Cognitive Behavioral Therapy is Associated with Enhanced Cognitive Control Network Activity in Major Depression and Posttraumatic Stress Disorder

Supplemental Information

SUPPLEMENTAL METHODS

Participant Ethnicity

The ethnicity of our longitudinal sample was as follows:

Healthy Controls: 16 Caucasians; 2 African Americans; 1 Hispanic

PTSD: 9 Caucasians; 3 African Americans; 1 Hispanic; 2 Other

MDD: 11 Caucasians; 3 African Americans; 2 Hispanic

Choice of MASQ-AA Subscale

The AA subscale has been factor analytically differentiated from core depressive features (1) and represents a cleaner 'anxiety' construct compared with, for example, the State Trait Anxiety Inventory (STAI), which, despite its name, includes many depression-specific items and distress features common to anxiety and depression (2).

Emotional Conflict Task

As a primary goal of CBT is to correct automatic thoughts with a more-controlled pattern of thinking, focusing on a realistic appraisal and ignoring a self-defeating perspective, we focused on the cognitive control component of this task. The goal was to tell whether the two items in the target axis were the same or different via button presses on a fiber optic response box interfaced with PsyScope. In all 4 conditions the task requires attention to stimuli presented in one axis while ignoring stimuli in another axis. Condition was included as a categorical variable with four levels in the model with attend houses ignore neutral faces as the reference. Our linear mixed model software (nlme in R) estimates a p-value that compares the mean activation across all four

conditions. As such it allows us to compare a general construct of cognitive control. *S*imilar to prior work using this task, we found a main effect of condition within critical cognitive control regions (3), including dorsal anterior cingulate, DLPFC, inferior frontal gyrus (IFG), anterior insular (aIns) cortex, dorsal premotor cortex, and posterior parietal cortex (**Figure S1B**). To exclude outliers and protect against spurious results due to inattention, participants (n=16) were excluded if they missed > 7 consecutive task responses. We checked the RT for each condition and each time point. Specifically, RT shorter than 250 msec or longer than 2200 msec (the maximally allowed RT for a given trial) were considered anticipatory or missed responses, and were discarded from analyses.

We analyzed accuracy and RT separately because the stimuli were designed to be presented rapidly (250 ms duration), which makes this task challenging. Participants were instructed to respond as soon as possible without worrying too much about making mistakes. Thus, RT is a more meaningful and sensitive measure than accuracy. Accuracy was used primarily to check whether the participants were engaged in the task.

Image Acquisition

A high-resolution structural image and four runs of the emotional conflict task scan (184 volumes/run) were acquired in a Siemens Tim Trio 3T MRI scanner (Siemens, Erlangen, Germany) at baseline and after 12-week of CBT treatment. Structural images were acquired using a T1-weighted MPRAGE sequence: TR 1900 ms, TE 3.93 ms, TI 1000ms, flip angle 7°, 1 × 1 × 1.25 mm^3 voxel resolution, no gap. Functional images were acquired using a gradient spin-echo echo-planar sequence: TR 2200 ms, TE 25 ms, flip angle 90°, field of view of 205 cm, 39 transverse slices, 3.2 mm slice thickness (no gap), and in-plane resolution 3.2mm × 3.2mm.

fMRI Processing and Timeseries Analysis

For each functional run, the first four volumes were discarded to allow the signal to reach T1 equilibrium. Imaging data quality were checked for registration misalignment and excessive head motion (mean relative displacement > 3 inter-quartile range). Only images that passed the quality

assurance were included in the subsequent analyses. Functional imaging data were preprocessed using tools that are part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (4) with the following steps: 1) motion correction (5), 2) nuisance signal regression (6), 3) spatial smoothing: Gaussian filter at 6 mm FWHM; and 4) high-pass temporal filtering. Pre-processed BOLD time series of each run was modeled using a general linear model, FILM with local autocorrelation correction implemented in the FMRI Expert Analyses Tool (FEAT) (7). Brain responses to each condition (and their temporal derivative) were evaluated by convolving task regressors (stimulus onsets extracted from PsyScope were recorded in FSL format as stimuli of 250 ms duration) with a canonical (double-gamma) hemodynamic response function. The temporal derivatives of task regressors and motion parameters were included in the model as nuisance regressors to account for slice-timing effects and the residual effect of motion. This yielded one statistical contrast map (a map of contrast of parameter estimates or COPE) to indicate the magnitude of activation for each condition and each run, which was co-registered to the T1 image using boundary-based registration (8) and normalized to the custom study-specific template space using the top-performing deformable registration included in ANTs (9). Outliers (n = 1) were excluded for movement > 3 inter-quartile range or poor quality registration (n = 0) on visual inspection.

CBT/CPT

CPT, based on CBT (10), has been shown to be an effective psychotherapy that significantly reduces symptoms in PTSD (11, 12). The 12-session CPT protocol uses CBT derived cognitive strategies, the same as those employed in CBT for MDD, but with an added element assisting participants to process trauma-related emotion-laden memories (13, 14). Each of the sessions was videotaped and closely supervised by the supervising clinical psychologist (SEB) to facilitate adherence to CBT/CPT. In addition, weekly supervision with Dr. Bruce was conducted to assure ongoing treatment adherence and competence.

SUPPLEMENTAL RESULTS

Comparison with Subjects Who Did Not Enter the Study or Dropped Out

To ensure generalizability of the results, we compared the patients who did not enter the longitudinal study or entered but dropped out (n = 50) with the patients who completed the treatment (n = 31) in demographics, depressive symptoms, and brain activation. The two groups did not differ in age, gender, years of education ($p > 0.20$), severity of depressive symptoms ($p > 0.05$), or left DLPFC activation during the task ($p > 0.20$).

Correlations between Task Activity and Depressive and Anxiety Symptoms in MDD and PTSD Excluding Normal Controls

When healthy controls were excluded, we found that the correlation between MADRS and the activation of the DLPFC as well as the correlation between MASQ-AA and activation of the DLPFC remain significant across the PTSD and MDD group (MADRS $r = -0.28$, $p = 0.01$, $n = 79$; MASQ-AA: $r = -0.40$, $p < 0.001$, $n = 76$) (**see Figure S2**).

Neural Correlates of Anxiety Symptoms

Anxiety symptoms are important in predicting medication treatment response in MDD (15, 16), providing evidence for the separation of anxious arousal from core depressive symptoms (1), evidence that anxious arousal is elevated in depressed and anxious patients (17), and that arousal symptoms in PTSD are a core feature of the disorder (18). We examined the association between severity of anxiety symptoms and the level of brain dysfunction, performing voxel-wise LME models on task activation that included the same fixed and random effects specified in the depression analyses, except that MADRS was replaced with the MASQ-AA score.

When examining the neural correlates of anxiety symptoms, we found that the activation of the left DLPFC (center of mass in MNI coordinates: $x = -47$, $y = 33$, $z = 16$) was negatively correlated with MASQ-AA scores across all participants ($r = -0.44$, $p < 0.001$, $n = 96$; **Figure 3C in the main text**) and this brain-symptom association did not differ between MDD and PTSD

patients ($p > 0.20$). When we examined the correlation between MASQ-AA and brain activation within clusters identified in the main analysis after controlling for MADRS scores there were no significant regions remaining (**Figure 3D in the main text**), suggesting that the unique variance explained by anxiety did not contribute to the relationship with brain activity independent of the depression effect.

Longitudinal Brain Activity Changes in Controls

Instead of including both patients and controls in the same LME model to detect a group by time interaction, we performed a within-group comparison to first identify regions that changed significantly in patients. To demonstrate that the changes observed in patients were not due to chance, we fit the same model in HC to identify brain regions that changed significantly from time 1 to time 2 in the HC group. The primary regions that changed significantly over time in controls included the sensorimotor and visual cortex (**Figure S3**), neither of which changed significantly following treatment in patients. These results suggest that the enhanced activity of the cognitive control regions during the task might be specific to CBT effects in patients. However, a significant group by time interaction term would have provided stronger evidence for this claim.

Longitudinal Brain Activity in Patients vs Controls (Group x Time Effect)

As described in the Results section of the paper, there were no significant group by time effects that survived multiple comparisons. The top panel of **Figure S4** displays the VLPFC, part of the cognitive control network, which demonstrated a significant activation increase in patients following CBT. The bottom panel displays the group by time effects, showing increases in patients, which were not significant after our multiple comparison correction procedure.

Longitudinal Brain Activity in MDD in Comparison with PTSD

In **Figure S5**, we stratified the task-induced activity in the 14 regions in which patients had significant changes in activity following CBT by group (MDD vs PTSD).

SUPPLEMENTAL DISCUSSION

PTSD in Patients with Multiple Traumas

We note that elevated startle responses are found typically in 'fear' type disorders such as panic disorder, social and specific phobia and that self-report questionnaire data suggests threat sensitivity is associated with increased startle responses (19). A diagnosis of PTSD includes a hyperarousal domain (20) that is commonly elevated in patients but does not seem to be associated with increased startle when, like in our patients, patients have experienced many traumas over time (21). This pattern is despite self-reported elevations in trait anxiety and threat sensitivity in the multiply traumatized PTSD patients as compared with single trauma patients and non-traumatized individuals (21). In retrospect, though we expected elevations on the MASQ-anxious arousal scale in PTSD patients, especially, it may be that because the vast majority of our intimate partner violence PTSD survivors were multiply traumatized their symptoms were less likely to be specific indicators of hyperarousal (startle, amygdala reactivity, etc.) and thus were less likely to change with treatment.

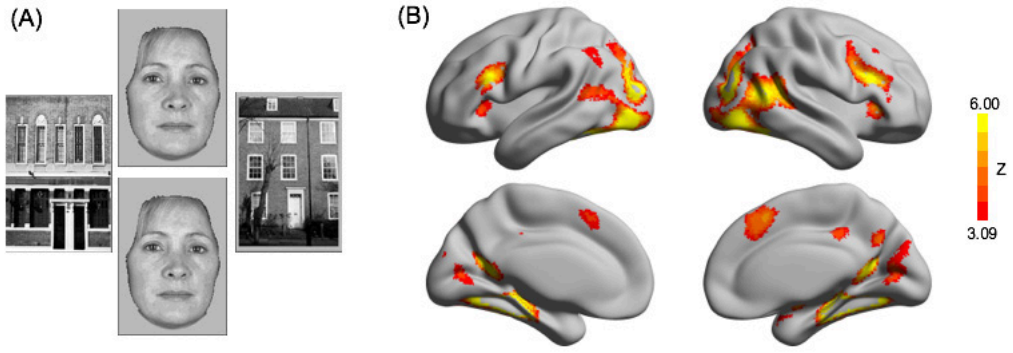

Figure S1. Exemplar stimulus screen of the emotional conflict task (**A)** and brain regions showing a significant task effect **(B)**. Brain regions were shown on surface map using BrainNet Viewer in MNI coordinates.

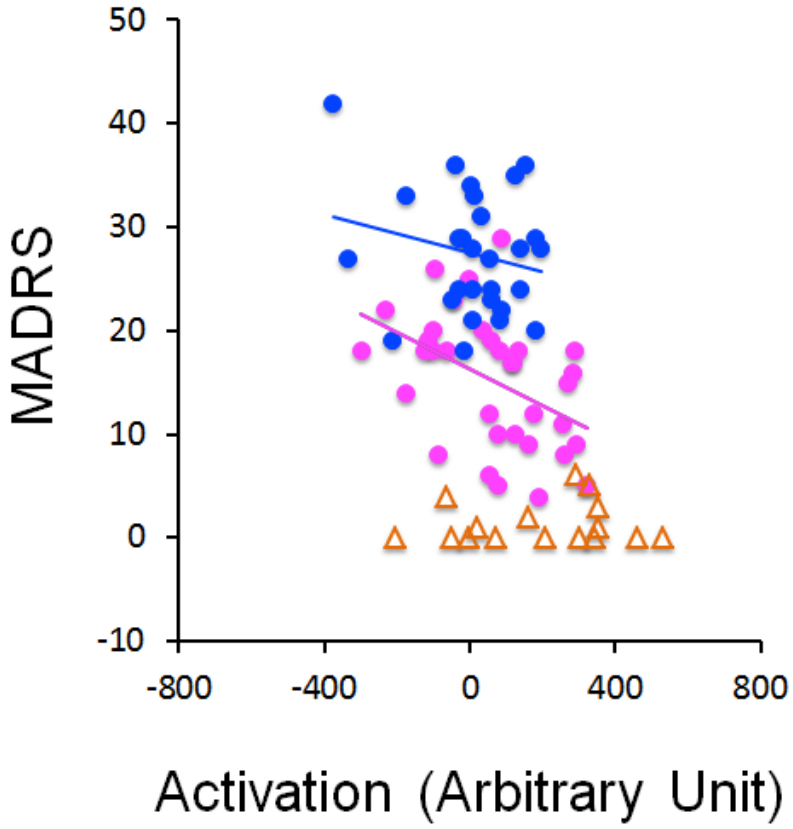

Figure S2: Correlation between MADRS score and DLPFC brain activation after excluding PTSD with comorbid major depression. The cluster mean activations were plotted against the baseline MADRS scores by diagnostic groups after excluding those PTSD patients (n = 17) with a HAMD score ³ 17. X-axis arbitrary activation units. Y axis MADRS score. Blue circles: MDD; pink circles: PTSD; orange triangles: controls.

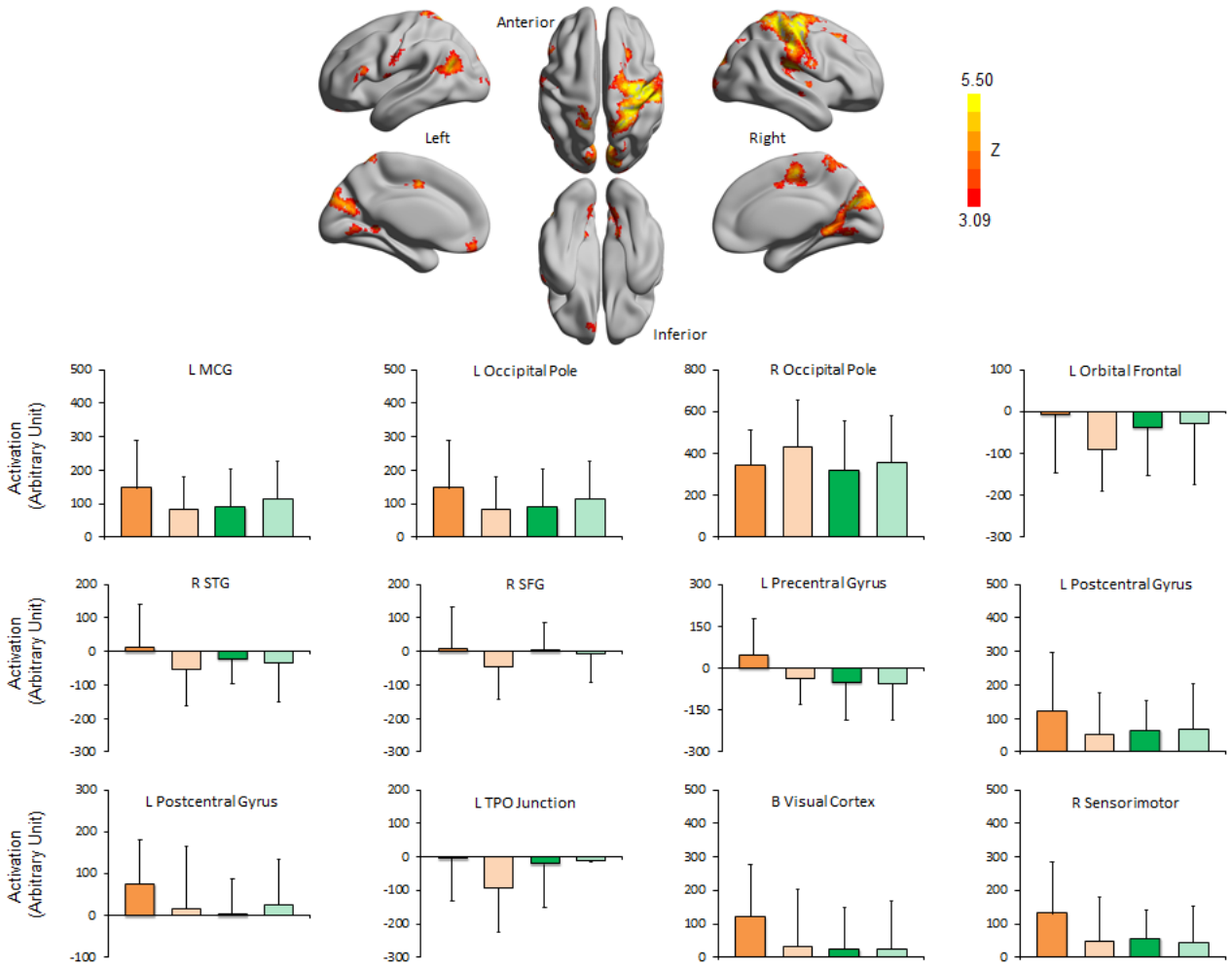

Figure S3: Longitudinal Brain Activity Changes in Controls. Regions that changed significantly in controls after 12 weeks included primarily visual and sensorimotor cortex

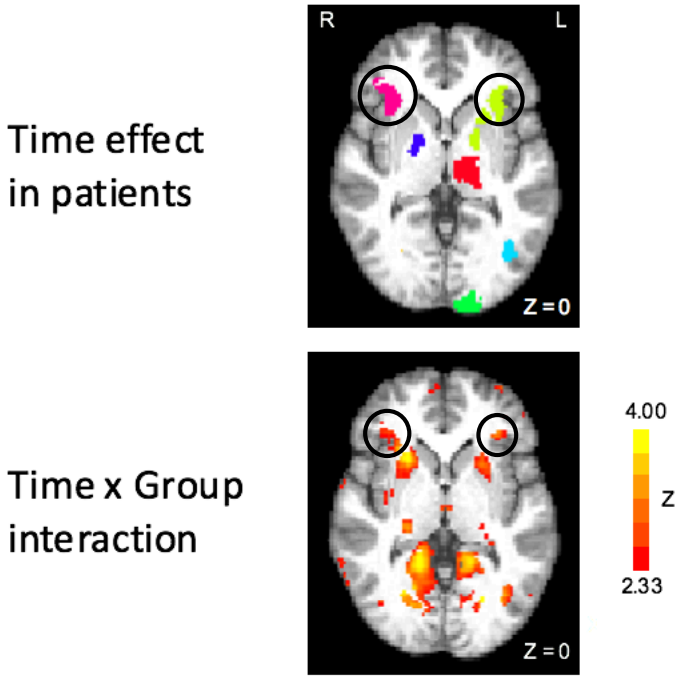

Figure S4. Top row: clusters with a significant time effect (pre- vs post-CBT) in patients are shown in slice view. Bottom row: the time (pre- vs post-CBT treatment) by group (HC vs patients) interaction effects in the corresponding slice. Circles indicate VLPFC.

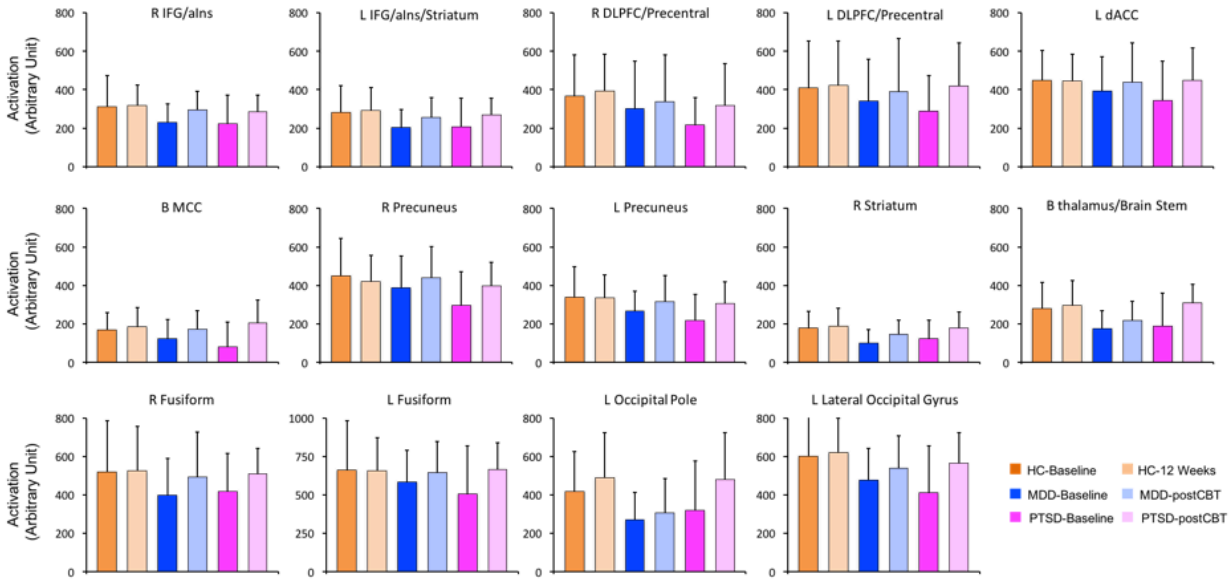

Figure S5. ROI mean activations stratified by diagnostic category (HC, MDD, and PTSD) in the 14 clusters that showed a significant increase in activation in patients (MDD and PTSD combined) following CBT treatment (see Figure 4 in the paper).

Table S1: Regions that changed significantly after CBT in patients but not in controls

Region (Harvard-Oxford Anatomical Atlas)	BAs	CM (MNI)			Volume (mm^3)
		X	Y	Z	
R Precentral/Middle Frontal Gyrus	6/9	47	1	38	584
L Precentral Gyrus	4/6	-47	-2	42	2600
R Inferior Frontal Gyrus/Anterior Insula	45/47	36	28	1	1840
L Inferior Frontal Gyrus/Anterior Insula/Putamen	47	-29	19	2	3712
L dorsal Anterior Cingulate/Supplementary Motor Cortex/Paracingulate Gyrus	6/24/32	-7	8	49	2976
B Cingulate Gyrus	23	1	-18	28	4608
R Superior Parietal Lobe/Precuneus/Lateral Occipital Cortex	7/40	25	-58	48	6016
L Superior Parietal Lobe/ Precuneus/Lateral Occipital Cortex	7/40	-23	-60	44	7256
R Temporal Fusiform Cortex	20/37	36	-39	-22	720
R Occipital Fusiform Gyrus	18/19	30	-77	-10	2936
L Temporal/Occipital Fusiform Gyrus	19/37	-36	-66	-7	4144
L Occipital Pole	17/18	-13	-102	4	1824
R Pallidum/Putamen	---	19	-1	-1	1424
B Thalamus/Brain Stem	---	-6	-16	5	9512

Note: L=left; B=bilateral; R=right; BAs= Brodmann areas; CM=center of mass.

SUPPLEMENTAL METHODS

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