Brain activity mediators of PTSD symptom reduction during real-time fMRI amygdala neurofeedback emotional training

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ARTICLE INFO

ABSTRACT

Self-regulation of brain activation with real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) is emerging as a promising treatment for psychiatric disorders. The association between the regulation and symptom reduction, however, has not been consistent, and the mechanisms underlying the symptom reduction remain poorly understood. The present study investigated brain activity mediators of the amygdala rtfMRI-nf training effect on combat veterans' PTSD symptom reduction. The training was designed to increase a neurofeedback signal either from the left amygdala (experimental group; EG) or from a control region not implicated in emotion regulation (control group; CG) during positive autobiographical memory recall. We employed a structural equation model mapping analysis to identify brain regions that mediated the effects of the rtfMRI-nf training on PTSD symptoms. Symptom reduction was mediated by low activation in the dorsomedial prefrontal cortex (DMPFC) and the middle cingulate cortex. There was a trend toward less activation in these regions for the EG compared to the CG. Low activation in the precuneus, the right superior parietal, the right insula, and the right cerebellum also mediated symptom reduction while their effects were moderated by the neurofeedback signal; a higher signal was linked to less effect on symptom reduction. This moderation was not specific to the EG. MDD comorbidity was associated with high DMPFC activation, which resulted in less effective regulation of the feedback signal. These results indicated that symptom reduction due to the neurofeedback training was not specifically mediated by the neurofeedback target activity, but broad regions were involved in the process.

1. Introduction

Real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) is an emerging, noninvasive method for learning to control brain activity, including potential use for treating various neurological and psychiatric disorders (Stoeckel et al., 2014). The rtfMRI-nf provides the subject with a real-time signal reflecting change in the blood oxygenation level dependent (BOLD) signal, which is used as a target for self-regulating (increasing or decreasing) their own brain activation (Weiskopf, 2012). For clinical use of rtfMRI-nf, abnormal brain activation associated with disorder symptoms is typically targeted with the assumption that correction and/or normalization of an abnormal brain response will lead to symptom relief.

While the effect of rtfMRI-nf on symptom reduction has been

demonstrated in many studies (deCharms et al., 2005; Scheinost et al., 2013, 2014; Young et al., 2017; Zhang et al., 2015; Zilverstand et al., 2015), the ability to self-regulate brain response has not always resulted in clinical improvement or changes in behavioral measures (Johnston et al., 2011; Li et al., 2016; Nicholson et al., 2017; Paret et al., 2016; Sarkheil et al., 2015; Thibault et al., 2018; Zweerings et al., 2018; see Linhartová et al. (2019) for review). A lack of behavioral and symptom change associated with successful rtfMRI-nf modulation could indicate either that a targeted region has no causal relationship with disorder symptoms, that a training effect could appear with a long delay after the training (Rance et al., 2018), or that regulation of the feedback signal did not depend on neural activity (Thibault et al., 2018). Studies further indicated that successful rtfMRI-nf brain regulation is not necessarily correlated with behavioral or

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Table 1
Numbers of PTSD participants, mean age (SD), and numbers of participants with MDD comorbidity in each session.

Group	Training day 1			Training day 2			Training day 3			Post		
	N	Age	MDD	N	Age	MDD	N	Age	MDD	N	Age	MDD
EG	25	31 (6)	12	23	31 (5)	10	21	31 (5)	10	20	30 (5)	10
CG	11	34 (8)	2	10	34 (9)	2	10	34 (9)	2	9	35 (7)	2

EG: experimental group, CG: sham-control group.

symptom change (Haller et al., 2010; Linden et al., 2012; Subramanian et al., 2011; Zotev et al., 2018). This suggests that the placebo effect or brain regions beyond the neurofeedback target might mediate the rtfMRI-nf training effects on symptom change.

Neurofeedback training recruits many mental processes, including multiple cycles of monitoring a feedback signal, executing a mental strategy to control the signal, and evaluating and adapting the strategy according to the signal (Lubianiker et al., 2019; Paret et al., 2018; Sitaram et al., 2017). Due to the multiple stages of the regulation process, the effect of the training could stretch across many brain areas (Emmert et al., 2016; Kopel et al., 2017; Lee et al., 2011; Ninaus et al., 2013). For example, the effect of amygdala rtfMRI-nf training on resting-state functional connectivity in combat-related PTSD (Misaki et al., 2018b) is observed in several other cortical regions beyond the amygdala. Recruitment of multiple regions in the rtfMRI-nf training suggests that the treatment effect could be mediated or moderated by activations in many brain regions. Thus, examining only the direct relationship between regulation success at the target region and symptom relief might be insufficient for delineating the process of the training effect on behavioral and symptom change.

The present study investigated the brain activations that mediated or moderated the neurofeedback training effect on symptom relief not limited to the rtfMRI-nf target region. For this purpose, we performed a structural equation modeling (SEM) analysis for each brain voxel independently, and then mapped the evaluated path coefficients onto the brain (called a structural equation model mapping [SEMM]). Modeling a mediation and moderation with SEM enables us to examine multiple direct and indirect effects of the neurofeedback training on symptom change while controlling other effects simultaneously. This is necessary for investigating a neurofeedback training effect that includes multiple factors (Lubianiker et al., 2019; Paret et al., 2018; Sitaram et al., 2017). Performing this analysis for each brain voxel could potentially reveal a whole brain process of a complex neurofeedback treatment effect that cannot be seen by examining a simple effect at a time.

We reanalyzed the data from Zotev et al. (2018) for the current investigation. The study applied rtfMRI-nf training to enhance left amygdala activity via recall of positive autobiographical memories among combat veterans with PTSD. Results demonstrated that veterans in the experimental group (who received neurofeedback from the left amygdala) showed significantly higher left amygdala activation than the sham-control group (who received neurofeedback from a region not involved in emotion processing) during the neurofeedback training. PTSD symptoms significantly decreased after three training sessions for the experimental group. The degree of regulation success, however, did not change across training sessions and the magnitude of regulation success was not correlated with the magnitude of symptom change. These results suggest that there might be a region that mediated symptom reduction other than the neurofeedback target area.

We note that the aim of the present study is not to examine the efficacy of the amygdala neurofeedback treatment relative to the control, which was presented in the previous study (Zotev et al., 2018). Rather, the current study explored both specific and nonspecific effects of the neurofeedback training on PTSD symptom change via possible mediating and moderating brain activations across the whole brain. The present analysis, therefore, did not hold an assumption that activation in the neurofeedback target region is a mediator of symptom change.

The analysis also examined the effect of comorbid major depressive disorder (MDD) on the rtfMRI-nf response. Since almost half of PTSD patients suffer from MDD comorbidity (Flory and Yehuda, 2015), there were possibly different treatment effects for the PTSD patients with versus without MDD comorbidity.

2. Materials and methods

2.1. Participants

The participants were the same as in Zotev et al. (2018). All participants were male combat veterans with PTSD. The study consisted of seven visits (on separate days) with an additional initial screening visit. RtfMRI-nf training was performed on the 3rd, 4th, and 5th visits. Participants were assigned to either the experimental group (EG) who received neurofeedback from the left amygdala or to the control group (CG) who received neurofeedback from a region that is not involved in emotion regulation (the left horizontal segment of the intraparietal sulcus). The feedback signal was given by the variable-height red bar on the screen. Participants were blind to group assignment. Table 1 shows the numbers of participants completing each neurofeedback training and post-training sessions. There was no group difference in age in any session. The number of participants with MDD comorbidity is shown in Table 1. The study was approved by the Western Institutional Review Board (IRB), Puyallup, WA. All procedures were conducted according to the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. More details about participant recruitment and the study schedule were described in previous reports (Misaki et al., 2018a; Zotev et al., 2018).

2.2. Neurofeedback fMRI

In the rtfMRI-nf training, participants were asked to increase the neurofeedback signal by recalling positive autobiographical memories. Details of the experimental procedure were described previously (Zotev et al., 2018) and are summarized here. Each neurofeedback run (lasting 8 min 46 s) consisted of alternating 40 s blocks of rest, happy (neurofeedback), and count (counting backward from 300) conditions, repeated four times. In the neurofeedback block, participants were asked to increase the neurofeedback signal by recalling positive autobiographical memories. One session consisted of five rtfMRI-nf runs; a practice run, three training runs (train1, train2, train3), and one transfer run in which no neurofeedback was provided. The neurofeedback signal was a percent signal change at each training run (TR) in the happy block relative to the average of the preceding rest block. A moving average of the current and two preceding neurofeedback signal values was used to reduce noise effects.

The fMRI results were analyzed with Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni/). The first three fMRI volumes were discarded to ensure the MRI signal reached a steady state. The process included despiking, RETROICOR (Glover et al., 2000), respiration volume per time (RVT) correction (Birn et al., 2008), slice-timing and motion corrections, nonlinear warping to the MNI template brain with resampling to $2mm^3$ voxels using the Advanced Normalization Tools (ANTs) software (Avants et al., 2008) (http://stnava.github.io/ANTs/), spatial smoothing with 6mm-

FWHM Gaussian kernel, and scaling signal to percent change relative to the mean in each voxel. The brain response in the neurofeedback block was evaluated with general linear model (GLM) analysis. The design matrix included modeled responses to the happy and the count blocks (boxcar function convolved with hemodynamic response function [HRF]), onset events of any blocks (delta function convolved with HRF), three principal components of the ventricle signal, local white matter average signal (ANATICOR) (Jo et al., 2010), 12 motion parameters (3 shift and 3 rotation parameters with their temporal derivatives), and low-frequency fluctuation (4th-order Legendre polynomial model). The GLM analysis was performed for each run independently. The beta coefficient of the happy block regressor was extracted as an estimate of brain activation during the neurofeedback period.

2.3. Symptom measurement

The Clinician-Administered PTSD Scale (CAPS) for DSM-IV (Blake et al., 1995; Weathers et al., 2001) and the PTSD Checklist - Military Version (PCL-M) (American Psychiatric Association, 2000; Weathers et al., 1993) were used to identify PTSD diagnosis and measure symptom levels. Depression symptom level was measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). The CAPS was administered at the first and the last visits by research staff trained to mastery in the administration of the interview and blind to group assignment. The staff was blind to which group the participants were assigned to. The PCL-M and MADRS were administered before the scan session at each visit from the 2nd to the 6th visit. Longitudinal linear mixed-effect (LME) model analysis (West et al., 2014) was performed for each symptom score with fixed effects of the visit, group (EG/CG), their interaction, and a random effect of participant on the intercept. The *lme4* package (Bates et al., 2015) in R language and statistical computing (R Core Team, 2018) was used for the analysis. Degrees of freedom for *F*-values were estimated by Satterthwaite's approximation in *lmerTest* package (Kuznetsova et al., 2017). Changes in symptom score from baseline were tested with *t*-tests with multiple testing correction by critical values from multivariate *t*-distribution using *lsmeans* package (Lenth, 2016).

2.4. Structural equation model mapping (SEMM)

We introduced a SEMM approach for the whole brain voxel-wise search and identification of brain activation that mediated or moderated the effect of rtfMRI-nf training on clinical symptom change. Fig. 1 shows the path diagram of the proposed SEM model. The model assumed that the neurofeedback signal (NF) affected brain activation (Br) in a certain region, and activation of a region was associated with symptom change after the training (SympChg). The model also included the effect of the group (Grp; EG/CG) on the neurofeedback signal. The direct paths from the neurofeedback signal to the symptom change and from the group to brain activation were also included, considering an unidentified mediating factor could exist. In addition, moderation paths (dotted arrows) from the experimental group onto the NF→Br path and from the neurofeedback signal onto the Br→SympChg path were included in the model. The moderation factors were modeled with the interaction of group by neurofeedback signal (Grp × NF) and interaction of neurofeedback signal by brain activation (NF × Br). The interaction factors were computed by multiplying the z-scored constituent terms with regressing out the effects of its first-order constituent terms. The mutual path between the interaction factors was also modeled as they shared the NF variable (see Little et al. (2007) for details of mediation and moderation analysis in SEM). Residual variance was modeled for all factors. A variance of the exogenous variable (e_{Grp}) was fixed to the sample variance. Correlation between a factor variable and a numerical variable was evaluated by the serial correlation using *polycor* package in R (Fox, 2016). The analysis was performed
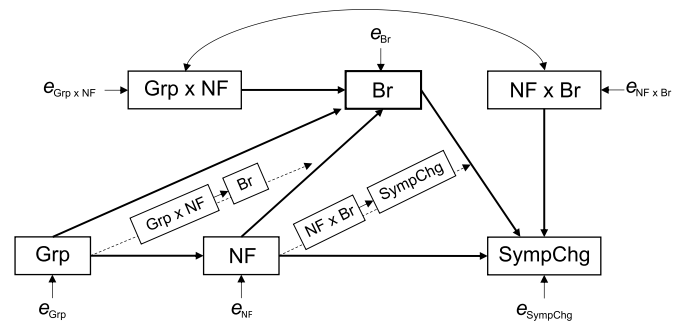
Fig. 1. Path diagram for the structural equation model (SEM) analysis. Grp: Exp/Ctrl group, NF: mean amplitude of neurofeedback signal across training runs, Br: mean brain activation across training runs at one voxel, SympChg: change in symptom score between the post- and the pre-training assessment (residualized with respect to baseline symptom score), Grp × NF: interaction of the group by z-scored neurofeedback signal orthogonalized with regard to Grp and NF variables, NF × Br: interaction of z-scored neurofeedback signal by z-scored brain activation orthogonalized with regard to NF and Br variables, e_x: residual variance of factor x. Paths from the interaction factors correspond to moderation effects (dotted paths).

with *sem* package in R (Fox et al., 2017).

We used PCL-M as a measure of symptom change since the post-training CAPS score was not available for eight participants. The SEMM analysis was performed with 29 participants (20 EG and 9 CG) who completed the post-training PCL-M assessment. Symptom change was the difference between the pre- and the post-training sessions (post − pre) with regressing out the effect of baseline (pre-training) score. The beta coefficient for the happy (neurofeedback) block regressor in the GLM analysis was used as the brain activation. The neurofeedback signal was the actual value presented to the participant during the neurofeedback session. It was a real-time evaluation of the percent change of the BOLD signal relative to the average in the preceding rest block with real-time motion correction and the moving average of three consecutive time points (Zotev et al., 2018). The brain activation and the neurofeedback signal were averaged across training runs (train1, train2, and train3) of all sessions to enter the SEM analysis.

The SEM analysis was performed for each voxel, and the path coefficient and its *p*-value were mapped onto the brain. We used a permutation test (2000 repetitions) for evaluating *p*-values of the path coefficients as the test is resilient to a false positive error (Ludbrook and Dudley, 1998). The map was thresholded with voxel-wise $p < 0.005$ (two-tailed) and cluster-extent $p < 0.05$ for whole-brain multiple testing correction. The cluster-extent *p*-value was also estimated with a permutation test (2000 repetitions).

Supplementary material includes the checklist of Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist) (Ros et al., 2019).

3. Results

3.1. Neurofeedback signal and symptom change

Fig. 2 shows the mean amplitude of neurofeedback signal for each run and session. Tests of neurofeedback signal amplitude in each group indicated that the EG showed a significantly higher neurofeedback signal than 0 ($t[27.0] = =3.746$, $p < 0.001$), while it was not significant for the CG ($t[26.8] = =0.453$, $p = 0.654$). Dividing each group as a function of MDD comorbidity indicated that a significant neurofeedback signal amplitude emerged only for PTSD patients without MDD comorbidity in the EG ($t[25.2] = =3.500$, $p = 0.002$). The neurofeedback signal amplitude was not significant for the patients with MDD comorbidity in the EG ($t[26.2] = =1.615$, $p = 0.118$). It also was not significant for participants in the CG with or without MDD
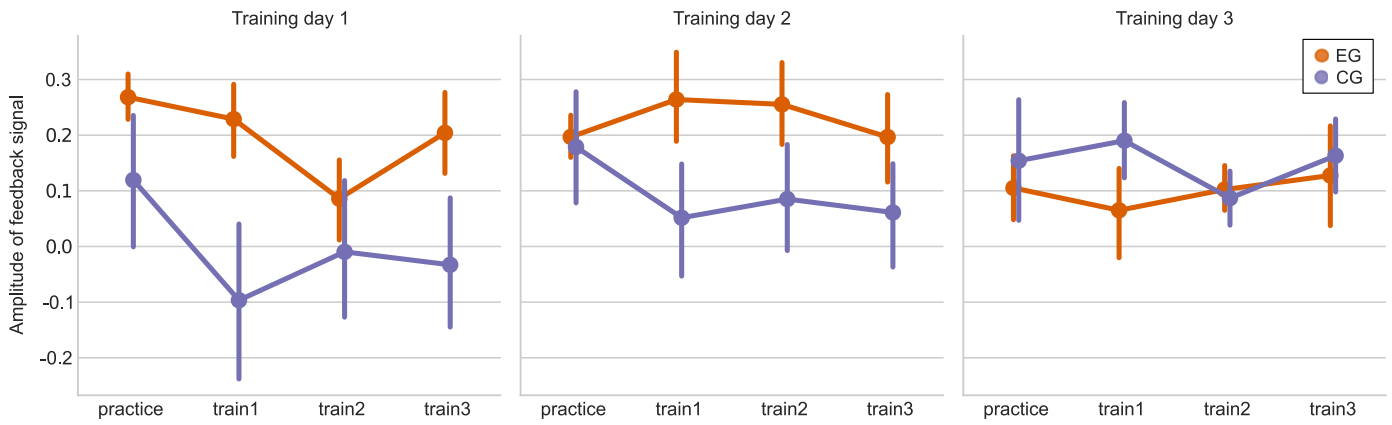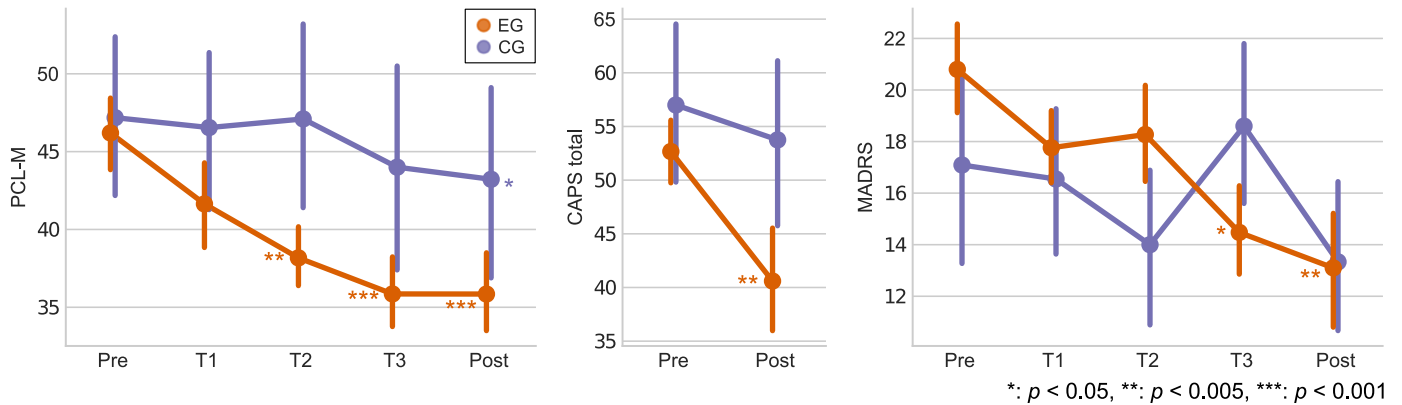
Fig. 2. Amplitudes of neurofeedback signal across runs and sessions. Error bars indicate standard error of the mean.

Fig. 3. Symptom changes across sessions. Pre and Post are the pre-training and post-training assessment sessions. T1, T2, and T3 are training day 1, training day 2, and training day 3 sessions, respectively. Error bars indicate one standard error of the mean. Asterisks indicate significant change compared to the Pre-session (corrected for multiple testing).
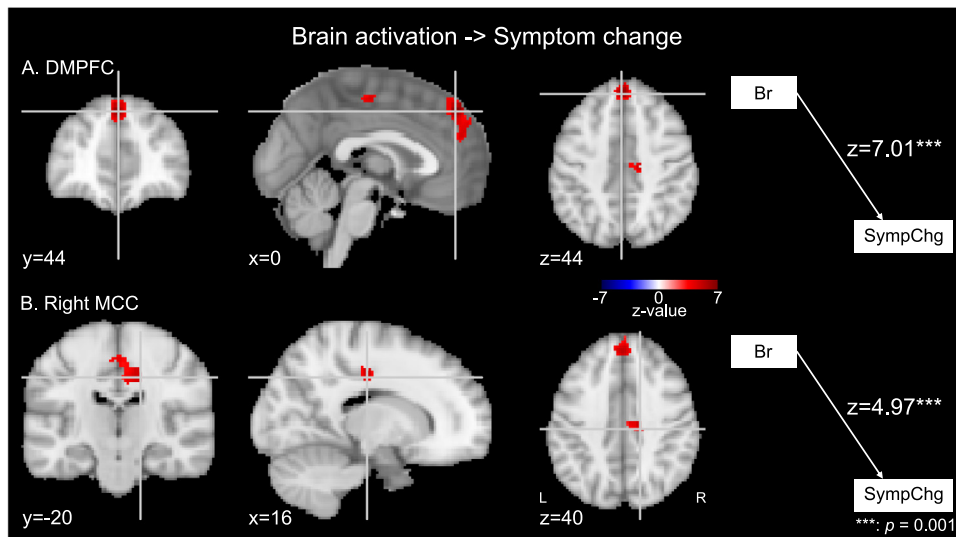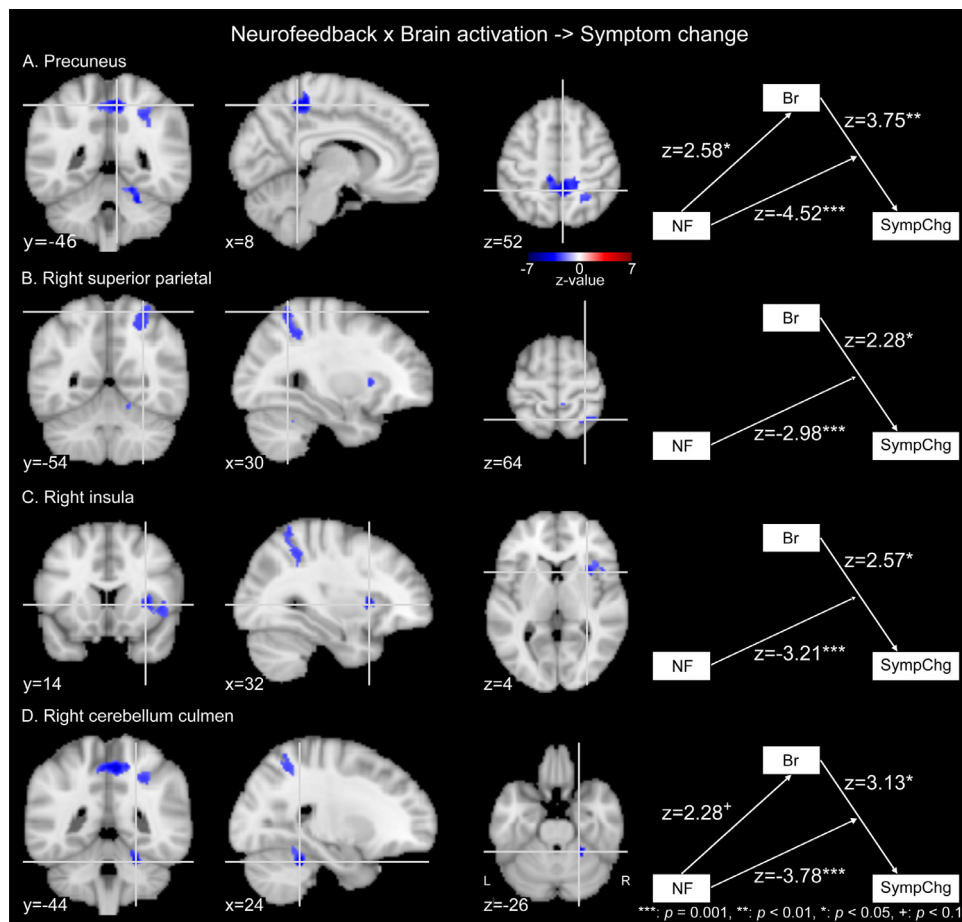

Fig. 4. . Regions with significant path coefficient for the mediating effect on PCL-M change. The right panels show the path with a significant coefficient for these regions. DMPFC: dorsomedial prefrontal cortex, MCC: middle cingulate cortex.

comorbidity ($t[24.6] = =0.633$, $p = 0.533$ and $t[25.6] = =0.166$, $p = 0.869$, respectively).

Fig. 3 shows time-course of symptom measures across sessions. Post-training CAPS score was not available for six EG and two CG participants who did not return for the post-training CAPS assessment. There was a significant main effect of session on PCL-M ($F[4,$ 121.1] $= =9.1378$, $p < 0.001$), CAPS scores ($F[1, 22.5] = =10.844$, $p = 0.003$), and MADRS ($F[4, 120.9] = =3.223$, $p = 0.015$), while interaction between session and group was not significant ($F[1, 22.5] = =1.115$, $p = 0.302$ for CAPS, $F[4, 121.1] = =0.967$, $p = 0.429$ for PCL-M, and $F[4, 120.9] = =1.359$, $p = 0.252$ for MADRS), which could be due to the large variance in the CG.

Fig. 5. Regions with significant path coefficient for the moderation effect of the neurofeedback signal onto the brain–symptom change path. The right panels show the paths with a significant coefficient for these regions.

When the effect of MDD comorbidity and its interaction with other fixed effects were included as additional factors in the analysis, no effect with MDD comorbidity was significant. While participants in the EG without MDD comorbidity tended to show lower symptom severity at the post-training session (supplementary figure S1), this difference was not statistically significant due to the large variance in each group. Association between symptom change and the mean magnitude of the neurofeedback signal was not significant.

3.2. SEMM analysis for exploring brain activations associated with symptom change

We focused on the paths linking brain activation and symptom change, Br→SympChg and NF × Br→SympChg, respectively, to explore mediating and moderating roles of brain activation for a therapeutic effect of neurofeedback training. The regions with significant effects of the group (Grp→Br) and the neurofeedback signal (Fb→Br) are shown in supplementary figures S2 and S3. Figs. 4 and 5 show the regions with a significant coefficient at Br→SympChg and NF × Br→SympChg, respectively. Table 2 shows path coefficients obtained from SEM analysis for mean activation in a 4mm-radius spherical region of interest (ROI) at peak coordinates. *P*-values for the ROI analysis were evaluated with a permutation test with 2000 repeats.

Activations in the dorsomedial prefrontal cortex (DMPFC) and the right middle cingulate cortex (MCC; Fig. 4) were associated with PCL-M symptom change. The significant positive coefficient on the Br→SympChg path (Table 2) indicates that less activation in these regions during the neurofeedback training was associated with a greater symptom decrease. There was a weak trend that these activations were

smaller for the EG than CG ($z = 2.67$, $p = 0.109$ for DMPFC and $z = 2.90$, $p = 0.060$ for right MCC, respectively). The effect of MDD comorbidity on these regions was examined in the secondary analysis. Specifically, a linear model analysis with predictors including group, neurofeedback signal, MDD comorbidity, and their interactions was performed for these brain activations. The significant main effect of MDD comorbidity ($F[1, 21] = =4.621$, $p = 0.043$) and the significant interaction between the MDD comorbidity and group ($F[1, 21] = =7.201$, $p = 0.014$) were observed for the DMPFC. This indicated that the MDD comorbidity increased the DMPFC activity and its effect was larger for EG than CG. There was no significant effect of the MDD comorbidity for the right MCC.

The regions with significant moderation paths (NF × Br→ SympChg) were found in the precuneus, the right superior parietal, the right insula, and the right cerebellum culmen (Fig. 5). They had a significant negative coefficient on the path from the NF × Br interaction to symptom change. These regions also had a significant positive coefficient on the Br→SympChg path (Table 2) indicating that less activation in these regions during the neurofeedback training was associated with greater symptom decreases. To further delineate the relationship between the factors in these regions, Fig. 6 shows the association between brain activation and symptom change for low- and high-neurofeedback signal groups (median split), respectively. This figure indicates that a significant association between brain activation and symptom change was observed for the participants receiving the low neurofeedback signal, but not for the participants achieving the high neurofeedback signal. This means that while the higher brain activation in the regions was associated with less symptom decrease, this disruptive effect was not seen when the feedback signal was high. This

Table 2
Regions of significant association with PCL-M score change.

| Region	Peak (mm in MNI)			Path coefficient (z-value)						
	X	y	z	Br → SympChg	NF → Br	Grp → Br	NF × Br → SympChg	NF → SympChg	Grp × NF → Br	Grp → NF
Dorsomedial prefrontal	0	44	44	7.01***	0.86	2.67	−0.99	1.83	−0.03	−1.45
Right middle cingulate	16	−20	40	4.97***	2.12	2.90+	−0.33	0.50	0.63	−1.45
Precuneus	8	−46	52	3.75**	2.58*	0.69	−4.52***	0.06	0.27	−1.45
Right superior parietal	30	−54	64	2.28*	1.95	0.04	−2.98***	0.59	−1.02	−1.45
Right insula	32	14	4	2.57*	1.41	0.54	−3.21***	0.88	0.41	−1.45
Right cerebellum culmen	24	−44	−26	3.13*	2.28+	1.31	−3.78***	0.48	0.53	−1.45

*** : $p = 0.001$,
** : $p < 0.01$,
* : $p < 0.05$,
+ : $p < 0.1$.

moderation effect did not differ across the EG and CG groups, suggesting the moderation was not specific to the signal from the left amygdala activation. No significant effect of MDD comorbidity was found for these regions in a follow-up analysis.

4. Discussion

The aim of the present study was to explore the brain activations associated with PTSD symptom relief by rtfMRI amygdala neurofeedback emotional training for veterans with combat-related PTSD. We employed the SEMM approach that could search mediator and moderator brain activations for PTSD symptom reduction in the whole brain. Low activation in the DMPFC and the right MCC were associated with more PTSD symptom reduction after the neurofeedback training. Low activation in the precuneus, right superior parietal, right insula, and right cerebellum culmen was also associated with more symptom reduction after the training, but these effects were moderated by the feedback signal; the effect on PTSD symptom reduction was significant when the feedback signal was low, but not significant when the feedback signal was high.

A previous report for the same study sample (Zotev et al., 2018) indicated that symptom decrease after the training sessions was associated with an increase in the left amygdala functional connectivity with the right amygdala/parahippocampal gyrus, the left dorsolateral prefrontal cortex (DLPFC), and the right superior precuneus regions during the neurofeedback training. The connectome-wide investigation of resting-state functional connectivity for the same sample (Misaki et al., 2018b) also showed that increased intrinsic connectivity between the left DLPFC and the precuneus was correlated with PTSD symptom reduction after the neurofeedback training, specifically in hyperarousal symptoms. These results indicated that the symptom reduction with the amygdala neurofeedback training did not depend solely on the amygdala activation. Instead, they suggest that a successful treatment could be supported by a synchronization across the emotion-regulation network including the DLPFC (Frank et al., 2014). Importantly, the current investigation also found that a mediator of the treatment effect with the amygdala neurofeedback training was seen in regions other than the left amygdala; high activation in the DMPFC and right MCC during the training hampered symptom reduction after the training. Activation in these regions could be a maker of a failed
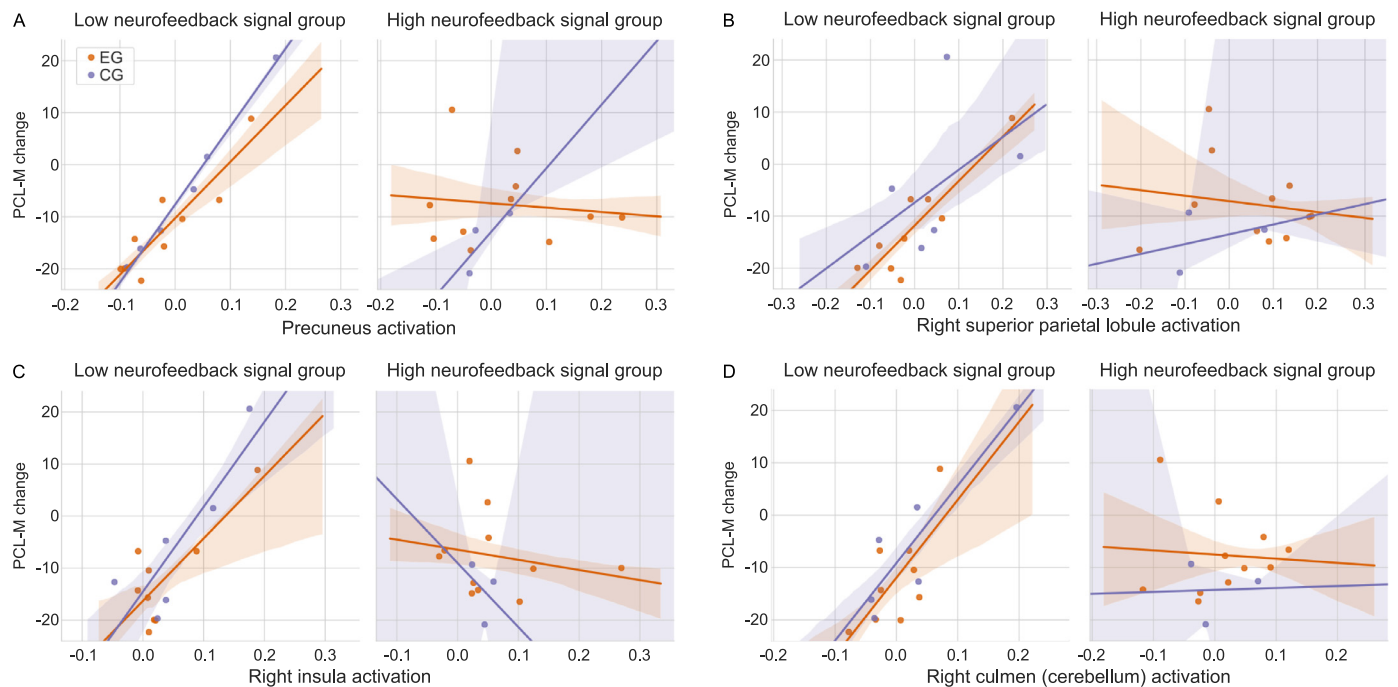
Fig. 6. Association between the PCL-M change (residualized w.r.t. the baseline score) and brain activations for low- and high-neurofeedback signal groups. Lines and shadows indicate a fitted line and its 95% confidence interval. The association between the brain activation and symptom change was significant for the low-neurofeedback group (A; $p < 0.001$, B; $p = 0.004$, C; $p < 0.001$, D; $p < 0.001$) but not for the high-feedback group (A; $p = 0.329$, B; $p = 0.897$, C; $p = 0.651$, D; $p = 0.968$) without significant difference between the experimental (EG) and control (CG) groups.

coordination of the emotion-regulation network.

An association between low DMPFC activity and self-regulation success in neurofeedback training has been demonstrated in several neurofeedback studies (Paret et al., 2018; Radua et al., 2018). DMPFC is included in the default mode network (DMN) (Buckner et al., 2008) (Raichle et al., 2001) and a correlation between high DMN activity and low perception of an emotional signal was demonstrated for healthy participants (Wiebking et al., 2011). Thus, the association between the high DMPFC activity and less symptom reduction suggests that a failure of emotion induction during the neurofeedback training could be the reason for the weaker treatment effect. The present result also showed that high activity in the precuneus, another hub region of the DMN, was associated with reduced treatment effect, which is compatible with this notion. As the DMN has an antagonistic activation to the executive control regions (Raichle, 2015), high DMN activity for participants with a low treatment effect may reflect an inactive regulation process during the neurofeedback training, which could result in a failure of emotion induction.

Another possible explanation of the DMPFC and the MCC activations was that the high activation in these regions could reflect an active search for an effective regulation strategy during neurofeedback training. A part of the DMPFC and the MCC have been implicated in emotion-regulation function (Frank et al., 2014). If patients could not increase the neurofeedback signal, they might ponder for an alternative regulation strategy. This effort could increase the DMPFC and MCC activity as well as the precuneus, which has been implicated in self-referential processing. Although patients were instructed to recall the same positive event across the training sessions, inducing positive emotion with that memory to increase the neurofeedback signal could be variable. Wondering for an effective mind strategy could impede stable coordination of the emotion-regulation network, which could result in low clinical improvement.

Patients with MDD comorbidity had high DMPFC activity, which is in line with the previous reports indicating high DMN activity for depressed patients (Hamilton et al., 2011; Sheline et al., 2009). The patients with MDD comorbidity also failed to increase the left amygdala activity even when they were in the EG. This also suggests that high DMPFC activity could be associated with a failure of emotion induction during the neurofeedback training. Symptom change, however, was not significantly different as a function of MDD comorbidity due to high variability in the CG (supplementary figure S1). Notably, previous studies using the same rtfMRI-nf protocol with MDD cohorts demonstrated successful self-regulation and significant symptom reduction (Young et al., 2016), suggesting MDD per se does not necessarily interfere with neurofeedback effects. Instead, comorbidity might increase individual variability in symptom severity and response to the neurofeedback procedure. Future work is needed to delineate what symptom profiles influence the effects of the rtfMRI-nf procedure.

High activation in the precuneus, the right superior parietal, the right insula, and the right cerebellum culmen interrupted the symptom reduction after the neurofeedback training, but this interruption was not significant when a high feedback signal was given during the training. This moderation effect was not specific to the EG so that perception of success in increasing the signal regardless of the source region might help to suppress their interference on symptom reduction. Several studies have reported that a positive autobiographical memory recall alone was not effective for improving mood for depressed patients (Joormann et al., 2007; Werner-Seidler and Moulds, 2012). Vanderlind et al. (2017) suggested that this inefficacy was due to 'fear of positive' emotion that detracted from the mood improvement effect. Werner-Seidler and Moulds (2012) also suggested that abstract memory processing in depressed patients could be the reason for the absence of mood improvement. Although it is not clear whether the activations observed in the present study were associated with such fear of positive emotion or abstract memory processing, the present results suggest that the inefficacy of recalling a positive autobiographical memory for mood

improvement might be due to disruptive brain activations that could be countered by perception of successful control of feedback signal.

This nonspecific effect suggests that even a sham neurofeedback signal could result in symptom reduction, or it could at least cancel the effect of disruptive brain activation on the mood improvement if participants achieved successful control of feedback signal with the expectation of the treatment effect. This demonstrates a need for controlling the feedback signal amplitude to examine the efficacy of neurofeedback from a specific region (Lubianiker et al., 2019; Sorger et al., 2018). In the present experiment, however, equalizing task difficulty between the conditions regulating different regions was not feasible. Even in such a situation, SEM analysis could identify a nonspecific effect apart from the group effect by employing multiple mediation and moderation models while controlling multiple factors simultaneously.

It is common to observe a nonspecific or placebo effect on symptom change, especially in response to neurofeedback procedures (Thibault et al., 2017), but what brain activation was associated with such effect has rarely been identified. The identification of brain activations mediating a placebo effect could be a valuable insight to improve the treatment procedure. We also note that identifying the nonspecific effect does not necessarily indicate the inefficacy of the experimental condition. In fact, the group difference has been seen in other brain regions (supplementary figure S2), self-regulation success in the left amygdala activity, and in functional connectivity reported in the previous reports (Misaki et al., 2018b; Zotev et al., 2018). The present results suggest that both specific and nonspecific effects could result in symptom change. Elucidating nonspecific effects is not problematic, but rather necessary to comprehensively delineating mechanisms of neurofeedback effects.

Altered functional connectivity in the intrinsic brain networks, including the DMN, have been indicated for PTSD patients. The patients showed decreased resting-state functional connectivity across the DMN regions (DiGangi et al., 2016; Koch et al., 2016), which is opposite of that for MDD, and increased connectivity across the salience network (SN) regions and between the DMN and SN (Sripada et al., 2012). Decreased resting-state functional connectivity between the SN and the left DLPFC has also been indicated for PTSD (Misaki et al., 2018a). In contrast to resting state, increased functional connectivity in the DMN, specifically between the PCC and the medial prefrontal region, was reported in PTSD during a working memory task (Daniels et al., 2010), suggesting difficulty in a task-induced switch of the brain state for PTSD patients. These abnormalities in the brain networks for PTSD patients suggest that disease symptoms are associated with a dysfunction of large-scale brain networks (Menon, 2011; Tursich et al., 2015) so that the whole-brain association of the treatment effect could be a matter of course. Indeed, associations between the neurofeedback treatment effect and changes in functional connectivity of intrinsic networks have been indicated. Our previous study in the same sample (Misaki et al., 2018b) demonstrated that increased connectivity between the left DLPFC and the precuneus was correlated with a decrease in hyperarousal symptoms of PTSD after the neurofeedback treatment. A study of EEG neurofeedback training to decrease alpha rhythm amplitude for PTSD patients (Kluetsch et al., 2014) also found that a rebound increase of resting-state alpha synchronization was associated with symptom relief, and the rebound amplitude was correlated with increased resting-state fMRI functional connectivity between the SN and the right insula and across the DMN regions including the bilateral posterior cingulate, the right middle frontal gyrus, and the left medial prefrontal cortex. As argued in Ioannides (2018), in a neurofeedback treatment, modifying the activity of a target area or frequency of EEG might not be the end of the treatment intervention but rather an entry point for modifying the underlying brain networks. An indication of the delayed treatment effect of neurofeedback training (Rance et al., 2018) is compatible with this argument.

Given the network-level association of the treatment effect,

targeting such a network as a neurofeedback signal could be more effective for treating psychiatric diseases rather than regulating a specific region. For example, regulating the DMN activity with rtfMRI-nf has been demonstrated for healthy participants (McDonald et al., 2017). According to the present result, training a patient to decrease the DMPFC and MCC activities with neurofeedback might have a treatment effect on PTSD symptoms. However, we should note that the DMN activity in the present result may not be a cause of the symptom change but a mediator of the effect of the emotion regulation training. Thus, regulating the DMN activity by itself may not have a treatment effect, at least for normalizing emotion-regulation function. Intervening the DMN activity might be useful to treat other types of PTSD symptoms, though. For example, the depersonalization/derealization symptom in the dissociative subtype of PTSD patients, which was associated with decreased connectivity in the DMN (Tursich et al., 2015), could be treated with DMN neurofeedback training. In future development of the neurofeedback treatment, a symptom- or process-based approach rather than a diagnosis-based one will improve the efficacy of the therapy (Lubianiker et al., 2019).

Limitations of the present study merit comment. Applying a complex model to a limited number of samples could have limited the findings. While we used a permutation test to reduce a false positive error (Ludbrook and Dudley, 1998), this could increase false negative risk. As the bias-variance trade-off in model complexity suggested (Bishop, 2007), null distribution in the permutation test could have large variance with a complex model, which makes it hard to find a significant effect. The model assumption also limits the findings. The reported results, therefore, should be considered as a part of the symptom relief process rather than as a full mechanism of the treatment. Lack of significant result in the analysis cannot be proof of the absence of the effect. While the present investigation found the activations that hampered the treatment effect, we did not find brain activations that enhanced symptom relief. Not observing such patterns suggest that supporting brain activation for symptom reduction might be more variable across patients than disruptive ones (Ioannides, 2018). To delineate such individual variability and to examine the more comprehensive model, a future study would need a larger sample size than the present one.

5. Conclusions

The whole-brain investigation of mediating and moderating brain activations in rtfMRI-nf training with the SEMM analysis revealed that symptom reduction with the amygdala neurofeedback emotional training was mediated by activations in broad areas of the brain not limited to the neurofeedback target region, specifically with low activations in the default mode network regions. As such, the result demonstrated that rtfMRI-nf training recruits broad brain regions beyond targeted regions and these co-activated regions could play major roles in the effects of the neurofeedback procedure. The present results also suggest a potential application of rtfMRI-nf in online monitoring of whole brain activation, not limited to the neurofeedback target region, which could enhance prediction of success or failure of the procedure. Such online monitoring could help to adjust the training protocol for individual patients and improve efficacy.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102047.

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