PTSD Psychotherapy Outcome Predicted by Brain Activation During Emotional Reactivity and Regulation

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Objective: Exposure therapy is an effective treatment for posttraumatic stress disorder (PTSD), but many patients do not respond. Brain functions governing treatment outcome are not well characterized. The authors examined brain systems relevant to emotional reactivity and regulation, constructs that are thought to be central to PTSD and exposure therapy effects, to identify the functional traits of individuals most likely to benefit from treatment.

Method: Individuals with PTSD underwent functional MRI (fMRI) while completing three tasks assessing emotional reactivity and regulation. Participants were then randomly assigned to immediate prolonged exposure treatment (N=36) or a waiting list condition (N=30). A random subset of the prolonged exposure group (N=17) underwent single-pulse transcranial magnetic stimulation (TMS) concurrent with fMRI to examine whether predictive activation patterns reflect causal influence within circuits. Linear mixed-effects modeling in line with the intent-to-treat principle was used to examine how baseline brain function moderated the effect of treatment on PTSD symptoms.

Results: At baseline, individuals with larger treatment-related symptom reductions (compared with the waiting list condition) demonstrated 1) greater dorsal prefrontal activation and 2) less left amygdala activation, both during emotion reactivity; 3) better inhibition of the left amygdala induced by single TMS pulses to the right dorsolateral prefrontal cortex; and 4) greater ventromedial prefrontal/ventral striatal activation during emotional conflict regulation. Reappraisal-related activation was not a significant moderator of the treatment effect.

Conclusions: Capacity to benefit from prolonged exposure in PTSD is gated by the degree to which prefrontal resources are spontaneously engaged when superficially processing threat and adaptively mitigating emotional interference, but not when deliberately reducing negative emotionality.

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Posttraumatic stress disorder (PTSD) is a prevalent condition (1) with a large burden of suffering (2). Effective treatments have been developed, the most widely utilized of which are trauma-focused psychotherapies such as prolonged exposure (3). Although psychotherapy is widely utilized and highly effective, it requires a considerable investment of time and effort, with roughly one-quarter of patients not completing treatment and one-third to one-half of those who complete treatment remaining symptomatic and impaired (4). It is therefore critical to identify who will benefit from this treatment and why—information that remains largely unknown. Noting that clinical and demographic characteristics are poor predictors (5), we suggest that brain-based characteristics may serve as particularly robust indicators of treatment outcome.

Data on how brain function prior to treatment predicts psychotherapy outcome in PTSD are sparse. Moreover, past studies offer limited insights or generalizability because of a lack of a patient waiting list condition or a control intervention arm (6), use of an uncommon treatment modality (7), or use of small samples (8). Critically, to our knowledge, there have been no reports of a comprehensive, multifaceted assessment of brain function in a single study; instead, data have been presented separately, from individual paradigms in partially overlapping participant groups.

Here, in a sample that is large relative to published fMRI treatment studies, we identified brain activation that moderates the relationship between treatment arm and symptom change in a randomized clinical trial of prolonged exposure for PTSD. We utilized a patient waiting list comparison group and examined multiple functional tasks united under a common conceptual theme—emotional reactivity and regulation, that is, how an individual recognizes an emotionally charged stimulus, processes that information, and resolves the emotional response. We investigated these processes

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under the assumption that appropriate reactivity to and regulation of emotion is essential for successful exposure therapy (9). This is consistent with emotional processing theory, the foundation of prolonged exposure, which holds that confronting feared stimuli to activate the fear response is needed to incorporate information that is incompatible with its pathological structure (10). This process promotes adaptive learning, which leads to a regulation of fear. Therefore, it is likely that the brain mechanisms that optimize balance between these processes must be intact for the patient to benefit from exposure treatment. Unfortunately, previous treatment imaging studies have typically analyzed data only in participants who complete treatment, which can fundamentally bias results (11). Here, we thus also adopted a full intent-to-treat analysis framework using linear mixed models, thereby incorporating all available imaging data.

Previous PTSD imaging studies examining predictors of psychotherapy treatment response have reported the following, all in the context of single-arm treatment studies. First, greater activation in the ventral anterior cingulate cortex and the medial prefrontal cortex during nonconscious fear processing was found to predict poorer response to cognitive-behavioral therapy (CBT) (6). Second, greater activation in the dorsal anterior cingulate during nonconscious fear processing (6) and anticipation of negative versus positive emotional images predicted better CBT response (12), but less dorsal anterior cingulate activation during image presentation also predicted better CBT response (12, 13). Third, less amygdala reactivity to nonconscious fear processing (6) and conscious processing of negative pictures (13) predicted a better response to CBT.

Therefore, we formulated the following hypotheses. First, we expected individuals with less amygdala activation during emotion detection at baseline to show a greater reduction in symptom scores after treatment. Second, we expected individuals with less ventromedial prefrontal activation during nonconscious fear processing to show a greater reduction in symptom scores after treatment (6). However, we also expected individuals with greater ventromedial prefrontal activation during emotional conflict regulation to show a greater treatment-related reduction in symptom scores. This is consistent with previous work implicating this region in emotional conflict regulation (14) and fear extinction (15), which we anticipated would support exposure habituation and improve treatment efficacy. Third, we predicted that activation of the rostral/dorsal anterior cingulate when processing an emotional cue would moderate the relationship between treatment arm and symptom change, consistent with previous work, although we did not have an a priori directional hypothesis, given inconsistent previous findings (6, 12). Finally, we hypothesized that individuals with greater activation of dorsolateral prefrontal regions during processing and deliberate regulation of negative emotion would demonstrate greater treatment-related reductions in symptom scores, given the role of these regions in emotion regulation and their importance in existing models of psychotherapy mechanisms (16).

METHOD

The study methods are presented here in brief, with additional detail available in the Supplemental Methods section in the data supplement that accompanies the online edition of this article.

Participants, Assessments, and Inclusion Criteria

Individuals 18–60 years of age were recruited through advertisements for participation in a psychotherapy treatment study. All participants provided written informed consent after receiving a complete description of the study.

Behavioral Paradigms

Emotional reactivity task. This task (17) probes goal-irrelevant emotional reactivity via conscious and nonconscious (backwardly masked) presentation of fearful and neutral faces. The goal is to identify the color tint of the emotional face.

Emotional conflict task. This task (14) induces emotional conflict through pairing fearful and happy faces with congruent or incongruent emotion words, and regulation occurs via an implicit process when conflict trials are preceded by other conflict trials. The task is to identify the facial emotion and ignore the emotion word.

Gender conflict task. Participants viewed the same facial stimuli as in the emotional conflict task (18), but here the goal is to identify gender and ignore an overlaid congruent or incongruent gender word.

Reappraisal task. Participants viewed either negative or neutral pictures from the International Affective Picture System under two conditions: "look" (for negative and neutral) and "decrease" (negative only). During "look" trials, participants experienced their natural emotional response, whereas during "decrease" trials, they reduced their emotional responses by interpreting the picture differently (19).

MRI Data Acquisition

See the Supplemental Methods section in the online data supplement.

Randomization

After clinical assessments and fMRI scanning, participants were individually randomly assigned either to immediate treatment with prolonged exposure (N=36) or to a waiting list condition (N=30).

Concurrent Transcranial Magnetic Stimulation–fMRI Causal Mapping

As an experimental probe of brain circuitry, a random subset of individuals in the immediate treatment group (N=17) underwent concurrent single-pulse transcranial magnetic stimulation (TMS) and fMRI prior to treatment according to established protocols (20). This session occurred about

2 weeks after the task-based fMRI session. Given our task-related moderation findings and existing evidence for the efficacy of repetitive TMS (rTMS) to the right dorsolateral prefrontal cortex in alleviating PTSD symptoms (21), we focused analyses on two right dorsolateral prefrontal sites: an anterior site in the middle frontal gyrus (part of the resting-state salience network), and a more posterior site in the middle frontal gyrus (part of the resting-state executive control network) (22). The primary site of interest was the right posterior middle frontal gyrus, given its proximity to our task-based moderator findings and to the location "5 cm anterior to the motor cortex" used in previous rTMS treatment studies in PTSD (23). The anterior middle frontal gyrus was utilized as a comparison site to control for the subjective effects of prefrontal stimulation.

Prolonged Exposure Treatment

Treatment sessions occurred either once or twice a week, for a total of nine to 12 sessions, 90 minutes each, that followed manualized procedures (24).

Posttreatment Clinical Assessment

Approximately 4 weeks after the final treatment session, participants completed a posttreatment clinical assessment. This duration was chosen to allow treatment changes to consolidate and symptom levels to equilibrate before the posttreatment assessment.

Image Preprocessing

See the Supplemental Methods section in the online data supplement.

Individual-Level Analysis of Task Data

For the emotional reactivity task, the a priori contrasts of interest were conscious fear versus neutral and nonconscious (masked) fear versus neutral. For the emotional conflict task, the contrasts of interest were incongruent versus congruent trials (conflict), postincongruent incongruent trials versus postcongruent incongruent trials (an established measure of conflict regulation) (14), and congruent fear versus congruent happy trials, an additional probe of emotional reactivity. For the gender conflict task, the contrasts of interest were those capturing conflict and conflict regulation. For the reappraisal paradigm, the contrasts of interest were "look" negative versus neutral and "decrease" (through reappraisal) negative versus "look" negative.

Assessing Treatment Moderation Effects

To identify brain activation moderating the relationship between treatment arm and symptom change, we employed the MacArthur approach (25) embedded in our longitudinal linear mixed-effects models on a voxel-wise level, treating baseline brain activation as a potential moderator of differential changes by treatment arm on our primary outcome measure of PTSD symptoms, which was total score on the Clinician-Administered PTSD Scale for DSM-IV (26). All region-of-interest analyses utilized the same anatomical mask (see Figure S1 in the online data supplement).

Assessing the Utility of Activation Moderators for Predicting Clinical Remission

See the Supplemental Methods section in the data supplement. Linear discriminant functions with leave-one-out cross-validation were used to determine the classification accuracy of brain activation moderators for predicting remission from PTSD.

RESULTS

Sample Characteristics, Task Behavior, and Treatment Response

The randomized sample included 66 individuals, with 36 assigned to immediate treatment and 30 to the waiting list condition (see Figure S2 in the online data supplement). The groups were well matched on all relevant clinical and demographic variables (Table 1). See the companion article (27) for a complete discussion of treatment outcome results. Briefly, the immediate treatment group demonstrated a significantly greater reduction in PTSD symptom scores relative to the waiting list group (Table 2).

Assessing Demographic and Clinical Variables as Moderators

See the Supplemental Results section in the data supplement.

Baseline Task Effects

See the Supplemental Results section and Table S1 in the data supplement.

Baseline Functional Brain Moderators in Regions of Interest

Emotional reactivity task. Conscious processing of fearful compared with neutral faces (Figure 1A) yielded significant moderation effects within our a priori mask, including large portions of the left and right dorsolateral prefrontal and frontopolar cortex (inferior, middle, and superior frontal gyri; Brodmann's areas [BA] 6, 8, 9, 10, and 46) (Figure 1C, 1D, 1F), the dorsal anterior cingulate (BA 32) (Figure 1B), the left anterior insula (BA 13 and 44) (Figure 1E), and the left amygdala (Figure 2A; see also Table S2 in the data supplement). Consistent with our hypotheses, for all prefrontal regions and the left anterior insula, greater baseline activation to fear versus neutral was associated with greater symptom reduction in the immediate treatment group relative to the waiting list group (p values <0.01). The waiting list group showed the opposite effect, whereby greater prefrontal activation was associated with less symptom improvement (all p values <0.03). As hypothesized, in the fear versus neutral contrast, less left amygdala activation was associated with greater symptom improvement in the treatment group ($p=0.012$) (Figure 2A), with the waiting list group again displaying the opposite pattern ($p=0.03$). The amygdala effect

TABLE 1. Demographic and Pretreatment Clinical Characteristics of Participants With PTSD Assigned to Either Immediate Prolonged Exposure Treatment or a Waiting List Condition

Measure	Immediate Treatment Group (N=36)		Waiting List Group (N=30)	
	Mean	SD	Mean	SD
Age (years)	34.42	10.23	39.03	10.35
Education (years)	14.72	2.17	15.17	2.78
Full-scale IQ (Wechsler Abbreviated Scale of Intelligence)	109.03	9.09	112.81	11.57
	N	%	N	%
Female	23	64	20	66
Diagnosis of major depression at intake[a]	18	50	17	57
Completed the study	25	69	26	87
Clinician-Administered PTSD Scale for DSM-IV				
Index trauma				
Natural disaster	3	8	1	3
Physical assault	9	25	7	23
Assault with a weapon	3	8	2	7
Sexual assault	12	33	9	30
Combat exposure	4	11	4	13
Injury, illness, suffering	5	14	7	23
Developmental stage at time of index trauma				
Adult	20	56	14	47
Teen	8	22	11	37
Child	8	22	5	17
How exposed to index trauma				
Experienced	27	75	17	57
Witnessed	9	25	13	43
Index trauma repeated	11	31	10	33
Multiple criterion A events	12	33	10	33
	Mean	SD	Mean	SD
Total score	66.33	15.17	71.37	14.99
Reexperiencing subscale	17.53	6.40	18.73	6.02
Avoidance/numbing subscale	26.94	7.86	28.77	8.89
Hyperarousal subscale	21.86	6.28	23.87	4.91
Beck Depression Inventory–II	23.69	8.68	23.17	8.60
PTSD Checklist for DSM-IV–Civilian Version				
Total	56.16	10.61	57.36	12.04
Reexperiencing subscale	16.47	3.83	16.29	3.98
Avoidance/numbing subscale	22.78	5.05	23.04	6.02
Hyperarousal subscale	16.91	4.22	18.04	4.19
WHO Quality of Life BREF Scale				
Physical health subscale	12.46	2.99	12.43	3.11
Psychological health subscale	10.04	2.29	10.83	2.34
Social relationships subscale	9.71	4.06	9.29	3.51
Environment subscale	12.30	3.48	12.79	3.37

[a] Three patients in the immediate treatment group and two in the waiting list group were taking selective serotonin and/or norepinephrine reuptake inhibitors at baseline.

arose from activation during the fear condition ($F=7.82$, $p=0.006$) but not the neutral condition ($F=3.17$, $p=0.08$). Nonconscious processing of masked fearful versus neutral faces did not yield significant moderation effects.

Emotional conflict task. We next analyzed the emotional conflict task, beginning with the congruent fear versus happy contrast, which isolates valence in the absence of conflict, in order to test the generalization of the emotional reactivity results described above. Bilateral activation of the dorsolateral prefrontal cortex (middle and superior frontal gyri; BA 6, 8, 9, and 10) and the dorsal anterior cingulate (BA 32) moderated the relationship between treatment arm and symptom change (Figure 3A) (see also Table S3 in the data supplement). Moreover, these effects overlapped with the conceptually similar effects in the emotional reactivity task. Consistent with our hypotheses, moderation effects in all dorsolateral prefrontal clusters were driven primarily by greater baseline activation being associated with larger reductions in symptom scores in the treatment condition compared with the waiting list condition (all p values <0.003). Less baseline activation was additionally associated with greater reductions in symptom scores in the waiting list group in two right and two left dorsolateral prefrontal clusters

TABLE 2. Posttreatment Symptom and Quality-of-Life Measures in Participants With PTSD Assigned to Either Immediate Prolonged Exposure Treatment or a Waiting List Condition

	Immediate Treatment Group (N=36)		Waiting List Group (N=30)				
Measure	Mean	SD	Mean	SD	F or χ^2	p	Cohen's d
Clinician-Administered PTSD Scale for DSM-IV							
Total	29.60	21.26	64.23	21.77	32.99	<0.001	1.61
Reexperiencing subscale	6.20	6.49	16.92	7.97	27.62	<0.001	1.48
Avoidance/numbing subscale	10.60	9.50	24.50	11.30	22.51	<0.001	1.33
Hyperarousal subscale	12.80	8.75	22.81	7.00	20.43	<0.001	1.26
Beck Depression Inventory–II	9.69	7.77	17.87	9.27	11.23	0.002	0.96
PTSD Checklist for DSM-IV–Civilian Version							
Total	26.13	7.80	49.00	13.35	45.55	<0.001	2.09
Reexperiencing subscale	7.41	2.63	14.38	5.14	31.76	<0.001	1.71
Avoidance/numbing subscale	10.36	3.36	19.24	6.32	33.46	<0.001	1.75
Hyperarousal subscale	8.41	3.11	15.38	4.15	39.05	<0.001	1.90
WHO Quality of Life BREF Scale							
Physical health subscale	14.63	3.29	12.65	3.19	4.09	0.049	0.61
Psychological health subscale	13.19	2.59	11.94	2.52	2.63	0.11	0.49
Social relationships subscale	11.83	3.20	10.73	3.20	1.29	0.26	0.34
Environment subscale	14.59	2.42	13.57	2.99	1.55	0.22	0.38

(p values <0.03). Finally, greater dorsal anterior cingulate activation at baseline was associated with greater reductions in symptom scores in the treatment group (p<0.001) but not in the waiting list group (p=0.074).

Examining the conflict regulation contrast, we observed that baseline activation in a posterior portion of the ventromedial prefrontal cortex extending into the rostroventral striatum (olfactory cortex, mid-orbital gyrus, caudate nucleus, and anterior cingulate; BA 25) moderated the relationship between treatment arm and symptom change (Figure 3B) (see also Table S3 in the data supplement). As predicted, this effect was driven primarily by greater ventromedial prefrontal/ventral striatal activation predicting a greater reduction in PTSD symptom score in the immediate treatment group (p<0.001). This effect was also significant in the waiting list group, but with less activation at baseline predicting greater symptom reduction (p=0.006). We next examined the emotional specificity of this effect by contrasting activation in the emotional conflict task to the gender conflict task. Previous work has shown that only the emotional conflict task engages and requires the ventromedial prefrontal cortex for conflict regulation (18, 28). Notably, our prediction effect was indeed specific for emotional compared with gender conflict regulation (Figure 3C) (see also Table S3 in the data supplement).

Lastly, we examined conflict-related activation for treatment moderation effects. No significant effects were observed.

Reappraisal task. For both contrasts of interest, we observed no brain activation that moderated the relationship between treatment arm and symptom change.

Baseline Functional Brain Moderators: Exploratory Whole Brain Analyses

See the Supplemental Results section in the data supplement.

Brain-Behavior Relationships

To assess the clinical significance of brain moderators, we conducted exploratory analyses of the relationship of between brain activation moderators and measures of task behavior and self-reported emotion regulation. As detailed in the Supplemental Results section in the data supplement, greater activation in the dorsal anterior cingulate and the right dorsolateral prefrontal cortex during conscious fear versus neutral in the emotional reactivity task and during congruent fear versus happy in the emotional conflict task was associated with less frequent deficits in emotion regulation. Consistent with previous work (14), greater ventromedial prefrontal cortex/ventral striatum activation during emotional conflict regulation was associated with better behavioral regulation of emotional conflict, that is, a larger decrease in reaction times, as well as lower distress ratings during the reappraisal task for "look" negative versus neutral.

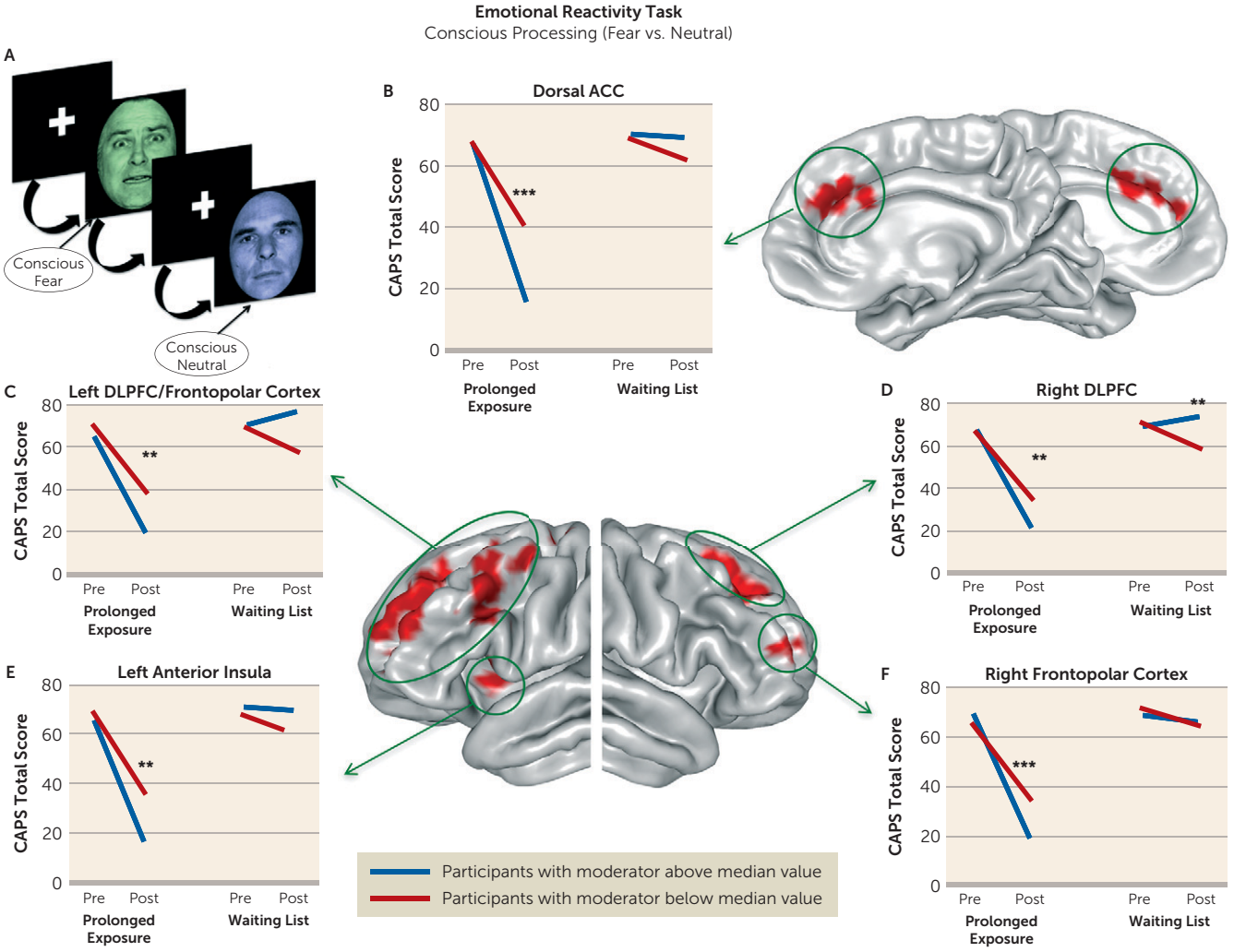
Assessing the Utility of Task Activation Moderators for Predicting Clinical Remission

See the Supplemental Methods and Results sections in the data supplement for details. In brief, the best combination of moderators across tasks was able to predict remission from PTSD with 95.5% leave-one-out cross-validated accuracy, which was significantly better than a predictive model that omitted brain measures.

Testing Dorsolateral Prefrontal Causal Control Over the Amygdala as a Mechanism Moderating Treatment-Related Symptom Reductions

We hypothesized that inverse prefrontal-amygdala moderation effects in the emotional reactivity task might reflect causal lateral prefrontal control over amygdala reactivity. To test this, we used concurrent TMS-fMRI in a random subset

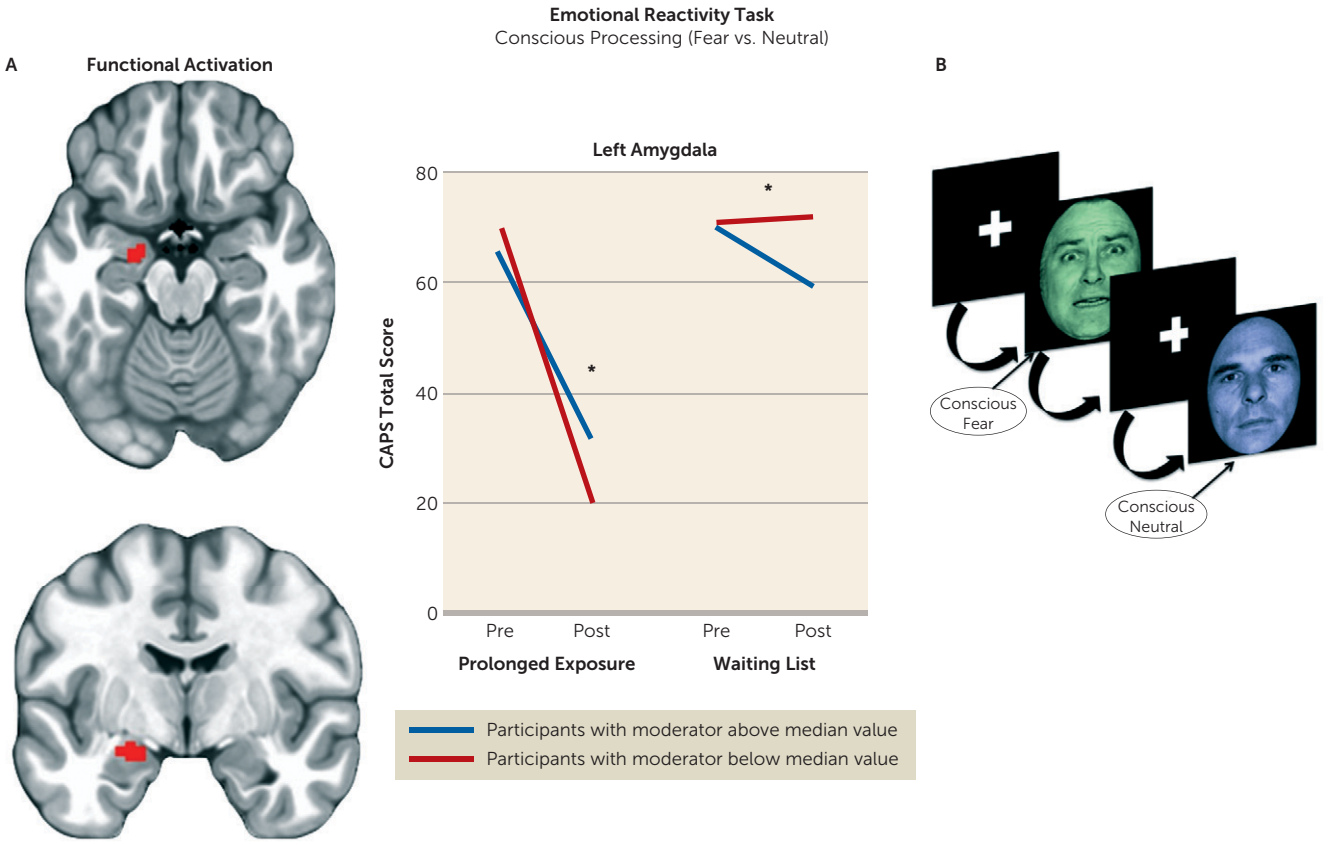
FIGURE 1. Baseline Prefrontal Activation Moderators of Treatment-Related Symptom Change During Emotional Reactivity[a]



[a] During emotional reactivity, that is, conscious processing of fearful versus neutral facial stimuli (panel A), a greater degree of activation in the dorsal anterior cingulate (panel B), the left dorsolateral prefrontal/frontopolar cortex (panel C), the right dorsolateral prefrontal cortex (panel D), the left anterior insula (panel E), and the right frontopolar cortex (panel F) predicted better treatment outcomes for participants in the immediate prolonged exposure treatment group compared with those in the waiting list group. Separate lines within each group represent individuals above and below the median level of activation across the entire sample for the purposes of visualizing disparate symptom change trajectories within each group. ACC=anterior cingulate cortex; CAPS=Clinician-Administered PTSD Scale for DSM-IV; DLPFC=dorsolateral prefrontal cortex.
**p<0.01. ***p<0.001.

of the individuals assigned to the immediate treatment arm to examine whether direct noninvasive stimulation of the right dorsolateral prefrontal cortex with TMS modulated left amygdala function in a way that predicted symptom reduction after treatment (much like the task effects above, but now allowing causal inference by virtue of TMS). The right dorsolateral prefrontal activation moderation effect in the emotional reactivity task greatly overlapped (369 voxels) with the resting-state executive control network (Figure 4A) (22), which we targeted with single-pulse TMS during fMRI. As an active control condition, we utilized a more anterior site in the right middle frontal gyrus, which is part of the resting-state salience network (22) and was more distant to the treatment-moderating clusters. Examining the effect of TMS to the right posterior middle frontal gyrus contrasted with TMS pulses to the right anterior middle frontal gyrus on left amygdala activation defined by the moderation effect from the emotional reactivity task, we observed that TMS-evoked activation in the left amygdala was associated with change in PTSD symptoms with treatment (p=0.003) (Figure 4B). Specifically, among individuals receiving immediate treatment, those who showed the largest reductions in left amygdala activation in response to right posterior middle frontal (versus right anterior middle frontal gyrus) TMS single pulses demonstrated greater reductions in PTSD symptoms. This arose from the effect of stimulation to the right posterior middle frontal gyrus in predicting treatment outcome (p=0.003) (Figure 4C) but no relationship between stimulation of the right anterior middle frontal gyrus and treatment outcome (p=0.141).

FIGURE 2. Left Amygdala Activation During Emotional Reactivity as a Moderator of Symptom Change After Prolonged Exposure[a]



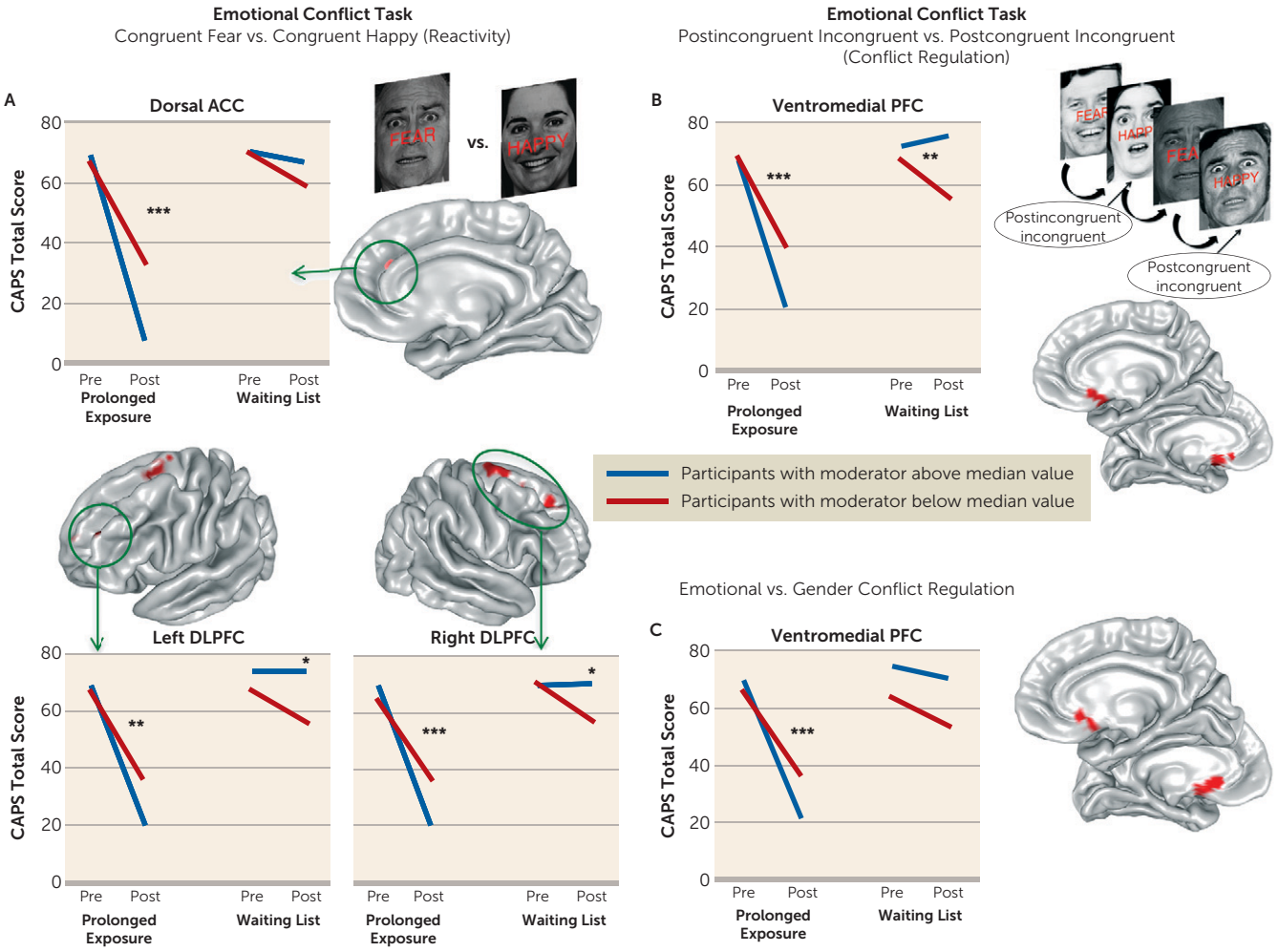
[a] In individuals assigned to immediate prolonged exposure compared with those assigned to a waiting list condition, less left amygdala activation (panel A) to consciously processed fearful versus neutral faces (panel B) predicted a better treatment response. Separate lines within each group represent individuals above and below the median level of activation across the entire sample for the purposes of visualizing disparate symptom change trajectories within each group. CAPS=Clinician-Administered PTSD Scale for DSM-IV.
*$p<0.05$.

DISCUSSION

We undertook a rigorous investigation of the functional brain characteristics during emotional reactivity and regulation that moderate differential symptom change from prolonged exposure therapy compared with a waiting list condition in PTSD. We also incorporated causality-focused TMS-fMRI manipulations to enhance the interpretability of the task findings. The primary results are as follows. First, individuals with greater baseline recruitment of the dorsal anterior cingulate, anterior insula, and dorsolateral prefrontal cortex as well as less amygdala activation when incidentally processing an emotional stimulus showed larger reductions in symptom scores after treatment. TMS-fMRI findings recapitulated this dynamic, demonstrating that the magnitude of downstream inhibition of the left amygdala from right dorsolateral prefrontal stimulation moderated the effect of treatment on symptoms. Second, individuals with greater baseline ventromedial prefrontal/ventral striatal activation during implicit regulation of emotional conflict demonstrated larger symptom reductions after treatment. Notably, this effect was specific for regulation of emotional (as opposed to nonemotional) content. Thus, an individual's capacity to benefit from exposure therapy is gated by 1) degree of spontaneous prefrontal control over amygdalar threat detection signals during incidental processing of a fear-conveying stimulus and 2) the brain's capacity to reduce interference from an emotional cue in the environment.

Interestingly, brain activation during deliberate regulation of one's emotional state did not predict treatment-related symptom change. This observation dovetails with clinical research, which emphasizes emotional engagement during an exposure while refraining from deliberate attempts to attenuate emotional responses (24, 29). The capability for this type of emotional engagement may actually depend on one's capacity to devote attention to both the emotional experience itself and other simultaneous aspects of one's experience (such as goals and intentions). We believe this capacity is engaged by the emotional reactivity task used here, which induces a goal orientation (color tint identification) concurrent with the emotional stimulus. Prefrontal engagement during this process may be indicative of greater top-down resources devoted to the appraisal of the emotional stimulus and modulation of attention toward nonemotional

FIGURE 3. Emotional Conflict Task Activation Moderators of Treatment Response[a]

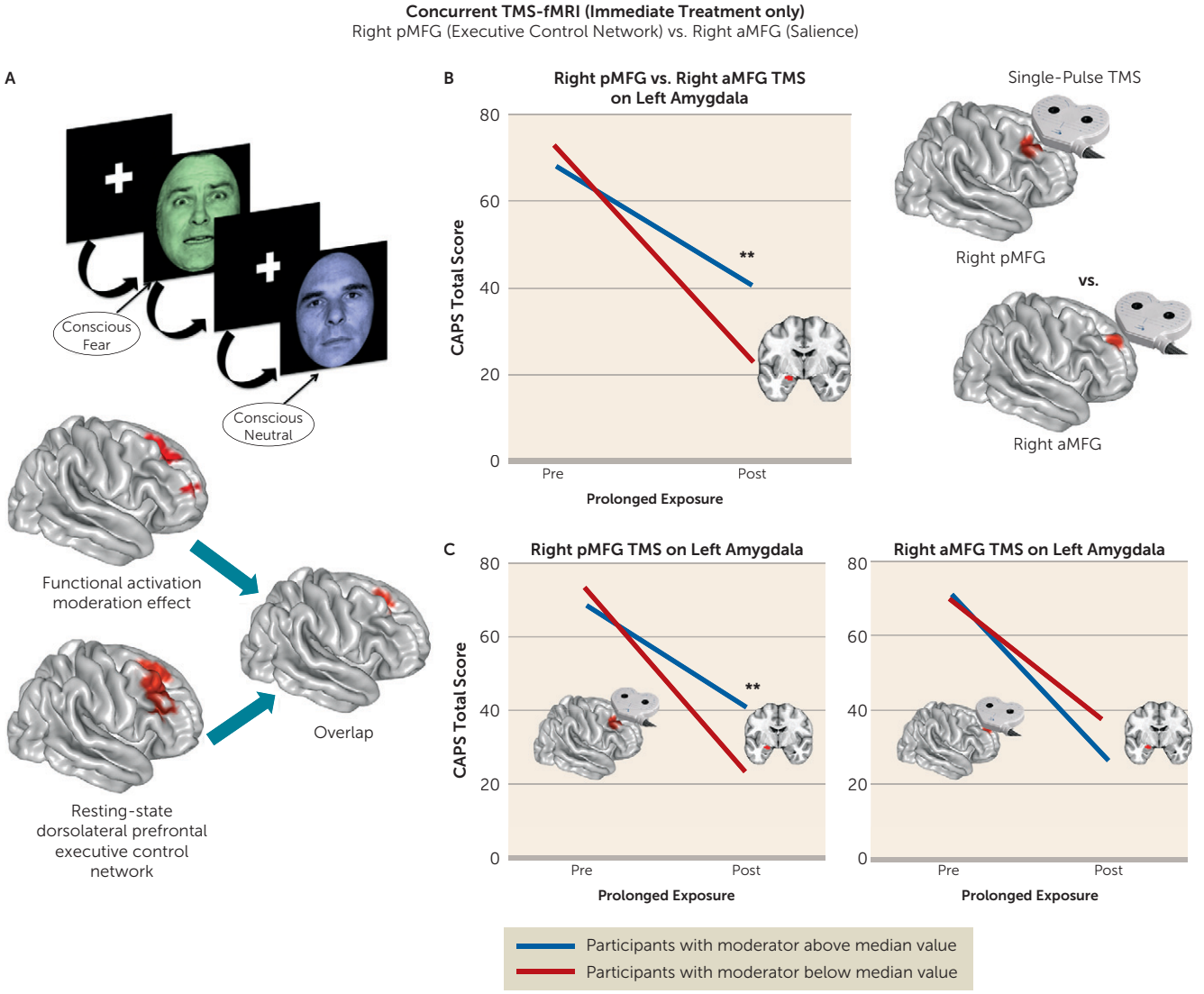


[a] During conflict-free trials of congruent fear versus congruent happy, participants in the immediate prolonged exposure treatment group (but not those in the waiting list group) who displayed greater activation in the dorsal anterior cingulate and the left and right dorsolateral prefrontal cortices demonstrated greater reductions in symptom scores (panel A). When we examined emotional conflict regulation, greater activation in the ventromedial prefrontal cortex/ventral striatum predicted greater symptom reduction in the immediate treatment group, but not in the waiting list group (panel B). This effect held when contrasting emotional conflict regulation with gender conflict regulation, indicating emotional specificity of the conflict regulation effect (panel C). Separate lines within each group represent individuals above and below the median level of activation across the entire sample for the purposes of visualizing disparate symptom change trajectories within each group. ACC=anterior cingulate cortex; CAPS=Clinician-Administered PTSD Scale for DSM-IV; DLPFC=dorsolateral prefrontal cortex; FDR=false discovery rate; PFC=prefrontal cortex.
*p<0.05. **p<0.01. ***p<0.001.

components (30), perhaps indexing an individual's capability to attend to goal-relevant processes in the presence of perceived environmental threat, for example, sustaining an exposure exercise in the presence of fear. This is consistent with the roles of the dorsal anterior cingulate in appraisal of fear (31) and the dorsolateral prefrontal cortex in top-down attentional control (30). Thus, this uninstructed individual tendency toward engaging greater prefrontal control when appraising an emotional stimulus and modulating attention in relation to it may be a type of "spontaneous" emotion regulation that augurs well for engagement in and therapeutic benefit from exposure therapy. This interpretation is consistent with the results of single-pulse TMS manipulations, which likewise provide a potential causal mechanism for the efficacy of repetitive TMS to the right dorsolateral prefrontal cortex in treating PTSD (23).

Anterior insula activation during emotional reactivity also moderated the relationship between treatment arm and symptom change. Although this region is involved in processing fear and is known to be hyperactive across anxiety manifestations (32, 33), it is involved in numerous processes, including attention, working memory, language, and perceptual processing (34, 35). The insula can be functionally subdivided into a dorsal cognitive region and a ventral emotional subdivision (34, 36). The effect we detected was located in the more dorsal portion (at z=6 in the cluster center of mass), which is consistent with the role of this more dorsal anterior insular region in attentional allocation (36). Conversely, emotion-related meta-analytic insular activations tend to be more ventrally located (34). We therefore interpret this effect to signify greater processing resources being

FIGURE 4. Prediction of Treatment Response to Prolonged Exposure by Degree of Inhibition of Left Amygdala Activation From Transcranial Magnetic Stimulation (TMS) Single Pulses Delivered to the Right Dorsolateral Prefrontal Cortex[a]



[a] The right dorsolateral prefrontal region observed to moderate treatment response during emotional reactivity largely overlapped with the right prefrontal node (posterior middle frontal gyrus) of the canonical resting-state executive control network (panel A). A random subset of individuals (N=17) in the immediate prolonged exposure treatment group underwent concurrent single-pulse TMS to this executive control network node as well as to another right prefrontal node (the anterior middle frontal gyrus) of the canonical resting-state salience network. The area of the left amygdala in which less activation during emotional reactivity was found to moderate treatment response (see Figure 2) was also modulated by single-pulse TMS to the right posterior middle frontal gyrus. Specifically, individuals displaying greater inhibition of the left amygdala in response to single TMS pulses to the right posterior middle frontal gyrus (versus right anterior middle frontal gyrus stimulation) displayed better treatment outcomes (panel B). This effect arose entirely from right posterior middle frontal stimulation and not right anterior middle frontal gyrus stimulation (panel C). The red areas representing the TMS targets in panel B are 8-mm spheres centered on the cluster centers of mass for the right executive control and right salience network prefrontal nodes independently derived from a separate healthy control data set. Separate lines represent individuals above and below the median level of left amygdala activation for the purposes of visualizing disparate symptom change trajectories within the immediate treatment group. aMFG=anterior middle frontal gyrus; CAPS=Clinician-Administered PTSD Scale for DSM-IV; pMFG=posterior middle frontal gyrus; TMS=transcranial magnetic stimulation.
**p<0.01.

devoted toward allocating attention away from the emotional content of the face and toward the color tint (the focus of the task), consistent with the observed concomitant moderating activation of the dorsal anterior cingulate and dorsolateral prefrontal cortex—regions heavily implicated in attention shifting (37) and in facilitating attentional control in conjunction with the insula (38).

Emotional conflict regulation normally recruits the ventromedial prefrontal cortex (14), is perturbed in individuals with ventromedial prefrontal lesions (28), is abnormal in some affective disorders (39), and is thought to index implicit regulation of interference from an irrelevant emotional stimulus (40). We found that ventromedial prefrontal/ventral striatal recruitment during emotional conflict regulation

moderated the relationship between treatment arm and symptom change in an emotion-specific manner. Activation here was also correlated with behavioral indices of emotional conflict regulation at baseline. Localization of this effect to the posterior portion of the ventromedial prefrontal cortex (BA 25, subgenual cingulate) and the adjoining rostroventral striatum may reflect how attunement to goal-relevant emotional information and reduction of perturbation from a salient stimulus results in reduced arousal or vigilance. This is consistent with the positive relationship between subgenual cingulate activation and parasympathetic processes (41) and the crucial role of nucleus accumbens shell (the rostroventral striatum) in mediating the resistance of the brain to associating a previously encountered harmless stimulus with a salience signal for a future aversive outcome (42). This is also consistent with translational neuroscience findings that implicate the infralimbic cortex in rats (the ventromedial prefrontal cortex in humans) in facilitating fear extinction (43), as conflict regulation and fear extinction share some conceptual and empirical overlap (31). In relation to exposure, we interpret this effect to be a marker of the brain's capacity to attenuate heightened arousal or vigilance following stimulus-cued fear responses.

It is notable that many of the brain activation moderator effects were predictive of outcomes in both the immediate treatment and waiting list arms in opposite directions. We speculate that these effects reflect regulatory mechanisms that are engaged differently by "long-term" and "short-term" symptom coping techniques. When we refer to "long-term" techniques, we denote therapeutic exercises such as in vivo and imaginal exposure, which promote recovery and lasting adaptive change. By "short-term" coping, we refer to techniques that are readily available and have a lower time and energy cost for the individual, such as active avoidance and distraction. Given the emphasis of the treatment on emotional processing via exposure (10) and minimization of avoidance, these opposite mechanistic relationships are therefore enforced by the randomization. Although "short-term" coping (the only type available to participants in the waiting list condition) may provide some limited symptom relief, we note that none of the participants in the waiting list condition demonstrated naturalistic recovery from PTSD, and only about half of those who completed the waiting list condition (N=13) showed any decrease in PTSD symptoms. Ultimately, naturalistic recovery would need to be studied in a controlled context without treatment, over a longer period, and in a larger sample for valid inferences to be made.

This study has several limitations. First, we did not examine a trauma-exposed healthy control sample, which may provide insight regarding how compensatory adaptations or pathological markers interact with treatment to guide outcomes. Second, we did not investigate trauma-specific domains, such as symptom provocation, or experimental constructs of proposed etiological pathways, such as fear conditioning/extinction. These are likely to provide useful complementary information. Third, the sample size, although large for a PTSD imaging treatment study, is relatively small for a randomized clinical trial and for examining moderation effects. Therefore, additional studies are needed to replicate and extend these findings and validate their utility for clinical decision making. This is particularly true of the TMS-fMRI findings, to which only a subset of the sample contributed. Fourth, we did not counterbalance task order across participants, as it was not possible to ensure balanced administrations across randomized groups. This could reduce generalizability of brain moderation effects if the order of administration exerted habituation effects on brain dynamics that moderated the effect of treatment on symptoms.

In conclusion, we highlight three primary insights from this study that speak to the importance of targeted brain assessments for identifying individuals with PTSD who are likely to benefit from exposure treatment and how the knowledge derived from these brain assessments can improve clinical outcomes. First, assessing individuals' brain activation patterns can greatly improve our ability to predict remission from PTSD with treatment, beyond typical clinical and demographic measures. Second, our findings identify neurostimulation-accessible cortical regions that could serve as treatment targets for augmenting brain function prior to or concurrent with psychotherapy, thereby potentially "conditioning" the brain to respond to therapy. Third, these findings highlight the relevant behavioral constructs likely to provide a useful predictive signal of an individual's response to exposure therapy. Further development of techniques to assess these predictive brain markers with clinic-friendly measurement tools, for example, electroencephalography, will allow for the determination of an individual's suitability for prolonged exposure in a clinic setting. The present findings thus inform future efforts at individualized treatment selection and provide much-needed mechanistic insights regarding the neural phenotypes that respond best to exposure therapy.

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REFERENCES

1. Seal KH, Metzler TJ, Gima KS, et al: Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002–2008. Am J Public Health 2009; 99:1651–1658
2. Cohen BE, Gima K, Bertenthal D, et al: Mental health diagnoses and utilization of VA non-mental health medical services among returning Iraq and Afghanistan veterans. J Gen Intern Med 2010; 25: 18–24
3. Foa EB, Gillihan SJ, Bryant RA: Challenges and successes in dissemination of evidence-based treatments for posttraumatic stress: lessons learned from prolonged exposure therapy for PTSD. Psychol Sci Public Interest 2013; 14:65–111
4. Bradley R, Greene J, Russ E, et al: A multidimensional meta-analysis of psychotherapy for PTSD. Am J Psychiatry 2005; 162:214–227
5. Cloitre M, Petkova E, Su Z, et al: Patient characteristics as a moderator of post-traumatic stress disorder treatment outcome: combining symptom burden and strengths. BJPsych Open 2016; 2: 101–106
6. Bryant RA, Felmingham K, Kemp A, et al: Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med 2008; 38:555–561
7. Lindauer RJ, Booij J, Habraken JB, et al: Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial. Psychol Med 2008; 38:543–554
8. Falconer E, Allen A, Felmingham KL, et al: Inhibitory neural activity predicts response to cognitive-behavioral therapy for posttraumatic stress disorder. J Clin Psychiatry 2013; 74:895–901
9. Jaycox LH, Foa EB, Morral AR: Influence of emotional engagement and habituation on exposure therapy for PTSD. J Consult Clin Psychol 1998; 66:185–192
10. Foa EB, Kozak MJ: Emotional processing of fear: exposure to corrective information. Psychol Bull 1986; 99:20–35
11. Lachin JM: Statistical considerations in the intent-to-treat principle. Control Clin Trials 2000; 21:167–189
12. Aupperle RL, Allard CB, Simmons AN, et al: Neural responses during emotional processing before and after cognitive trauma therapy for battered women. Psychiatry Res 2013; 214:48–55
13. van Rooij SJ, Kennis M, Vink M, et al: Predicting treatment outcome in PTSD: a longitudinal functional MRI study on trauma-unrelated emotional processing. Neuropsychopharmacology 2016; 41:1156–1165
14. Etkin A, Egner T, Peraza DM, et al: Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 2006; 51:871–882
15. Milad MR, Wright CI, Orr SP, et al: Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007; 62:446–454
16. Messina I, Sambin M, Palmieri A, et al: Neural correlates of psychotherapy in anxiety and depression: a meta-analysis. PLoS One 2013; 8:e74657
17. Etkin A, Klemenhagen KC, Dudman JT, et al: Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron 2004; 44:1043–1055
18. Egner T, Etkin A, Gale S, et al: Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cereb Cortex 2008; 18:1475–1484
19. Minkel JD, McNealy K, Gianaros PJ, et al: Sleep quality and neural circuit function supporting emotion regulation. Biol Mood Anxiety Disord 2012; 2:22
20. Chen AC, Oathes DJ, Chang C, et al: Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proc Natl Acad Sci USA 2013; 110:19944–19949
21. Berlim MT, Van Den Eynde F: Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials. Can J Psychiatry 2014; 59:487–496
22. Seeley WW, Menon V, Schatzberg AF, et al: Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007; 27:2349–2356
23. Boggio PS, Rocha M, Oliveira MO, et al: Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J Clin Psychiatry 2010; 71:992–999
24. Foa EB, Hembree EA, Rothbaum BO: Prolonged Exposure Therapy for PTSD. Oxford, UK, Oxford University Press, 2007
25. Kraemer HC, Wilson GT, Fairburn CG, et al: Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 2002; 59:877–883
26. Blake DD, Weathers FW, Nagy LM, et al: The development of a Clinician-Administered PTSD Scale. J Trauma Stress 1995; 8: 75–90
27. Fonzo GA, Goodkind MS, Oathes DJ, et al: Selective effects of psychotherapy on frontopolar cortical function in PTSD. Am J Psychiatry 2017; 174:1175–1184
28. Maier ME, di Pellegrino G: Impaired conflict adaptation in an emotional task context following rostral anterior cingulate cortex lesions in humans. J Cogn Neurosci 2012; 24:2070–2079
29. Craske MG, Kircanski K, Zelikowsky M, et al: Optimizing inhibitory learning during exposure therapy. Behav Res Ther 2008; 46:5–27
30. Comte M, Schön D, Coull JT, et al: Dissociating bottom-up and top-down mechanisms in the cortico-limbic system during emotion processing. Cereb Cortex 2016; 26:144–155
31. Etkin A, Egner T, Kalisch R: Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 2011; 15: 85–93
32. Simmons A, Strigo I, Matthews SC, et al: Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. Biol Psychiatry 2006; 60:402–409
33. Etkin A, Wager TD: Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 2007; 164:1476–1488
34. Kurth F, Zilles K, Fox PT, et al: A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 2010; 214:519–534
35. Craig AD: How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 2009; 10:59–70
36. Nelson SM, Dosenbach NUF, Cohen AL, et al: Role of the anterior insula in task-level control and focal attention. Brain Struct Funct 2010; 214:669–680
37. Kondo H, Osaka N, Osaka M: Cooperation of the anterior cingulate cortex and dorsolateral prefrontal cortex for attention shifting. Neuroimage 2004; 23:670–679

38. Menon V, Uddin LQ: Saliency, switching, attention, and control: a network model of insula function. Brain Struct Funct 2010; 214:655–667
39. Etkin A, Schatzberg AF: Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. Am J Psychiatry 2011; 168:968–978
40. Gyurak A, Gross JJ, Etkin A: Explicit and implicit emotion regulation: a dual-process framework. Cogn Emotion 2011; 25:400–412
41. Lane RD, Weidenbacher H, Smith R, et al: Subgenual anterior cingulate cortex activity covariation with cardiac vagal control is altered in depression. J Affect Disord 2013; 150:565–570
42. Weiner I, Feldon J: The switching model of latent inhibition: an update of neural substrates. Behav Brain Res 1997; 88:11–25
43. Milad MR, Rauch SL, Pitman RK, et al: Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol 2006; 73:61–71