

2015 Donald F Klein Investigator Award Finalist

ALTERED DEFAULT MODE NETWORK (DMN) RESTING STATE FUNCTIONAL CONNECTIVITY FOLLOWING A MINDFULNESS-BASED EXPOSURE THERAPY FOR POSTTRAUMATIC STRESS DISORDER (PTSD) IN COMBAT VETERANS OF AFGHANISTAN AND IRAQ

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Background: Recent studies suggest that mindfulness may be an effective component for posttraumatic stress disorder (PTSD) treatment. Mindfulness involves practice in volitional shifting of attention from “mind wandering” to present-moment attention to sensations, and cultivating acceptance. We examined potential neural correlates of mindfulness training using a novel group therapy (mindfulness-based exposure therapy (MBET)) in combat veterans with PTSD deployed to Afghanistan (OEF) and/or Iraq (OIF). **Methods:** Twenty-three male OEF/OIF combat veterans with PTSD were treated with a mindfulness-based intervention (N = 14) or an active control group therapy (present-centered group therapy (PCGT), N = 9). Pre-post therapy functional magnetic resonance imaging (fMRI, 3 T) examined resting-state functional connectivity (rsFC) in default mode network (DMN) using posterior cingulate cortex (PCC) and ventral medial prefrontal cortex (vmPFC) seeds, and salience network (SN) with anatomical amygdala seeds. PTSD symptoms were assessed at pre- and posttherapy with Clinician Administered PTSD Scale (CAPS). **Results:** Patients treated with MBET had reduced PTSD symptoms (effect size $d = 0.92$) but effect was not significantly different from PCGT ($d = 0.46$). Increased DMN rsFC (PCC seed) with dorsolateral dorsolateral prefrontal cortex (DLPFC) regions and dorsal anterior cingulate cortex (ACC) regions associated with executive control was seen following MBET. A group \times time interaction found MBET showed increased connectivity with DLPFC and dorsal ACC following therapy; PCC-DLPFC

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connectivity was correlated with improvement in PTSD avoidant and hyperarousal symptoms. Conclusions: Increased connectivity between DMN and executive control regions following mindfulness training could underlie increased capacity for volitional shifting of attention. The increased PCC–DLPFC rsFC following MBET was related to PTSD symptom improvement, pointing to a potential therapeutic mechanism of mindfulness-based therapies. Depression and Anxiety 33:289–299, 2016. © 2016 Wiley Periodicals, Inc.

Key words: *mindfulness/meditation; PTSD/posttraumatic stress disorder; brain imaging/neuroimaging; functional MRI; treatment*

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a highly debilitating disorder affecting ~20% of combat veterans returning from Afghanistan (OEF) and Iraq (OIF).^[1] There is considerable empirical support for exposure-based psychotherapies for PTSD involving processing of traumatic memories, such as prolonged exposure (PE) and cognitive processing therapy (CPT), and these treatments show very large effect sizes compared to baseline (pre-post Cohen's *d* in the 1.0–2.5 range) and often in comparison to active therapies.^[2,3] In fact, trauma-based exposure therapies are the only form of psychotherapy currently endorsed by the Institute of Medicine as first line, empirically supported treatments.^[4] However, even with the strong evidence of efficacy for exposure therapy, some combat veterans decline these treatments, and furthermore, dropout rates in both RCT trials,^[5–7] and clinic-based studies^[8–10] range from 30 to 40%, and likely contribute to suboptimal outcomes.^[3,10] These data suggest additional strategies, such as the kinds of emotional regulation and distress tolerance found in mindfulness training, might be useful to help PTSD patients to accept and engage in effective trauma-focused exposure therapies.

Mindfulness-based interventions have gained increased attention for their efficacy for relapse prevention in patients with chronic major depressive disorder. Several RCTs have found mindfulness-based cognitive therapy (MBCT) to be effective for preventing depression relapse,^[11–13] and there is accumulating evidence that MBCT and mindfulness-based stress reduction (MBSR) may be helpful for active depression^[14,15] and generalized anxiety disorder (GAD).^[16] A small number of recent studies have also suggested that mindfulness training might be a useful modality for treatment of PTSD, however as yet evidence is still preliminary. An uncontrolled pilot study of adapted MBSR led to acute and long-term (3 years) improvements in PTSD and depression symptoms in adults with childhood sexual abuse history.^[17,18] Improvement in depression and PTSD symptoms has also been reported in combat veterans who participated in MBSR groups not focused on PTSD.^[19,20] We found an 8-week MBCT adapted for PTSD led to improvement in avoidant symptoms in highly chronic PTSD (Vietnam veterans) patients,^[21]

and a recent larger RCT of MBSR adapted for combat PTSD in primarily Vietnam veterans reported similar results.^[22]

Mindfulness training involves prolonged practice in volitional shifting of attention, for example, from distraction and “mind wandering” to present-moment attention to perception of sensations, as well as cultivating an attitude of acceptance of current phenomena.^[23,24] There has been speculation that mindfulness training may lead to alterations in resting-state functional connectivity (rsFC) in a network associated with task-negative self-referential processing, the “default node network” (DMN),^[23,24] which is associated with mind-wandering.^[25,26] Several recent cross-sectional studies of long-term meditators or people exposed to several weeks of meditation training such as MBSR have implicated potential changes in rsFC in DMN and potentially other networks, such as the central executive network (CEN).^[27–33] PTSD is also associated with alterations in rsFC, which could be related to PTSD symptoms.^[34–40] Here, we examined the effect of mindfulness training on DMN function in PTSD, studying OEF/OIF veterans treated with a novel nontrauma-focused PTSD group intervention incorporating PTSD psychoeducation, mindfulness training, self-compassion exercises, and in vivo exposure, “mindfulness-based exposure therapy” (MBET), or an active control therapy not including mindfulness training, present-centered group therapy (PCGT).

METHODS

PARTICIPANTS

The study was approved by the Institutional Review Boards at the University of Michigan Medical School and the Ann Arbor VA. One hundred eighty-one OEF/OIF veterans seeking treatment for PTSD at the VA Ann Arbor PTSD program and potentially meeting inclusion criteria were approached. (See Supporting Information Table S1 for details of screening, enrollment, and retention in the study). Of these patients approached, *N* = 65 were consented into this study (*N* = 67 were enrolled into other PTSD treatment studies offered over the same time period), *N* = 57 were scheduled for pretherapy scan, *N* = 43 completed pretherapy, functional magnetic resonance imaging (fMRI) and were assigned to therapy (MBET *N* = 26, PCGT *N* = 17), *N* = 40 started therapy, and *N* = 23 completed posttherapy scans and

TABLE 1. Demographics

Characteristic	MBET (<i>N</i> = 14)	PCGT (<i>N</i> = 9)	<i>t</i> / χ^2	<i>P</i>
Age, <i>M</i> (<i>SD</i>)	32.43 (7.54)	31.67 (10.14)	0.207	.838
Race, <i>N</i> (%)			0.109	.742
European American	13 (93%)	8 (89%)		
African American	1 (7%)	1 (11%)		
Education, <i>N</i> (%)			1.431	.489
Some grad school or graduate degree	1	1		
Some college or college degree	11	5		
High school grad	2	3		
CAPS, <i>M</i> (<i>SD</i>)	72.29 (18.32)	74.11 (15.34)	0.213	.833
Comorbidities, <i>N</i> (%)				
Mood disorder	13 (93%)	6 (67%)	2.616	.106
Anxiety disorder	3 (21%)	1 (11%)	0.406	.524
Substance use disorder	3 (21%)	0	2.218	.136
Psychiatric medications				
None	2 (14%)	3 (33%)	1.168	.280
SSRI	4 (29%)	3 (33%)	0.059	.809
Sleep	2 (14%)	2 (22%)	0.240	.624
Pain	2 (21%)	1 (11%)	0.406	.524
Other	5 (36%)	2 (22%)	1.028	.311

thus were included in the study sample. (See Table 1 for demographics, symptom severity, and medications at intake). All participants met DSM-IV criteria for current (past month) PTSD, as assessed by the Clinician Administered PTSD Scale (CAPS).^[38] Participants were also assessed for comorbid disorders using the Mini-International Neuropsychiatric Interview (MINI).^[39] Participants with psychosis, personality disorders, or suicidal risk were excluded. Psychiatric medications were allowed, but no changes in medications were allowed from 4 weeks before the intake scan until the end of the interventions and postintervention scan.

PROCEDURE

Written informed consent was obtained after a complete description of the study was provided. Both the MBET and the PCGT interventions described in detail to all participants in the consent process. Participants underwent an fMRI scan and were randomly assigned to one of two 16-week group therapy groups for PTSD: either MBET or PCGT, each with four to six patients per group. The final recruitment cohort had both interventions described in detail, but were all assigned to MBET. Within 2 weeks after the interventions, participants underwent a second diagnostic interview and fMRI scan.

THERAPISTS AND RATERS

Therapists (N.G., A.K., K.P., S.R.) were doctoral and masters-level psychologists at a VA PTSD clinic who had training in MBCT (A.K., N.G., and S.R.) and in present-centered therapy (S.R.). Trained, experienced clinical raters (CAPS and MINI) were blind to treatment condition.

MINDFULNESS-BASED EXPOSURE THERAPY

This 16-week nontrauma-focused intervention was developed by the authors at the VA Ann Arbor, incorporating mindfulness training from MBCT, PTSD psychoeducation, and in vivo exposure from PE therapy, and self-compassion exercises. In vivo exposures were conducted only to avoided (and objectively safe) situations or activities. It was explicitly stated that no imaginal exposure or processing of trauma memories would be done in this group. The intervention consists of four "modules": (1) PTSD psychoeducation and relaxation,

(2) mindfulness of body and breath exercises and in vivo exposure, (3) mindfulness of emotion in vivo exposure, and (4) self-compassion training. The classes were 2 hr each and participants complete daily homework in between sessions.

PRESENT-CENTERED GROUP THERAPY

This therapy was initially developed by Schnurr et al. (2003) to represent all of the elements of effective PTSD treatment that are not specifically trauma focused. PCT controls for nonspecific therapeutic factors such as group bonding and therapist support, as well as specialized knowledge about PTSD. It focuses on identifying and discussing current life stressors that contribute to PTSD, psychoeducation, and promotion of wellness and physical health. Similar to the MBET group, the intervention contains daily homework assignments, and meets for 2 hr a week for 16 weeks. It does not contain any instructions on mindfulness, exposure, or cognitive restructuring.

MRI SCANNING

Prior to starting group therapy and within 2 weeks after group termination participants underwent both structural and functional MRI scanning. The functional MRI session included a resting-state scan and separate emotion regulation tasks (to be reported elsewhere). The resting-state task always occurred before the emotional regulation tasks. During the resting-state task, a white fixation cross on a black background was displayed at the center of the screen for 8 min. Participants were instructed to relax and to keep their eyes open and fixed on the cross.

fMRI DATA ACQUISITION AND ANALYSES

All scanning was performed using a Philips 3 Tesla MRI scanner (Phillips Medical Systems, Andover, MA) in the fMRI laboratory at the Ann Arbor VA. Two hundred forty T2*-weighted echo planar gradient-recall echo volumes were acquired during rest (echo time = 30 ms, repetition time = 2,000 ms, 64 × 64 matrix, flip angle = 90 degree, field of view = 22 cm, 42 contiguous 3 mm axial slices per volume). Five additional volumes were discarded at the beginning of each run to allow for equilibration of the MRI signal. A high-resolution T1-weighted structural image (3D turbo fast field echo, 1 mm isotropic voxel, 256² matrix, 180 slices, repetition time = 9.8 ms, echo time

TABLE 2. Effect of MBET and PCGT on PTSD symptoms (CAPS scores)

	MBET (<i>N</i> = 14)					PCGT (<i>N</i> = 9)				
	Intake	Post	<i>t</i>	<i>P</i>	Pre-post <i>d</i>	Intake	Post	<i>t</i>	<i>P</i>	Pre-post <i>d</i>
CAPS total	72.29 (18.32)	56.71 (22.0)	3.20	.007	0.92	74.11 (15.34)	67.11 (20.49)	1.85	.101	0.46
CAPS intrusive	17.43 (7.10)	12.43 (9.07)	2.40	.032	0.72	17.88 (7.16)	15.00 (10.80)	1.49	.182	0.40
CAPS avoidant	30.00 (8.00)	22.64 (11.34)	2.39	.032	0.97	28.38 (8.67)	26.25 (9.10)	1.22	.263	0.25
CAPS hyperarousal	22.86 (6.23)	20.29 (8.84)	1.98	.069	0.73	27.75 (3.65)	24.88 (4.71)	2.59	.036	0.79

= 4.6 ms, flip angle = 8 degrees) was also obtained to provide for more precise anatomical localization. fMRI data were analyzed using the statistical parametric mapping software package, SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional slices within each volume were sinc-interpolated, weighted in time, slice by slice, to correct for the sequence of slice acquisition. The functional volumes were realigned to correct for head motion and structural images coregistered to the mean of functional images. The structural images were spatially normalized to a standard MNI template using the voxel-based morphometry toolbox (VBM8 <http://dbm.neuro.uni-jena.de/vbm>) and DARTEL high-dimensional warping.^[41] Estimated deformation fields from warping were applied to normalize images to MNI space, and smoothed using an 8-mm FWHM Gaussian kernel. Functional data are detrended to account for scanner drift. To control for nonneuronal noise sources due to heart beat, respiration, and motion,^[43] we first extracted the average BOLD time series from structural MRI-derived white matter and cerebrospinal fluid masks. A PCA was performed and the top five components of the time series were added to the model as nuisance covariates. Motion parameters, their first derivatives, and quadratic terms of original and derivatives were used as nuisance covariates to remove signal related to spin history related motion artifacts. Additionally, due to motion's large potential effects on regional correlations^[44] we performed motion scrubbing (removal of volumes) based on a framewise displacement threshold of 0.5 (as previously calculated).^[42] Finally, participants with >60% of time points removed due to motion were excluded.^[44] Motion parameters (maximum displacement, mean displacement, maximum angle, mean angle) for the two groups were compared via independent-samples Kruskal–Wallis tests. We did not perform global-signal regression because it has been suggested that it may result in spurious anticorrelations.^[47] However, since rsFC measures low-frequency spontaneous BOLD oscillations (0.01 to 0.10 Hz band), the time course for each voxel was band-pass filtered in this range.^[10]

We examined DMN rsFC using regions of interest (ROI) “seeds” in PCC and vmPFC adopted from previous studies of the DMN in participants with PTSD^[38,39] using 4.24 mm radius spheres centered at MNI:(0,−56,20) for PCC and MNI:(−2,48,−4) for vmPFC. We also examined salience network rsFC using anatomical Automated Anatomical Labeling (AAL) amygdala “seeds” from the WFU pick-atlas.^[43] Pearson product–moment correlation coefficients were calculated between the average BOLD time course in the seed region and all other voxels in the brain. Each correlation resulted in a 3D correlation coefficient image (r-image). R-images were then transformed to z scores using a Fisher r to z transformation. Z score images from the individual functional connectivity analyses were entered into second-level random effects analyses (factorial ANOVA and *t*-tests) implemented in SPM8. Second-level maps were initially thresholded at whole-brain $P < .001$, uncorrected (extent threshold, $k = 10$). We first investigated the main effect of time over the two groups for DMN and bilateral amygdala seeds, with cluster threshold of $P < .05$, corrected for whole-brain family-wide error (FWE). In this intervention outcome study, we were specifically interested in group \times time interactions characterized by both a main effect of time, and group differences at

postintervention due to the experimental group changing greater than the control intervention over time, but no difference at preintervention. Such interactions are known as “spreading” (ordinal) interactions, as opposed to “cross-over” (disordinal) interactions, which could reflect preexisting brain differences in groups at intake (failure of randomization). To test for spreading interactions, we utilized the conjunction analysis of Friston and colleagues^[44] within flexible ANOVA *F* test maps to test the likelihood of voxels having a consistent main effect of time, main effect of group, and group \times time interaction effect (each of which should exist in a consistent direction at a minimum threshold in a true spreading interaction, although each may not be individually significant) with search area restricted to areas where direction of all three effects agreed, and thresholded at $P = 0.001$. Connectivity values in identified clusters were extracted with 7 mm spheres.

RESULTS

PARTICIPANTS

The two PTSD groups did not significantly differ by PTSD symptom severity (CAPS scores), number of Axis I comorbidities, age, race, or medication use at intake (see Table 1).

EFFECTS OF MBET AND PCGT GROUP THERAPY ON PTSD SYMPTOMS

The participants in this fMRI study were a subset of a larger controlled trial comparing MBET and PCGT. The overall outcomes in the entire sample, as well as details of study design, compliance, and retention, and detailed description of the interventions, are reported separately (King et al., unpublished data). Patients in the MBET group attended more group therapy sessions than patients treated with PCGT [average of 13.5 vs. 7.5 sessions, respectively, $t(19) = 5.39$, $P < .001$]. In this subsample, recruited for pre-post fMRI experiment, MBET ($N = 14$) was associated with a significant decrease in PTSD symptom severity and PCGT was associated ($N = 9$) with a trend level improvement (Table 2 and Fig. 1). MBET showed a significant reduction in total CAPS score (pre vs. post MBET $t(13) = 3.20$, $P = .007$, average 15.6 point decrease in total CAPS, effect size Cohen's $d = 0.92$). PCGT was associated with a smaller decrease (pre vs. post PCGT $t(8) = 1.81$, $P = .10$, average 7.0 point decrease in total CAPS, effect size $d = 0.46$). In between condition analyses, RM-ANOVA condition \times time interaction were not significant for pre-post analyses ($F [1,20] = 1.62$, $P = .22$) in total CAPS scores. The

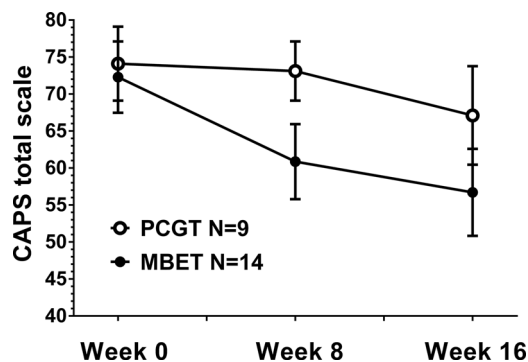


Figure 1. Change in PTSD symptoms (total CAPS scores) in PTSD patients receiving a mindfulness-based group therapy (MBET) and a group therapy without mindfulness training (PCGT). Main effect of time $F(1, 43) = 6.23, P = .002$; group \times time interaction $F(2, 42) = 1.75, P = .185$.

between condition posttherapy CAPS score effect size was $d = 0.41$.

fMRI DATA

Resting-state data from two participants were excluded from the following analyses due to technical problems with data acquisition that made the data unusable, and one participant's data were excluded due to excessive movement. There were no significant differences between the groups in head motion at the pre- or postscan, nor were there any significant changes in head motion from pre- to posttherapy.

RESTING-STATE CONNECTIVITY

We first analyzed pretreatment resting-state data comparing the two treatment groups. rsFC analyses of the pretreatment scans using the PCC seed produced the expected clusters of connectivity in vmPFC and frontal medial wall, and using the vmPFC seed showed frontal wall, PCC, cuneus, and precuneus areas. Left and right amygdala seeds also showed expected patterns of rsFC with bilateral amygdala, hippocampus, insula, subgenual ACC, and dorsal anterior cingulate. No significant differences in connectivity were observed between PTSD patients assigned to MBET and PCGT at intake (data not shown).

CHANGES IN DMN rsFC IN PTSD PATIENTS TREATED WITH MBET OR PCGT

DMN: PCC Seed. Changes in DMN connectivity (using PCC seed) from pre- to posttherapy with MBET and PCGT were assessed using paired-samples t -tests using whole-brain peak threshold $P < .001$ uncorrected and cluster threshold family-wide error (pFWE) correction $< .05$ (Table 3, Fig. 2). In the MBET group, significant increases in DMN connectivity with several regions in frontal cortex and ACC were found following mindfulness training. Post- > pre-MBET contrasts revealed increased post-MBET PCC connectivity with bilateral dorsolateral prefrontal cortex (DLPFC), and with dorsal ACC (Table 3). A contrast of pre- > post-MBET revealed no significant clusters, indicating no decreases in PCC rsFC were detected following MBET. In the

TABLE 3. Resting-state connectivity (PCC-seed) results from paired-sample t -test comparisons of PTSD patients pre- and posttherapy with MBET ($N = 12$) and PCGT ($N = 8$)

Contrast map and brain region	MNI [x, y, z]	Z-score	Cluster K	Cluster pFWE
PCC seed				
MBET post > pre				
Left DLPFC	-21, 53, 7	4.37	212	< .001
	-24, 53, 16	4.05		
	-27, 38, 28	4.02		
Right DLPFC	30, 53, 25	3.92	119	< .001
	30, 28, 28	3.88		
	36, 44, 19	3.66		
Dorsal ACC	6, 11, 28	3.98	78	.005
	-6, 23, 19	3.80		
	-6, 17, 40	3.57		
PCGT post > pre				
Left precuneus	-12, -85, 43	4.47	46	.009
Right precuneus	3, -85, 46	4.18	49	.006
Left cuneus	-3, -70, 16	4.18	105	< .001
Sup parietal lobule	33, -55, 61	3.84	39	.020
Left amygdala seed				
MBET post > pre				
Left hippocampus	-21, -28, -5	4.33	136	<.001
	-15, -34, -8	4.08		
Dorsal ACC	0, 2, 40	3.95	51	.025
	-9, 5, 40	3.77		
	6, 5, 34	3.55		

Shown are clusters with FWE corrected $P < .05$.

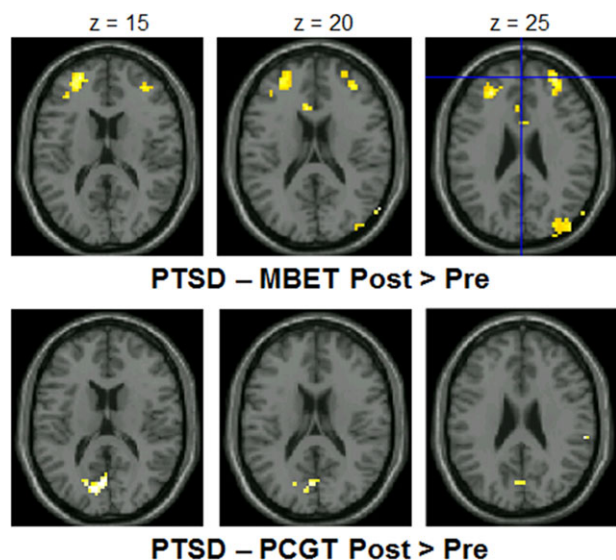


Figure 2. Change in DMN (PCC seed) resting-state functional connectivity following mindfulness-based group psychotherapy. (A) PTSD patients who completed mindfulness-based group psychotherapy (MBET). (B) PTSD patients who completed group psychotherapy with no mindfulness training (PCGT).

PCGT group a pre- > posttherapy contrast had no significant clusters, indicating no decreases in PCC rsFC were detected following PCT. Post- > pre-PCGT contrasts found increased post-PCC connectivity with bilateral precuneus and left cuneus (Table 3).

DMN: vmPFC Seed. No significant clusters were discovered in any contrast.

Right Amygdala Seed. No significant clusters were discovered in any contrast.

Left Amygdala Seed. The MBET Post- > precontrast revealed increased connectivity between left amygdala with left hippocampus and dorsal ACC following MBET (post > pre; Table 3), but no significant clusters were discovered in any other contrast.

PTSD THERAPY GROUP BY TIME INTERACTION EFFECTS ON rsFC

Therapy group (MBET vs. PCGT) by time (posttherapy vs. pretherapy) interactions in PCC and left amygdala rsFC were tested in whole-brain RM-ANOVA analyses that tested “spreading interactions” (interactions that occur primarily due to changes in one group and are not due to differences at intake). Group \times time spreading interactions in DMN connectivity (threshold $P < .001$) were detected in bilateral DLPFC and dorsal ACC (Table 4, Fig. 3). The interactions were characterized by a lack of significant differences in PCC connectivity with DLPFC and dorsal ACC in participants before engaging in either therapy, and an increase in DMN connectivity with left DLPFC and dorsal ACC following the MBET group only (an analogous cluster in right DLPFC is also

shown at threshold $P < .002$). No significant spreading interactions were detected in the left amygdala seed.

CORRELATIONS OF POSTTHERAPY PCC AND AMYGDALA rsFC WITH PTSD SYMPTOM IMPROVEMENT

The level of PCC–DLPFC connectivity following mindfulness training (MBET) was significantly correlated with improvement in avoidant and hyperarousal PTSD symptoms (Fig. 3D and 3E). DLPFC activity following MBET was correlated with pre- to posttherapy change in CAPS avoidant scale ($r(12) = .623, P = .032$) and hyperarousal scale ($r(12) = .675, P = .016$), but not with improvement in intrusive symptom scale. DLPFC activity following PCGT was not significantly correlated with any CAPS subscale, but was correlated with PTSD avoidant and hyperarousal symptom improvement across all patients, $r(20) = .592, P = .006$, and $r(20) = .624, P = .003$, respectively. In contrast, rsFC in PCC–dorsal ACC and left amygdala–hippocampus following MBET, PCGT, or across all patients was not correlated with improvements in any PTSD symptom subscale.

DISCUSSION

This study presents evidence of changes in DMN rsFC in combat veteran PTSD patients following a 16-week group psychotherapy that involved daily mindfulness training (MBET). PTSD patients who completed MBET showed increased pre- to posttherapy DMN (PCC seed) connectivity to DLPFC regions within the CEN. This increased DMN–CEN connectivity was seen only in the group who had engaged in mindfulness training, and not in those who had completed an active control therapy (PCGT), and a treatment-group (MBET vs. PCGT) \times time (post- vs. pretherapy) interaction was observed in whole brain analyses. These findings are consistent with the long-standing concept that the prolonged forms of attention training found in mindfulness-based intervention might lead to increased capacity to volitionally switch ones attention from “narrative” forms of self-referential states (which can be associated with anxiety and rumination), to other forms of self-referential states, such as “experiencing” sensation and interoception.^[23,24] This is consistent with the primary skills explicitly trained in mindfulness training: developing metacognitive awareness of one’s attention and the capacity to volitionally “shift” one’s attention from “mind-wandering” self-narrative to explicit tasks of interoception and attention to breath (i.e., to the object of meditation, the sensations of the breath). Increased recruitment of executive network circuits (and in particular, with DLPFC regions associated with volitional control of attention) during resting state could reflect a potential mechanism underlying the salutary effects of mindfulness training on emotional regulation, involving increased volitional control of mental states. We

TABLE 4. Resting-state connectivity results: therapy group (MBET vs. PCGT) x time (post- vs. pretherapy) interactions

Contrast map and brain region	MNI [x, y, z]	F-score	Cluster K
PCC seed			
Left DLPFC	-30, 47, 10	20.82	26
	-33, 47, 19	20.60	
Right DLPFC ^{a)}	36, 41, 16	11.95	30 ^{a)}
Dorsal ACC	-3, 23, 40	15.84	26
	-6, 32, 37	14.53	

a) Thresholded at $P < .002$ to detect bilateral effect.

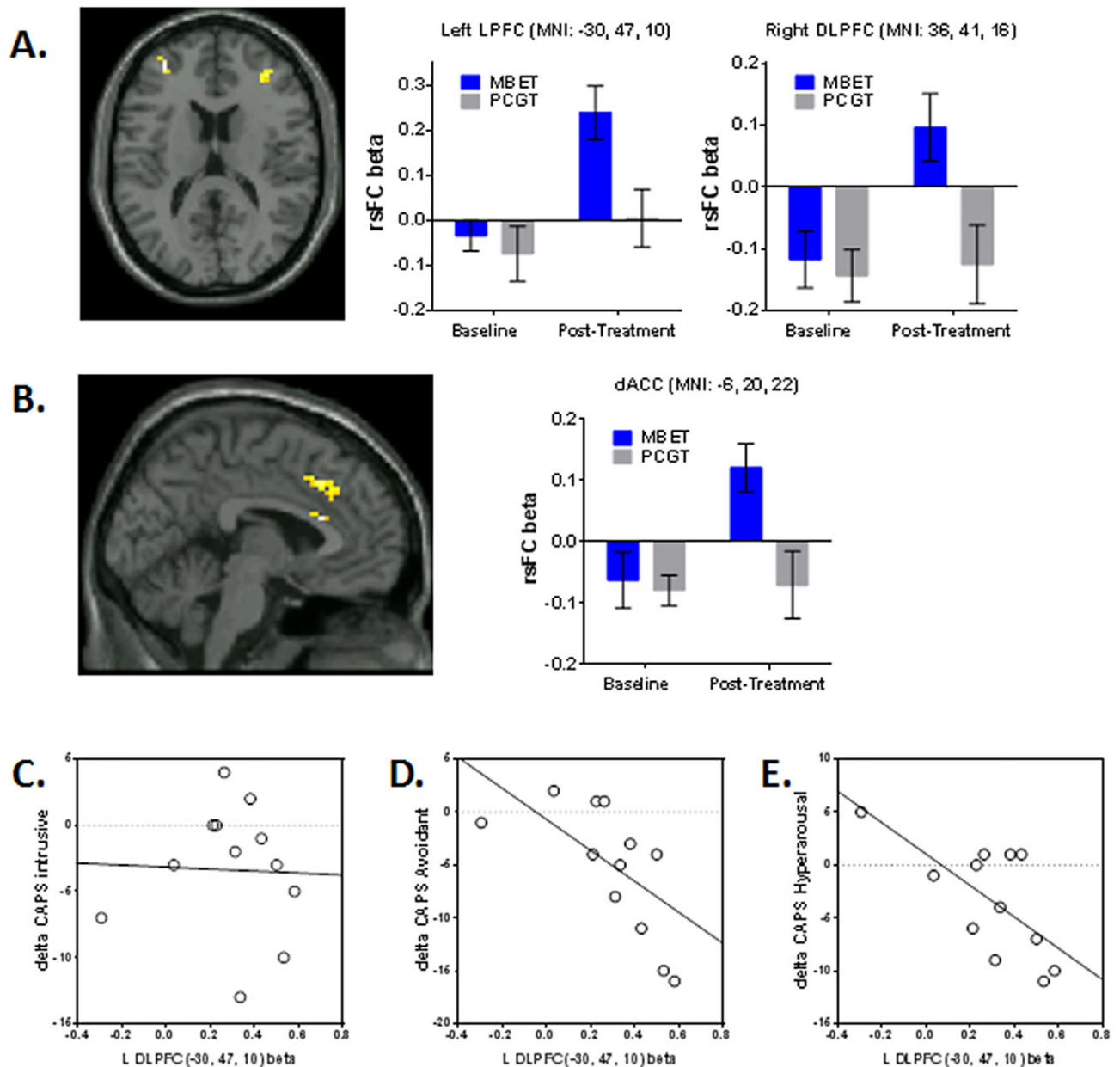


Figure 3. PTSD treatment group x time interaction in DMN resting-state functional connectivity. (A) Coronal slice showing interaction effect in PCC-seed connectivity with DLPFC. (B) Sagittal slice showing interaction effect in PCC-seed connectivity with dorsal ACC. (C–E) Correlation of PCC and left DLPFC with pre-post change in (C) intrusive, (D) avoidant, and (E) hyperarousal PTSD symptoms in the MBET group.

also found that the level of DMN–CEN connectivity following 16 weeks of mindfulness training in MBET was significantly correlated with improvement in PTSD avoidant and hyperarousal symptoms, further suggesting that the mindfulness-training effect to increase connectivity between DMN and executive network at rest could be a neural mechanism underlying therapeutic change in mindfulness-based interventions. However, this conclusion must be tempered the fact that we did not see a significant difference in effects of the novel MBET and PCGT on PTSD symptom improvement, and that the number of patients, particularly in the PCGT group, was small (discussed in “limitations” below). MBET showed a large pre- to posteffect size (Cohen’s $d = 0.92$) and PCGT a moderate effect ($d = 0.46$) that was not statistically significant, but N was small for both interventions. The between-group effect size comparing MBET to PCGT ($d = 0.41$), and the group \times time interaction of PTSD symptoms in RM-ANOVA were not significant. However, the effect of MBET in this small neuroimaging sample was consistent with previous reports in larger samples of predominately Vietnam veterans of effects of MBCT^[21] and MBSR^[22] interventions that were focused on PTSD. To our knowledge, this is the first study of a mindfulness-based intervention specifically focused on PTSD in all OEF/OIF veterans.

Our findings are consistent with accumulating evidence from cross-sectional studies comparing long-term meditators to nonmeditators,^[27,29–31] participants randomized to several week meditation trainings,^[45] and correlations with self-reported measures of mindfulness^[28,32] that have implicated alterations in resting-state FC associated with mindfulness training. A cross-sectional study comparing long-term meditators to controls showed a pattern of greater rsFC between PCC and bilateral DLPFC and dorsal ACC^[27] that was nearly identical to the increased PCC–DLPFC and PCC–dorsal ACC we observed in PTSD patients following MBET in this study. Another very recent study of healthy but “stressed” (unemployed) persons undergoing a brief, 3-day intensive mindfulness training also found a highly similar increase PCC–DLPFC rsFC in participants completing the mindfulness arm, but not the 3-day active control (relaxation training).^[46] Other work with long-term meditators has also reported increased connectivity between DLPFC and posterior cingulate.^[31] Some cross-sectional studies report mindfulness training or self-reported mindfulness scores are associated with relatively decreased within DMN connectivity in meditators,^[30] or that self-report mindfulness is associated with increased DMN and SN anticorrelation,^[28] while others report relative increases in rsFC in attention networks (including DLPFC).^[29]

Although there have been fewer longitudinal (i.e. pre- to postmindfulness intervention) studies of rsFC, existing work also suggests that mindfulness training may lead to altered rsFC. A small study of elders with mild cognitive impairment (MCI) found increased DMN (PCC seed) connectivity with bilateral dorsal mPFC, as well

as left hippocampus, following MBSR.^[33] Another recent study of pre-post MBSR rsFC in patients with tinnitus found strengthened connectivity in executive attention network (inferior frontal gyrus (IFG) seeds) but not in DMN following MBSR.^[47] Another very small pilot study ($N = 7$) in elite athletes with pre-post fMRI reported decreased rsFC between the PCC and the right medial frontal cortex and rostral ACC.^[48] There is also evidence of that brief mindfulness training may decrease amygdala–subgenual ACC connectivity in stressed adults.^[49] Although it seems likely that in different populations (patients vs. healthy vs. elite athletes), different levels, and length of mindfulness training likely influences the variability in the data reported to date, there is support for the notion that mindfulness training may lead to altered cross-network connectivity between DMN and CEN and that this could be related to the salutary effects of mindfulness on emotional regulation.

Our finding of increased rsFC of PCC with dorsal ACC (a component of the salience network), while also consistent with previous work in long-term meditators,^[27] could be somewhat unexpected in PTSD patients, given previous work showing that PTSD is associated with relatively increased cross-network connectivity between DMN and SN. We have hypothesized that desegregation of intrinsic connectivity networks at rest, in particular DMN–SN disequilibrium, could be a potential mechanism underlying PTSD symptoms.^[39] Our group and others have reported evidence that PTSD is associated with decreased within-network DMN connectivity (PCC–vmPFC and PCC–hippocampus),^[35,39,50] increased within-network SN connectivity (amygdala–insula/peri-insula) and aberrantly increased cross-network connectivity between DMN and SN (e.g. PCC–insula, PCC–putamen, vmPFC–SMA),^[39] DMN and SN are typically highly anticorrelated at rest, and thus increased DMN–SN connectivity at rest could reflect a dysfunctional activation of SN during rest (when SN is normally not active), which could be associated with PTSD hyperarousal symptoms. However, it is also possible that increased resting connectivity between DMN, DLPFC, and dorsal ACC seen following mindfulness training could reflect somewhat different processes. Although dorsal ACC is a part of the SN, it is also part of the anterior executive attention/executive control network proposed by Posner and colleagues.^[51,52] The dorsal ACC is involved in a range of executive control processes,^[53] including executive attention,^[54] conflict monitoring,^[55,56] and forms of cognitive–emotional regulation involving reappraisal and distancing,^[57,58] and metacognitive regulation.^[59] Whereas increased DMN–SN cross-network connectivity (in particular PCC–insula and vmPFC–SMA), could be related to inappropriate “intrusion” of threat-related signals during rest, it is also plausible that the concurrent increases in PCC–DLPFC and PCC–dorsal ACC connectivity we observed in PTSD patients following mindfulness training could be related to increased capacity for executive attention, volitional shifting of attention,

and improved metacognitive emotional regulation. Future studies examining the effects of dACC resting-state connectivity and emotional regulation will be needed to address these competing hypotheses.

LIMITATIONS

This longitudinal neuroimaging study contained a relatively small number of PTSD patients ($N = 23$), particularly in the PCGT group ($N = 9$), limiting our ability to make strong inferences regarding between-group effects. It is possible that a similar DMN connectivity change was not seen in the PCGT due to lack of power; however our data are also consistent with two studies in healthy people that find similar changes in DMN in mindfulness but not control conditions^[27,46]. The MBET group was reasonably powered for within-subjects analyses, given the large effect size observed. Although MBET was associated with a large effect size on PTSD symptoms, we did not observe a statistically significant difference in pre-post effects of MBET and PCGT in this small imaging sample. Although it appears that the increased rsFC between PCC and DLPFC was related to the differences in the interventions, and that PCC–DLPFC connectivity was related to improvement in PTSD symptoms in the MBET group, the small N and lack of significant difference in PTSD symptoms between the interventions limits our ability to make causal inferences. Although DLPFC connectivity following PCGT was not correlated with improvements in avoidant and hyperarousal symptoms, combining all patients showed correlation in hyperarousal symptoms that was significant when corrected for multiple comparisons, suggesting DLPFC connectivity could be associated with decreases in PTSD symptoms that was not specific to mindfulness training. Furthermore, while PCGT did control for several nonspecific factors, including therapist contact, group support, and homework, the “dose” of therapy (number of sessions attended) was lower, and PCGT did not control for other aspects of mindfulness training, such as movement and quiet time alone, as has been done in other control groups (e.g.^[49]). The MBET intervention contained components other than mindfulness training, including in vivo exposure and self-compassion exercises, which were also not in PCGT. It is also possible that these other components may have influenced DMN–CEN connectivity.

SUMMARY

This pilot study of a novel mindfulness-based intervention for PTSD reports preliminary evidence suggestive of changes in rsFC in DMN and DLPFC following MBET treatment. DMN–DLPFC rsFC changes were related to PTSD symptom improvement, and are consistent with other cross-sectional and longitudinal studies in meditators and psychiatric patients. Further work is needed to determine if such changes in rsFC might be related to improved volitional control of attention,

distress tolerance, and metacognitive emotional regulation, which could lead to improved ability of PTSD patients to engage in and successfully process traumatic memories.

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