = 2 s, FOV = 192 × 192 mm, flip angle = 80°, in-plane resolution = 3 × 3 mm, GRAPA acceleration factor = 2, multi-band acceleration factor = none). Each volume will consist of 36 ascending interleaved slices, angled − 20° from the AC-PC axis, with a slice thickness of 3 mm and a 1 mm inter-slice gap, ensuring whole-brain coverage. High-resolution T1-weighted anatomical images will be obtained using a Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence (TE = 4.18 ms, TR = 2.0 s, 176 slices, FOV = 256 × 256 mm, resolution = 1 mm isotropic, GRAPA acceleration factor = 2).

Statistical analyses

Clinical analyses

To evaluate the effectiveness of rt-fMRI-NFB on the primary (i.e., PCL-5) and secondary (i.e., BDI-II, DERS,

MDI, DASS-21, MAIA, ISI) clinical outcome measures, we will use separate mixed-design three (Group) x five (Timepoint) repeated measures ANCOVAs. To evaluate the effectiveness of rt-fMRI-NFB on RSDI scores, we will use a mixed-design three (Group) x three (Session) x four (NFB run) repeated measures ANCOVA. We will conduct both intent-to-treat (ITT) and per-protocol (PP) analyses to provide complementary insights into treatment effectiveness. The ITT analysis will include all participants randomized into the study, regardless of intervention completion, preserving the benefits of randomization and offering a conservative estimate of the treatment effect. The PP analysis will include only participants who completed the intervention as per the study protocol, providing an estimate of the treatment effect under optimal conditions. Conducting both ITT and PP analyses offers a comprehensive understanding of the intervention's effectiveness from pragmatic and explanatory perspectives, respectively (e.g., 107, 108). For significant main effects or interactions identified in the ANCOVA models, post-hoc pairwise comparisons will be conducted using paired t-tests for within-group changes over time and independent sample t-tests for between-group comparisons. To control for multiple comparisons, we will apply a correction method (e.g., Bonferroni or False Discovery Rate) as appropriate. Any baseline demographic or clinical variables (e.g., socioeconomic status, psychotropic medication use, trauma exposure) that differ significantly between groups and were not accounted for during the VM randomization procedure will be included as covariates in all statistical analyses. Additionally, prior to conducting ANCOVA analyses, we will assess missing data patterns using descriptive analyses. If data are determined to be missing at random (MAR), multiple imputation will be considered. To assess normality, we will visually inspect histograms and Q-Q plots and perform statistical tests such as the Shapiro-Wilk test. Homogeneity of variance will be evaluated using Levene's test. If assumptions of normality or homogeneity of variance are violated—or if missingness is extensive—we will consider data transformations or the use of analytic approaches, such as linear mixed models (LMMs), which offer a flexible framework for handling repeated measures and unbalanced data.

Additionally, to further investigate individual variability in neurofeedback response, we will conduct an exploratory follow-up analysis comparing responders and non-responders on primary and secondary clinical outcomes. Responders will be defined as participants who demonstrate successful regulation of their assigned target region (PCC or amygdala) across neurofeedback sessions, while non-responders will be those who do not show reliable regulation.

fMRI analyses

To analyze the neural effects of rt-fMRI-NFB, offline data analysis will be conducted using MATLAB and SPM (Wellcome Department of Cognitive Neurology, London, UK) or another appropriate software package. Data preprocessing will follow our group's standard preprocessing pipeline [66, 67, 72–74] which includes discarding the first four functional volumes for each subject, slice-time correction to the middle slice, reorientation to the AC-PC axis, spatial alignment via rigid body transformation, co-registration of the functional volumes to each participant's anatomical image, segmentation, normalization to MNI space, smoothing, and identification of outlier volumes with excessive head motion.

The preprocessed data will be used in first-level (i.e., single-subject) analyses, in which the timing of experimental conditions will be convolved with the canonical hemodynamic response function and used in a general linear model to estimate brain responses during rt-fMRI-NFB. First-level results will then be used in second-level (i.e., group) analyses to estimate differential activation within- and between-groups and examine associations with clinical variables. Additionally, the effect of rt-fMRI-NFB on both task-based and resting-state functional brain networks will be assessed using a variety of connectivity analyses. These will include psychophysiological interaction (PPI) analysis to explore task-specific changes in connectivity, seed-based functional connectivity analysis to investigate the resting-state connectivity patterns of specific brain regions of interest (e.g., PCC, amygdala), and independent component analysis (ICA) to identify changes in large-scale brain networks, such as the default mode network, salience network, and central executive network. Effective connectivity approaches, such as Dynamic Causal Modeling, will be employed to examine the directional influences between brain regions and how these interactions are modulated by rt-fMRI-NFB. Exploratory analyses will also be conducted to identify other relevant neural markers or patterns of brain activity associated with rt-fMRI-NFB. We plan to conduct interim clinical and fMRI analyses prior to final completion of data collection, particularly in the event of a scanner upgrade or replacement.

Exploratory qualitative analyses

For the qualitative data, participant interviews will be transcribed and analyzed using thematic analysis [109], which involves systematically identifying, analyzing, and documenting patterns or themes within the data. Two researchers will independently code and analyze the interviews. The identified themes will be explored in relation to clinical and neural outcome measures to investigate potential associations with participants' subjective experiences, including the use of regulation strategies, their perceived efficacy, and treatment effects.

Exploratory actigraphy analyses

Actigraphy data will undergo standard preprocessing including the removal of periods of non-wear and missing data, identification and exclusion of erroneous data points, and the application of established algorithms to classify sleep/wake periods and physical activity [110]. We will examine changes in key actigraphy-derived variables, including total sleep time, sleep efficiency, wake after sleep onset, sleep regularity index, and level of physical activity. Correlational analyses will also be conducted to explore the relationship between changes in actigraphy-derived variables and clinical and neural outcome measures.

Power & sample size

Given the novel nature of this study, we conducted the power analysis for between-group differences in the primary outcome variable (PCL-5 scores) by drawing on multiple sources of information. Specifically, we considered: (1) A recent meta-analysis of 17 studies comparing rt-fMRI-NFB to control groups across multiple clinical populations (including major depressive disorder, anxiety, PTSD, and borderline personality disorder) which reported a medium effect size for depressive score improvement (Hedges' $g = 0.49$; 11 RCTs) and a large effect size for anxiety score improvement (Hedges' $g = 0.77$; 6 RCTs) at post-treatment [50]. (2) A meta-analysis on effect size and power among 11 rt-fMRI-NFB clinical trials in varied psychiatric populations (primarily depression, PTSD, and addiction) which reported a large average effect size of Cohen's $d = 0.74$ at 95% power for clinical measures [111]. (3) Most relevant to the current trial, another meta-analysis investigated RCTs comparing multi-session neurofeedback (both EEG and fMRI) versus control groups in PTSD and found medium effect sizes for improvements in PCL-5 scores at post-treatment (Hedges' $g = 0.47$; 7 RCTs) and follow-up (Hedges' $g = 0.67$; 4 RCTs) [112]. Taken together, we conservatively opted for the detection of at least a medium effect size (i.e., Cohen's $f = 0.25$). This would require the inclusion of $N = 72$ participants (24 per group) for a repeated measures, between-group design. To account for potential dropout, we will recruit an additional 10% of participants. We used G*Power 3.1 [113] with the following criteria to calculate sample size: repeated measures ANOVA with between-group factors, effect size $f = 0.25$, α error probability = 0.05, Power = 0.80, number of groups = 3, number of measurements = 5, correlation among repeated measures = 0.3.

Discussion

Given the limitations of current first-line psychotherapies and pharmacotherapies in providing clinically meaningful symptom relief for many individuals with PTSD, there is an urgent need for innovative, neurobiologically-informed treatment strategies. Preliminary evidence suggests that rt-fMRI-NFB, which enables the direct regulation of PTSD-related neural disruptions, holds promise as an effective therapeutic approach. However, several critical research gaps remain, necessitating further exploration. The current study aims to address these gaps by evaluating the therapeutic and neural effects of multiple sessions of rt-fMRI-NFB targeting the PCC and amygdala, two brain regions critically implicated in PTSD. Utilizing a rigorous randomized, double-blind, sham-controlled design, this study seeks to elucidate the neurophysiological specificity of rt-fMRI-NFB and control for possible placebo effects, optimize the selection of neurofeedback target regions, and delineate dose-response relationships essential for refining neurofeedback therapeutic protocols in PTSD. Additionally, this study will be the first to integrate comprehensive qualitative interviews and biometric data collection to investigate the phenomenological experiences and physiological impacts of rt-fMRI-NFB in PTSD. Taken together, this investigation will advance our understanding of rt-fMRI-NFB as a targeted therapeutic intervention for PTSD and may contribute to the development of more effective and enduring treatment modalities.

Abbreviations

PTSD	Post-traumatic Stress Disorder
fMRI	Functional Magnetic Resonance Imaging
rt-fMRI-NFB	Real-time fMRI Neurofeedback
RCT	Randomized Controlled Trial
PCL-5	PTSD Checklist for DSM-5
PCC	Posterior Cingulate Cortex
DMN	Default Mode Network
EEG-NFB	Electroencephalography-based Neurofeedback
SN	Salience Network
PFC	Prefrontal Cortex
HSREB	Health Sciences Research Ethics Board
CAPS-5	Clinician Administered PTSD Scale-5
MINI	Mini-International Neuropsychiatric Interview
CBT	Cognitive Behavioural Therapy
EMDR	Eye Movement Desensitization and Reprocessing
Min	Minutes
LEC-5	Life Events Checklist-5
REDCap	Research Electronic Data Capture
PCL-5	PTSD Checklist for DSM-5
BDI-II	Beck Depression Inventory-II
DERS	Difficulties in Emotion Regulation Scale
MDI	Multiscale Dissociation Inventory
DASS-21	Depression Anxiety Stress Scale-21
MAIA	Multidimensional Assessment of Interoceptive Awareness
ISI	Insomnia Severity Index
RSDI	Response to Script-Driven Imagery Scale
CTQ	Childhood Trauma Questionnaire
MP-RAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
IIT	Intent-to-treat
PP	Per-protocol
PPI	Psychophysiological Interaction Analysis
ICA	Independent Component Analysis

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization: JL, AN. Writing—Original Draft: JL. Writing—Reviewing & Editing: JL, RL, JT, BF, PF, FS, DS, TR, MD, ET, VM, NHK, SN, FH, RJ, AN. Data collection: JL, MD, ET, VM, AN. Software design/fMRI methodology: JT. Funding acquisition: AN. Supervision: AN. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study involving humans was approved by the Western University Health Sciences Research Ethics Board (HSREB) (project ID: 121170) and the Lawson Health Research Institute (project ID: 12521). This study was conducted in accordance with the local legislation and institutional requirements. Participants will provide their written informed consent to participate prior to enrollment, and recruitment is ongoing.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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