Inhibitory Neural Activity Predicts Response to Cognitive-Behavioral Therapy for Posttraumatic Stress Disorder

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ABSTRACT

Objective: Despite cognitive-behavioral therapy (CBT) being an effective treatment for posttraumatic stress disorder (PTSD), many patients do not respond to CBT. Understanding the neural bases of treatment response may inform treatment refinement, thereby improving treatment response rates. Adequate working memory function is proposed to enable engagement in CBT.

Method: This study employed a Go/No-Go task to examine inhibitory function and its functional brain correlates as predictors of response to CBT in PTSD. Participants were recruited between October 2003 and May 2005. Thirteen treatment-seeking patients who met *DSM-IV* criteria for PTSD completed the Go/No-Go task while undergoing functional magnetic resonance imaging (fMRI), after which they entered 8 once-weekly sessions of CBT. PTSD severity was measured before treatment and again at 6 months following treatment completion using the Clinician-Administered PTSD Scale (primary outcome measure).

Results: After controlling for initial PTSD severity and ongoing depressive symptoms, greater activity in left dorsal striatal ($Z = 3.19$, $P = .001$) and frontal ($Z = 3.03$, $P = .001$) networks during inhibitory control was associated with lower PTSD symptom severity after treatment, suggesting better treatment response.

Conclusions: These results suggest that neural circuitry underpinning inhibitory control plays a role in the outcome of CBT for patients with PTSD.

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Cognitive-behavioral therapy (CBT) is the current treatment of choice for posttraumatic stress disorder (PTSD).[1,2] Cognitive-behavioral therapy involves systematic exposure to trauma memories and reminders, as well as cognitive restructuring.[3] However, a substantial proportion (30%–50%) of patients do not respond to this treatment.[4] Therefore, there is a need to better understand the mechanisms that predict and mediate successful psychotherapy in PTSD. Examining neural correlates of treatment response is one such area of investigation.

Recent neuroimaging studies[5–7] have investigated the neural mechanisms associated with PTSD response to CBT. In line with the proposed importance of fear extinction to CBT,[8] greater fear-related amygdala activity prior to treatment predicts a poorer outcome from CBT for PTSD,[5] and better treatment response has been associated with increased anterior cingulate cortex (ACC) activity and reduced amygdala activity during fear processing from pretreatment to posttreatment.[7] These findings suggest that a greater ability to regulate fear-related processing may facilitate satisfactory treatment outcome in PTSD.

Along with fear extinction processes, successful treatment of PTSD has been posited to involve the ability to engage cognitive control systems in order to process, contextualize, and integrate trauma-related information or memories.[9,10] Treatment may therefore require the ability to flexibly engage information-processing systems, while a rigid information processing style and disturbances in cognitive flexibility may impede PTSD recovery.[11] Relatedly, neural systems involved in working memory and executive control have been shown to be compromised in PTSD,[12–14] and these are relevant to successful CBT because one needs to exert executive control over impulses for reactivity to both environmental and internal stimuli. Inhibiting unwanted responses is therefore central to management of PTSD, including control of thoughts, emotional reactions, and tendencies to avoid and ruminate. Reduced ability to engage executive or inhibitory control systems and to inhibit habitual responses in PTSD may underlie PTSD symptoms in general[15] and failed regulation of intrusive symptoms in particular.[16,17] Accordingly, disturbances in the ability to engage cognitive/behavioral inhibitory control might be expected to maintain PTSD symptoms and possibly impede PTSD treatment response.

The ability to flexibly control cognition, attention, and internal and external responding relies on an array of cortical control areas, including activation of the ACC/medial prefrontal cortex, ventromedial prefrontal cortex, orbitofrontal cortex, and lateral areas of prefrontal cortex.[18] Various studies[19,20] have implicated the dorsolateral prefrontal cortex, orbitofrontal cortex, and ventrolateral prefrontal cortex in both the control of emotion and the inhibitory control of action and impulse. Additional evidence[21,22] suggests that a neural circuit involving the coactivation of the prefrontal cortex and the dorsal striatum underlies cognitive and behavioral control. Indeed, activity across the basal ganglia, ACC/medial prefrontal cortex, lateral prefrontal cortex, and posterior parietal cortex has been associated with moment-to-moment task performance during a task of

cognitive flexibility.[23] These networks implicate the functions relevant to response to CBT because they are recruited when one is performing a task (ie, CBT) that involves utilizing executive control to maintain attention on performing cognitively demanding tasks, such as exposure therapy, cognitive restructuring, and responding to stimuli during in vivo exposure and related tasks.

Previous neuroimaging findings indicate that PTSD is associated with disturbances in dorsal striatal and frontal (right ventrolateral prefrontal cortex, orbitofrontal cortex) behavioral/cognitive control networks during inhibitory control.[24] Considering the hypothesized role of cognitive/inhibitory control in PTSD treatment response, this study aimed to examine whether alterations in inhibitory control network function may predict PTSD outcome in CBT. It was hypothesized that efficient engagement of inhibitory control neural networks (particularly a frontostriatal inhibition network) in PTSD prior to treatment would predict improved treatment response. Conversely, it was hypothesized that reduced capacity for flexible inhibitory control prior to treatment would predict poorer treatment response. Reduced capacity for control was expected to be evident in an inability to engage executive control networks (and associated behavioral deficits). We focused on symptom change at the 6-month assessment following treatment completion because this reflects a more accurate index of the enduring effects of CBT than posttreatment symptom levels.

Clinical Points

- Inhibitory skills are deficient in posttraumatic stress disorder (PTSD) but may be important in using cognitive-behavioral therapy strategies to regulate emotions.
- Response to cognitive-behavioral therapy is predicted by recruitment of inhibitory networks in PTSD patients prior to treatment and may suggest that strategies that facilitate greater inhibitory capacity prior to treatment may lead to better treatment outcomes.

METHOD

Participants

Participants were recruited through the Traumatic Stress Clinic, Westmead Hospital, Sydney, Australia, between October 2003 and May 2005. Participants were 13 treatment-seeking individuals with PTSD (5 males, 8 females; mean [SD] age = 38.30 [12.16] years; 12 right-handed, 1 left-handed) following physical assault (n = 6) or motor vehicle accident (n = 7), who participated for a mean (SD) of 54.0 (71.4) months since the precipitating traumatic event. Diagnosis of PTSD was made using the Clinician-Administered PTSD Scale (CAPS)[25] (the primary outcome measure) according to *DSM-IV*[26] criteria, and comorbid disorders were assessed using the Structured Clinical Interview for *DSM-IV* Axis I and II Disorders.[27] Levels of anxiety and depressive symptoms were measured by using the Depression Anxiety Stress Scales (DASS).[28] Exclusion criteria included any current substance abuse or alcohol abuse or dependence, any history of traumatic brain injury or neurological condition, commencement of psychotropic medication within 6 months of the study, any significant medical condition, history of psychosis or borderline personality disorder, or any loss of consciousness. Comorbid disorders in the PTSD group included major depressive disorder in 8 participants and panic disorder in 1 participant. Six individuals were taking current selective serotonin reuptake inhibitors, which were not altered during the course of the study. The Western Sydney Area Health Service Human Research Ethics Committee approved the study, and all participants gave written informed consent prior to participating. The study was registered on anzctr.org (identifier: ACTRN12610000017022).

Behavioral Procedure and Acquisition of Image by Functional Magnetic Resonance Imaging

For the purposes of assessing changes in behavior and function related to inhibitory performance, a Go/No-Go task procedure[24] was performed by participants while they underwent functional magnetic resonance imaging (fMRI) scanning (see Figure 1). In this task, participants were required to respond during "Go" trials and then to withhold this prepotent response during "No-Go" trials; inhibition of responding during No-Go trials was employed as a measure of executive inhibition.[29] The Go/No-Go paradigm involves an all-or-none decision to action (Go) or nonaction (No Go) and, as such, is suggested to measure executive inhibitory control.[30] Omission errors (failure to respond) reflect a deficit in response execution, and commission errors (the inability to withhold a response) reflect a deficit in inhibitory control. Response time and the variability of response time were also measured, as changes in the speed of responding may impact the demand on inhibitory control,[31] and intra-participant variability in response time has been suggested to reflect an inefficiency of response preparation that may impact on or reflect differences in inhibitory control (in attention-deficit/hyperactivity disorder).[32]

To examine the localization of changes in neural responding, we employed fMRI. Participants were placed on a magnetic resonance scanner table and fitted with magnetic resonance imaging–compatible headphones, and a mirror was fitted into the head coil, which projected a visual display from an external projector (Sanyo ProX, Multiverse Projector, maximum 60 Hz; Moriguchi, Osaka, Japan). Once inside the scanner, participants received instructions through headphones to perform the behavioral task. Go stimuli ("PRESS," presented in green-colored type in the center of a black screen) and No-Go stimuli ("PRESS" in red-colored type in the center of a black screen) were presented to participants by the projector and mirror system. Participants received standardized visual and audio instructions to tap a response box as quickly as possible when the Go stimulus appeared and to withhold responding to No-Go stimuli. Participants were instructed to button-press simultaneously with both their left and right thumbs (to counterbalance for motor activity). Commission errors were considered to be those

Table 1. Behavioral Correlational Findings

	Commission Errors		Omission Errors		Response Time (Mean)		Response Time (SD)	
Measure	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Pretreatment CAPS	0.57	.04*	0.004	.99	−0.17	.59	0.33	.28
Pretreatment DASS depression	0.73	.004*	−0.32	.29	−0.32	.28	−0.02	.95
Pretreatment DASS anxiety	0.70	.007*	0.20	.52	−0.25	.41	0.42	.15
Residual change	0.29	.33	−0.07	.82	−0.21	.49	−0.15	.64

*Significant effect ($P < .01$).
Abbreviations: CAPS = Clinician-Administered PTSD Scale, DASS = Depression Anxiety Stress Scale, PTSD = posttraumatic stress disorder, SD = standard deviation.

No-Go trials in which the participant responded with a button press. Omission errors were those Go trials in which the participant failed to respond with a button press. In order to create a tendency to respond, Go stimuli were randomly presented 75% of the time and No-Go stimuli presented 25% of the time. A total of 126 Go and 42 No-Go stimuli were grouped into "pseudoblocks" of 6 stimuli each (to form Go and No-Go stimulus blocks). Blocks were presented in a pseudorandom sequence (with no more than 2 No-Go blocks presented in a row). Each Go and No-Go stimulus was presented for 500 ms, with an interstimulus interval of 1,139 ms (a total of 1,693 ms for interstimulus interval plus stimulus duration, which takes into account fMRI repetition time [TR] delay).

Ninety T2*-weighted volumes depicting blood oxygen level–dependent (BOLD) contrast were acquired with a Siemens MAGNETOM Vision Plus 1.5 Tesla scanner (Munich, Germany), fitted with a standard quadrature head coil. Three initial "dummy" scans were acquired before stimuli were presented in order to familiarize participants with scanning noise and to ensure BOLD saturation. T2*-weighted images were obtained by using a gradient echo echoplanar sequence, and 15 axial noncontiguous slices of 6-mm thickness (0.6 interslice gap) were measured, positioned in parallel to the anterior commissure-posterior commissure line (TR = 3,200 ms, echo time = 40 ms, matrix 128 × 128; field of view = 24 cm × 24 cm^2, flip angle = 90°).

Following the behavioral and scanning procedure, participants received 8 once-weekly sessions of CBT that involved education, imaginal exposure, cognitive restructuring, and relapse prevention.[33] Six months following treatment completion, each participant received a clinical assessment that included the CAPS; assessments were conducted by clinicians who were independent of the treatment and the imaging protocol.

fMRI Image Processing

Images were processed by using Statistical Parametric Mapping version 2 software (SPM2, Wellcome Department of Neurology, London, United Kingdom). All T2*-weighted volumes were realigned, unwarped, and spatially normalized into standardized Montreal Neurologic Institute (MNI) space and smoothed by using a Gaussian kernel (full width at half maximum = 8 mm). A hemodynamic response functions–convolved boxcar model with temporal derivative was created to correspond to Go and No-Go stimuli and a high pass filter applied to remove low-frequency fluctuations in the BOLD signal.

Statistical Analysis

Behavioral analysis. Associations between each behavioral measure (omission error, commission error, response time, variability of response time) and each pretreatment clinical measure (total CAPS, DASS depressive symptom score, DASS anxiety symptom score) were examined via Pearson correlations. Regression analyses were used to examine the association between each pretreatment behavioral measure (the predictor variable) and residual PTSD severity (the outcome variable). (See fMRI Analysis section below for an explanation of how residual PTSD severity was determined.)

fMRI Analysis. To examine voxel-wise effects of signal changes, we analyzed hemodynamic signal change for each participant based on a between-condition contrast (No-Go minus Go conditions), which was then used for whole-brain random-effects analyses (with statistical threshold set at $P < .005$ [uncorrected] and an extent threshold of greater than or equal to 5 contiguous voxels per cluster).

To calculate PTSD severity change independent of initial PTSD severity, we determined residual change from a regression of pretreatment total CAPS scores on posttreatment total CAPS scores.[34] Whole-brain regressions of residual PTSD severity on fMRI signal were used to detect neural activity associated with treatment response, using both DASS anxiety and depressive symptom scores as covariates of noninterest.

RESULTS

Clinical Response

The mean pretreatment CAPS score was 75.5, and posttreatment score was 38.6. Seven participants were treatment responders (defined as a reduction of 50% of pretreatment scores), and 6 were nonresponders. Participants who were using medication were comparably represented in both responder (n = 2) and nonresponder (n = 2) groups (N = 13, $\chi^2 = 0.33$, $P = .57$).

Behavioral Data

Pretreatment total CAPS scores and DASS depression and anxiety symptom scores were each associated with greater number of commission errors during inhibitory control but not with number of omission errors, response time, or variability of response time during task performance (Table 1).

Table 2. Areas of Activation During Inhibitory Control Related to Cognitive-Behavioral Therapy Outcome in PTSD[a]

Region	Hemisphere	MNI Coordinates, mm X	Y	Z	Voxels	*Z* Score	*P*
Improved treatment response (negative relationship with residual change)							
Dorsal striatum	L	−18	8	4	50	3.19	.001
Orbitofrontal/inferior frontal	L	−28	22	−20	8	2.86	.002
Anterior medial prefrontal cortex[b]		0	62	14	39	3.67	<.001
Medial prefrontal cortex	R	8	56	26	25	3.03	.001
Parahippocampus	R	42	−28	−4	36	3.03	.001
Poorer treatment response (positive relationship with residual change)							
Inferior parietal	L	52	−34	42	442	3.58	<.001
Precuneus	R	2	−22	46	32	3.54	<.001
Dorsal striatum	L	−24	−4	10	11	3.77	<.001
	L	−22	−10	−2	29	3.32	<.001
Brainstem	R	14	−30	−6	238	3.74	<.001
Cerebellum	L	−22	−68	−26	81	3.47	<.001
	R	−2	−52	−6	19	3.37	<.001
Inferior frontal/ventrolateral prefrontal cortex	R	46	40	−2	5	2.65	.004
Inferior frontal/ventrolateral prefrontal cortex/insula	R	44	10	−2	136	4.85	<.001
	R	36	−14	6	33	3.08	.001
Middle temporal	L	−54	−62	8	12	3.44	<.001
Precuneus	L	−22	−50	8	22	3.29	<.001
Cingulate	R	10	−42	14	13	3.02	.001
Temporal	R	40	−6	−38	13	2.94	.002
Orbitofrontal cortex/ventrolateral prefrontal cortex	L	−4	42	−12	22	2.91	.002
Supplementary motor area	R	2	0	50	9	2.86	.002
Inferior parietal	L	−32	−60	48	7	2.79	.003
Dorsal striatum (putamen)	R	28	10	−4	25	3.37	<.001
Dorsal striatum (putamen)	R	36	−4	0	6	2.76	.003
Temporal	L	−56	−26	0	9	2.71	.003
Precuneus[b]		0	−66	58	7	2.71	.003

[a]Accounting for initial PTSD severity, level of depression, and level of anxiety; $P < .005$.
[b]No hemisphere is listed because the X coordinate = 0, indicating location between hemispheres.
Abbreviations: L = left, MNI = Montreal Neurological Institute, PTSD = posttraumatic stress disorder, R = right.

Posttraumatic stress disorder treatment response (ie, residual change) was not significantly related to any pretreatment differences in behavior during Go/No-Go task performance (ie, omission errors, response time, and variability of response time during Go responding and commission errors during No-Go responding; all *P* values > .05, 2-tailed).

fMRI Data

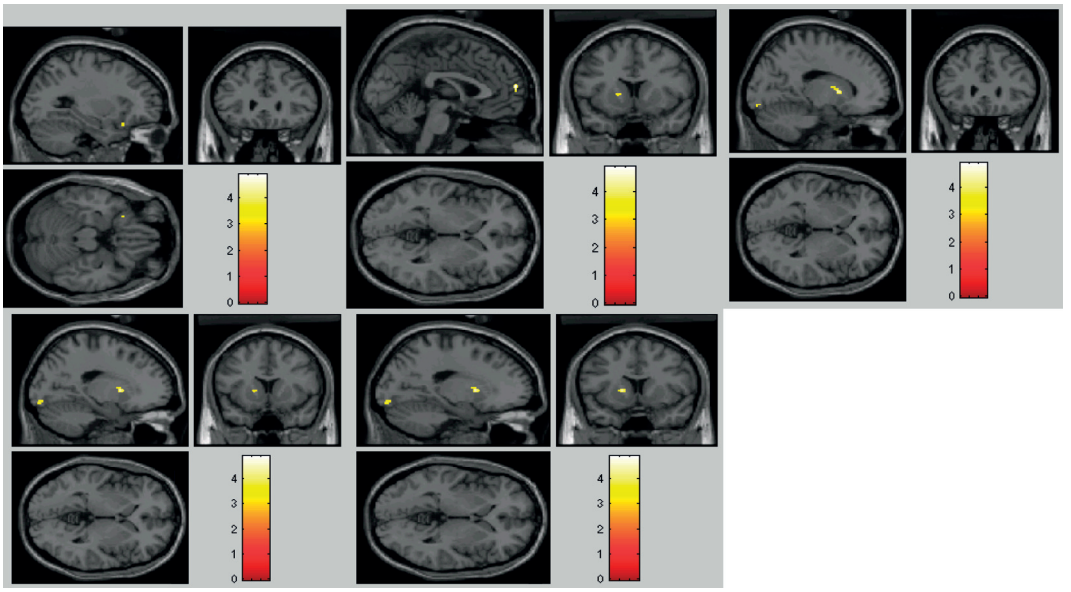
Table 2 and Figure 1 present the findings showing significant areas of activation during inhibitory control related to CBT treatment outcome. The recruitment of a localized left frontostriatal inhibition network (involving the left inferior frontal cortex (IFC)/orbitofrontal cortex and dorsal striatum), as well as regions of the anterior medial prefrontal cortex and parahippocampus during inhibitory control, was associated with greater treatment-related symptom reduction (PTSD improvement). In contrast, poorer CBT treatment response was associated with activation of a more distributed network involving both inhibition- and arousal-related regions, including the right brainstem, right IFC/ventrolateral prefrontal cortex/insula, left dorsolateral prefrontal cortex, bilateral dorsal striatum/insula, bilateral parietal cortices, posterior cingulate, thalamus, insula, and midbrain/periaqueductal gray during inhibitory processing.

DISCUSSION

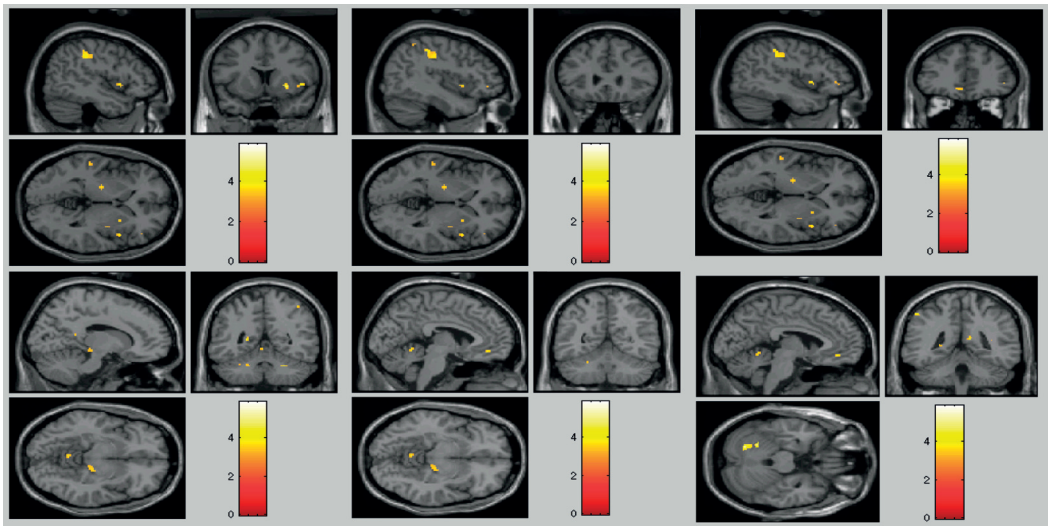
The current study showed for the first time that the extent and efficiency of inhibitory neural network activation at pretreatment are predictive of PTSD response to CBT. The current findings indicate that a better response to CBT in PTSD was associated with greater (pretreatment) activation of a localized left dorsal striatal and frontal network during inhibitory control (along with activation in the parahippocampus and anterior medial prefrontal cortex). In contrast, poorer treatment response was associated with activation of a more distributed fronto-parieto-striatal and cerebellar network during inhibitory control, which included greater activation in the right ventrolateral prefrontal cortex. While (pretreatment) functional activations during inhibitory control were related to treatment outcome, inhibitory behavioral performance at pretreatment did not relate to differential PTSD treatment response. Taken together, these findings suggest that, while improved treatment response is associated with the activation of a more discrete frontostriatal network to support inhibitory behavioral performance, when there is a requirement for greater and more distributed activation of cortical and subcortical regions in order to support similar levels of behavioral performance (at pretreatment), there

Figure 1. Significant Activations Related to Response to Cognitive-Behavioral Therapy[a]

A. Better treatment response was associated with greater pretreatment activation of the left ventrolateral prefrontal cortex/orbitofrontal cortex, dorsal striatum, and anterior medial prefrontal cortex (along with parahippocampus) during inhibitory control



B. Poorer treatment response was related to greater pretreatment activation across arousal-related and inhibitory control regions, including the brainstem, parietal cortex, right ventrolateral prefrontal cortex, and cerebellum



[a]Whole brain random-effects analyses with statistical threshold set at $P < .005$ (uncorrected) and an extent threshold of greater than 5 contiguous voxels per cluster.

is a poorer treatment outcome in PTSD. This evidence is consistent with the hypothesis that an increased efficiency of inhibitory control (or a reduced demand/load on inhibitory control networks) in PTSD may predict better treatment outcome.

It is interesting that greater activation of the right ventrolateral prefrontal cortex during inhibitory control was related to poorer treatment outcome in the PTSD group, given its role in inhibitory control in healthy participants[19] and its reduced activation in PTSD relative to control participants during inhibitory control.[24] Taken with the observation that right ventrolateral prefrontal cortex activation was accompanied by more widespread and greater activation across parietal, striatal, and cerebellar networks, the evidence may indicate that poorer treatment response is associated with a greater demand on inhibitory control (or a reduced efficiency of executive control) at pretreatment. This proposal accords with evidence of comparable network activations in populations characterized by less developed inhibitory control. For example, children and adolescents have been shown to recruit larger and more diffuse fronto-striato-cerebellar and parietal networks during cognitive and inhibitory control,[21,35] with this distributed network activation suggested to reflect the requirement for more processing resources to maintain

inhibitory control. In depression, a greater and more distributed recruitment of neural systems during inhibitory control has been suggested to reflect the greater demand on and need for regulatory systems to counteract hyperactive emotional and symptom-related processing.[36] Similarly, the findings in PTSD suggest that a greater pretreatment demand on regulatory control may be predictive of poorer PTSD treatment outcome. The observation that poorer treatment outcome was associated with greater activation of more distributed inhibitory control regions (including ventrolateral prefrontal cortex, dorsal striatum, orbitofrontal cortex, and cerebellum), as well as arousal-related regions (brainstem), is consistent with this hypothesis, as greater activation of the lateral prefrontal cortex is suggested to be involved in behavioral control during greater cognitive demand or more effortful control.[37]

The finding that better treatment response was associated with the engagement of a left-lateralized fronto-striatal control network at pretreatment supports the hypotheses that (1) treatment response is associated with the ability to engage control systems in PTSD and (2) the ability to more efficiently engage those systems may predict improved CBT response. The finding that this activation related to better treatment response in both a dorsal striatal and IFC/orbitofrontal cortex network is also relevant to the notion that cognitive and behavioral flexibility requires orbitofrontal-dorsal striatal systems related to stimulus salience and motivational relevance,[38] and engagement of the striatum is suggested to be particularly important for new cognitive skill learning.[39] Disruption of the orbitofrontal-striatal system has been shown to lead to behavioral inflexibility, perseveration, and stereotyped behavior, including deficits in the ability to flexibly use abstract task rules.[40] An improved ability to flexibly direct behavior and inhibit perseveration would be expected to be associated with improved CBT treatment response, as the perseveration on previous behavioral associations may impede the integration of new associations that may be required for effective CBT response.[11]

The current work is limited by the small sample size and the possibility that comorbid disorders (panic, depression) or use of medications may impact the findings. We note the association between depression, anxiety, and commission errors, and, accordingly, it is possible that the factor underpinning impaired inhibitory function may be related to psychopathological processes beyond PTSD. We adopted an uncorrected $P = .005$ due to the small sample size and possibility of type 2 errors; future replications should be conducted with larger samples and corrected P values. Also, the absence of alternative treatments to CBT means the specificity of current findings to CBT cannot be determined. We did not retain these participants for posttreatment imaging sessions, and therefore we cannot make inferences about the impact of treatment on inhibitory functions. We also did not include a wait-list comparison condition, which future research could compare with participants who receive CBT. Finally, we note that the Go/No-Go paradigm is only 1 index of inhibitory processes, and it is possible that other measures could provide different outcomes. In this context, it is interesting that commission errors were not predictive of treatment outcome. It is possible that employing paradigms that index more automatic inhibitory responses (eg, the Stroop task) or emotional inhibition (eg, the emotional Stroop task) would provide more sensitive measures of inhibitory dysfunction.

Notwithstanding these limitations, this study shows for the first time that neural activation patterns of inhibitory control networks at pretreatment are associated with PTSD response to CBT. The findings suggest that the ability to more efficiently recruit a left-lateralized fronto-striatal inhibitory control network in PTSD at pretreatment is associated with an improved CBT response. Conversely, the findings also suggest that a greater load or reduced efficiency of inhibitory control at pretreatment may predict poorer treatment outcome in PTSD. How efficiency in fronto-striatal networks is related to treatment requires further research. It is premature to infer that this finding permits definitive prediction of who will respond to CBT because, despite the statistical relationship, this finding sheds light on possible mechanisms of treatment rather than pretreatment biomarkers for therapy success; the latter requires demonstration that sensitivity and specificity are sufficient to accurately categorize patients as likely treatment responders. The next step in research should be to replicate these findings to larger sample sizes, using a variety of inhibitory measures, to determine the predictive power for treatment success.

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