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Selective Effects of Psychotherapy on Frontopolar Cortical Function in Post-Traumatic Stress Disorder

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Abstract

Objective—Exposure therapy is an effective treatment for posttraumatic stress disorder (PTSD), but a comprehensive, emotion-focused perspective on how psychotherapy impacts brain function is lacking. Here, we assess changes in brain function following prolonged exposure therapy across three emotional reactivity and regulation paradigms.

Methods—Individuals with PTSD underwent functional magnetic resonance imaging (fMRI) at rest and while completing three tasks assessing emotional reactivity and regulation. Individuals were then randomized to prolonged exposure treatment (N=36) or waitlist (N=30) and underwent

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a second scan approximately four weeks following the last treatment session or a comparable waiting period, respectively.

Results—Treatment-specific changes were observed only during cognitive reappraisal of negative images. Psychotherapy increased lateral frontopolar cortex activity and its connectivity with the ventromedial prefrontal cortex/ventral striatum. Greater increases in frontopolar activation were associated with improvement in hyperarousal symptoms and psychological well-being. The frontopolar cortex also displayed a greater variety of temporal resting state signal pattern changes following treatment. Using concurrent transcranial magnetic stimulation and fMRI in healthy participants, we demonstrate the lateral frontopolar cortex exerts downstream influence on the ventromedial prefrontal cortex/ventral striatum.

Conclusions—Changes in frontopolar function during deliberate regulation of negative affect is one key mechanism of adaptive psychotherapeutic change in PTSD. Given that: a) frontopolar connectivity with ventromedial regions during emotion regulation is enhanced by psychotherapy; and b) frontopolar cortex exerts downstream influence on ventromedial regions in healthy individuals, these findings inform a novel conceptualization of how psychotherapy works and identify a promising target for stimulation-based therapeutics.

Posttraumatic stress disorder (PTSD) is persistent (1) and impairing (2) but can be treated with psychotherapy (3). Prolonged exposure is one such effective treatment (4), which utilizes therapeutic exposure as its primary technique for promoting recovery (5). Formulated from emotional processing theory (6), prolonged exposure helps the patient confront the trauma memory and real-life situations that provoke symptoms. This allows the patient to integrate new, adaptive information regarding safety from threat. Repeated exposure usually results in a reduced fear response and promotes corrective learning, whereby the likelihood and intensity of a future fear response to that stimulus is lessened (6).

This framework suggests that treatment may alter a range of emotional behaviors, from initial detection and orienting towards emotional cues (emotional reactivity) through control of emotional responses (emotion regulation). Though exposure therapies for PTSD have been utilized for decades (4), little is known regarding how these treatments alter brain function. The extent literature is largely composed of imaging studies in small samples that assess changes in brain function during a single task before and after treatment (Supplemental Table 1), often without comparison to a control intervention. While this work has provided valuable insight regarding brain changes in the particular process examined, the role of these changes within the larger context of potential mechanisms conveying treatment efficacy has been unclear. As these studies often lacked patient control arms, it is also unclear whether changes reflected the intervention per se or other confounding factors, e.g., passage of time or repeated assessments.

Here, we provide a comprehensive assessment of functional brain changes following prolonged exposure therapy for PTSD across three experimental paradigms assessing emotional reactivity and regulation. We used a randomized patient waitlist as a control condition and analyzed results using voxelwise linear mixed effects modeling in line with the intent-to-treat principle. To identify whether treatment-related changes might reflect one
brain region’s direct influence over another, we combined single-pulse transcranial magnetic stimulation (TMS) with functional magnetic resonance imaging (fMRI) in a separate sample of healthy individuals. We assessed whether single TMS pulses to one brain region influenced activation in another, thereby demonstrating downstream influence. TMS is a non-invasive brain stimulation technique shown to produce elevated activity in the cortical area stimulated by the magnetic field as well as in downstream targets (7), thus mimicking endogenous volitional activation of the targeted region and allowing for experimental manipulation of neural circuitry. Finally, we examined resting state fMRI in a focused manner to follow-up on how task-related neural dynamics altered by treatment might generalize beyond an emotional reactivity and regulation context.

Prior PTSD psychotherapy imaging studies have observed increased prefrontal recruitment post-treatment during recall of the trauma memory (8–10), though decreased recruitment has also been observed during trauma memory recall (11), processing of negative (12) and trauma-related pictures (13), and conflict processing (14). Similarly, increased anterior cingulate recruitment has been noted during processing of fearful vs. neutral faces (15) and during anticipation of negative vs. positive pictures (12), while activation in limbic structures such as the amygdala and anterior insula have shown attenuations post-treatment during recall of the trauma memory (16), a classic (14) and affective Stroop task (17), and anticipation of affective pictures (12). Thus, the predominant pattern of experimental results is consistent with proposed mechanisms of psychotherapy—increased prefrontal recruitment and control over limbic structures involved in threat detection and emotion induction (18). On the basis of these findings, we expected individuals randomized to prolonged exposure to display a greater attenuation of amygdala and anterior insula activation during the processing and detection of emotional stimuli. We also expected to see increased prefrontal recruitment during all phases of emotion processing—from initial detection and processing of stimuli to deployment of automatic and effortful regulatory strategies.

Methods

See Supplemental Methods for complete details.

Participants, Assessments, and Inclusion Criteria

Individuals, age 18–60, were recruited to participate in a psychotherapy treatment study for PTSD. Participants provided written informed consent after receiving a complete study description and completed a baseline structured clinical interview to assess PTSD symptoms and other diagnoses.

Behavioral Paradigms

Emotional Reactivity Task—This task (19) probes goal irrelevant emotional reactivity via conscious and non-conscious presentation of color-tinted fearful and neutral faces. Participants identified the color tint of the face stimulus.
**Emotional Conflict Task**—This task (20) induces emotional conflict and conflict adaptation through pairing fearful and happy faces with congruent or incongruent emotion words. Subjects were instructed to identify the facial emotion and ignore the emotion word.

**Reappraisal Task**—Participants viewed negative and neutral IAPS pictures under two conditions: “Look” (for negative and neutral) and “Decrease” (negative only). During “Look” participants were instructed to experience their natural emotional response, while during “Decrease” they were instructed to reduce their level of emotional distress by interpreting or seeing the picture differently (21).

**Resting State**—Participants completed an 8 minute eyes-open resting state scan in which they were told to lie still, stay awake, focus on a fixation cross, and allow their mind to wander.

**MRI Data Acquisition**

See Supplemental Methods.

**Concurrent TMS-fMRI causal mapping in healthy participants**

To investigate normative patterns of downstream influence in neural circuits demonstrating treatment-related change, a separate cohort of 14 healthy individuals underwent a concurrent TMS-fMRI scanning session conducted according to established protocols (22). See Supplemental Methods for further details.

**Randomization**

Following initial assessments and scanning, participants were randomized to one of two arms: 1) Immediate treatment with prolonged exposure (N=36); or 2) Treatment waitlist (N=30).

**Prolonged Exposure Treatment, Therapist Competency, and Supervision**

Treatment sessions occurred either once or twice-weekly, for a total of 9 to 12 90-minute sessions according to manualized procedures (5).

**Post-Treatment Assessment**

Approximately 4 weeks after the final treatment session, participants completed a post-treatment clinical assessment and repeated the imaging protocol. A 4-week period was chosen to intercede between the final session and post-treatment assessment in order to allow treatment changes to consolidate and symptom levels to equilibrate.

**Image Preprocessing**

See Supplemental Methods.

**Individual-Level Analysis of Task Data**

See Supplemental Methods.
Individual-Level Analysis of Resting Brain Entropy

To test a hypothesis regarding flexibility of brain states at rest as a follow-up to the primary activation analyses, we investigated regional brain entropy during resting state fMRI and whether this changed with psychotherapy in regions showing task-related changes. Entropy is a measure of the variety of change patterns in a time series signal (23), which could index shifts in the way the range of potential brain states available are manifested moment-to-moment (24). Entropy is also closely related to flexibility, i.e. the ability to shift among different states (25).

Assessing Treatment Effects

We analyzed brain activation and connectivity on a voxelwise level by employing the MacArthur approach (26) embedded in our longitudinal linear mixed effects models to identify changes over time that were specific to the treatment group. We used a voxelwise false discovery rate correction within a pre-specified anatomical mask to control for Type I error. In addition to voxelwise analyses, we also conducted region of interest analyses using extracted average activation beta weights from the bilateral amygdala and anterior insula for each task and contrast of interest. These complement primary voxelwise analyses by facilitating detection of limbic effects that may be larger in spatial extent but smaller in magnitude, which are unlikely to survive voxelwise FDR correction.

Results

Sample Characteristics

The final sample included 36 individuals randomized to immediate treatment and 30 randomized to waitlist. The groups were well matched on clinical and demographic variables (Table 1).

Treatment Outcome

The immediate treatment group showed significantly greater reductions in PTSD and depressive symptoms, and greater improvements in certain quality of life domains compared to the waitlist group (Table 1).

Baseline Task Effects

See Supplemental Results and Supplemental Table 2.

Treatment Effects on Task Behavior

During reappraisal, patients in the treatment arm compared to waitlist showed a significantly greater reduction in distress ratings in response to picture presentation regardless of experimental condition or picture valence. No other significant treatment effects were detected on task behavior.

Treatment Effects on Task Brain Function in Limbic Regions of Interest

There was no significant treatment arm × time interaction effects on activation for any task contrast examined in the bilateral amygdala or anterior insula (Supplemental Table 3).
Voxelwise Analyses for Treatment Effects on Task Brain Function: Regions of Interest

**Emotional Reactivity Task**—We observed no significant time × treatment arm effects for unmasked fear vs. neutral faces or for masked fear vs. neutral faces.

**Emotional Conflict Task**—We observed no significant time × treatment arm effects for emotional conflict, conflict regulation, or emotional reactivity (congruent Fear vs. Happy) contrasts.

**Reappraisal Task**—In the regulation contrast from the Reappraisal paradigm (Reappraise Negative vs. Look Negative), we observed a significant time × treatment arm effect on left lateral frontopolar cortex activation (middle frontal gyrus; Brodmann area 10)(Supplemental Table 4). Post-hoc extractions revealed an increase in activation over time in the immediate treatment arm ($t=3.32, p=0.002$)(Fig. 1) with no change in the waitlist arm ($t = −1.25, p=0.22$). We observed no other significant effects in regions of interest. We detected no significant time × treatment arm interactions for the Look Negative vs. Look Neutral contrast. Follow-up analyses across tasks demonstrated that left frontopolar activation change was selective to reappraisal (see Supplemental Results).

Voxelwise Treatment Effects on Task Brain Function: Whole Brain Analyses

Across all of the tasks and contrasts tested, there were no significant effects detected in the exploratory whole brain analyses.

**Exploratory Analyses: Differential Brain Changes as a Function of Remission Status**

We also examined whether there were additional brain changes as a function of remission status at end of treatment (see Supplemental Results). We observed no additional differential brain activation change effects.

**Frontopolar Context-Dependent Connectivity During Reappraisal**

To deepen our mechanistic understanding of the reappraisal effect, we tested left lateral frontopolar context-dependent functional connectivity for treatment-related changes using a generalized psychophysiological interaction analysis (27). We observed a significant time × treatment arm interaction effect in the ventromedial prefrontal cortex (olfactory cortex/ anterior cingulate/mid-orbital gyrus; Brodmann areas 25 and 32) extending into the adjacent ventral striatum (nucleus accumbens/caudate nucleus)(Supplemental Table 5). Post-hoc extractions revealed increased connectivity between this region and the lateral frontopolar cortex in the immediate treatment arm at post-treatment ($t=3.09, p=0.003$)(Fig. 2A), with a trend towards decreased connectivity in the waitlist arm ($t = −1.73, p=0.087$). No effects were detected in the whole brain analysis.

**Brain-Behavior Relationships: Frontopolar Activation Change**

Next, we assessed if change in left lateral frontopolar reappraisal activation was clinically meaningful by examining its relationship to change in PTSD symptoms and quality of life. These measures were selected to represent outcomes that are both disorder-specific, symptom-focused, and proximal treatment targets as well as those which are transdiagnostic,
life functioning-focused, and more distal indicators of treatment success, respectively. Controlling for baseline symptoms and activation in a generalized linear model (with separate models for Clinician-Administered PTSD Scale (CAPS) total score, its 3 subscales, and the 3 subscales of the WHO-Quality of Life Inventory (WHO-QoL)) and using Bonferroni correction for multiple comparisons (p<0.007), we observed that greater increases in activation were associated with greater improvements in CAPS hyperarousal symptoms in the treatment group (Wald $\chi^2=7.71$, $p=0.005$). This relationship was significantly different (Wald $\chi^2=8.28$, $p=0.004$) from the relationship between these two measures in the waitlist group (Fig. 3A), which was non-significant. We also observed that increases in left frontopolar activation were associated with improvement in psychological well-being (WHO-QoL Psychological Health subscale) in the treatment group (Wald $\chi^2=95.07$, $p<0.001$). Again, this relationship was significantly different (Wald $\chi^2=7.93$, $p=0.005$) from the relationship between these two measures in the waitlist group (Fig 3B), which was also non-significant.

Assessing Treatment-Related Changes in Frontopolar Resting Entropy and Connectivity

With prior work implicating the lateral frontopolar cortex in cognitive flexibility and switching between stimulus-dependent and stimulus-dependent mental states (28, 29), we reasoned that frontopolar cortex change might be of a more general relevance and extend beyond emotional reactivity and regulation per se. Thus, we tested whether the BOLD signal at rest in the lateral frontopolar cortex and its ventromedial connectivity target display properties of greater flexibility following psychotherapy, one potential brain marker of a more varied repertoire of mental states. We therefore calculated BOLD sample entropy (24) (Fig. 4A), which provides a quantitative measure of the variety of change patterns over time. Using entropy values extracted from the clusters identified above, we observed a significant time × treatment arm interaction on entropy change in the lateral frontopolar cortex ($F=26.57$, $p<0.001$) but not in the ventromedial prefrontal cortex/ striatum ($F=1.98$, $p=0.162$). In this frontopolar region, the effect was due to an entropy increase in the treatment group ($t=3.968$, $p<0.001$) as well as an entropy decrease in the waitlist group ($t=−3.080$, $p=0.003$)(Fig. 4B). We also examined resting connectivity between these regions. We seeded the left frontopolar cortex region showing change during reappraisal and examined whether intrinsic connectivity with the ventromedial prefrontal cortex/ventral striatum at rest changed with treatment. There was no significant treatment arm × time interaction effect on resting state connectivity (see Supplemental Results). Thus, the resting dynamics of the lateral frontopolar cortex displayed changes in patients following treatment. Specifically, this region showed no changes in intrinsic connectivity with the ventromedial prefrontal cortex/ventral striatum, but rather showed a time course of activity that was more entropic, i.e. varied and changed in a greater number of ways than prior to treatment.

Follow-Up Experiment in Healthy Individuals: Testing Frontopolar Influence on the Ventromedial Prefrontal Cortex/Ventral Striatum using Single-Pulse Transcranial Magnetic Stimulation (TMS) with fMRI

Given evidence for functional and structural interactions of the frontopolar and ventromedial prefrontal cortex in humans (28, 30, 31), we hypothesized their interactions arise from a direct downstream influence of the frontopolar cortex on the ventromedial prefrontal cortex/
ventral striatum. To test this hypothesis, we applied single TMS pulses to the left frontopolar cortex in a separate sample of healthy participants undergoing concurrent TMS/fMRI ($n=14$). Single TMS pulses to the right hand knob of the primary motor cortex were used as an active comparison. We then compared average within-subject BOLD signal in the region defined by the ventromedial prefrontal/ventral striatal connectivity change during reappraisal (Supplemental Table 5) for each stimulation site. In healthy individuals, TMS stimulation to the left frontopolar cortex induced significant deactivation in this ventromedial prefrontal cortex/ventral striatal region ($t = −3.89, p=0.002$), and this was significantly different relative to right motor cortex stimulation ($t= −2.80, p=0.016$; Fig. 2B), which itself did not have an effect ($t=0.11, p=0.91$). This effect was replicated in a voxelwise analysis, and additional effects were seen in a whole brain analysis (see Supplemental Results and Supplemental Table 6).

**Discussion**

Here, we assessed brain function in individuals with PTSD during emotional reactivity and regulation to better understand how prolonged exposure conveys therapeutic benefit. No treatment-related changes were observed in reactivity to emotional cues or regulating interference from emotional conflict. However, the left lateral frontopolar cortex displayed increased activation and increased connectivity with the ventromedial prefrontal cortex/ventral striatum during cognitive reappraisal following treatment. Concurrent TMS-fMRI in healthy participants demonstrated frontopolar cortex stimulation modulates activity in this connectivity target. Increases in frontopolar activation were related to improvement in hyperarousal symptoms and psychological well-being. Finally, the lateral frontopolar region showing activation change during cognitive reappraisal also demonstrated a wider variety of resting state signal fluctuation patterns over time. Taken together, these findings indicate: a) the most prominent therapeutic brain change following prolonged exposure is prefrontal rather than limbic and manifests during deliberate emotion regulation; b) this change is clinically relevant and relates to improvement in symptoms and psychological well being; c) this change manifests in the lateral frontopolar cortex and its interactions with the ventromedial prefrontal cortex/ventral striatum, a recipient of frontopolar downstream influence; and d) this change is evident during both regulation of emotion and at rest and may therefore reflect a generalized shift in frontopolar function.

These results inform a novel view on the brain mechanism of exposure therapy. In contrast to existing accounts of psychotherapy mechanisms (18, 32), we observed no limbic attenuation during emotional reactivity, no increased recruitment of posterior lateral prefrontal substrates implicated in top-down control (33), and no prefrontal change during emotional reactivity, emotional conflict, or emotional conflict regulation. Importantly, this contrasts with treatment moderation results in this sample, wherein emotional reactivity and emotional conflict regulation-related brain function predicted treatment outcome (34). Instead, we demonstrate that exposure therapy alters functioning of the most anterior portion of the human prefrontal cortex (Brodmann Area 10) during deliberate emotion regulation, as well as its connectivity with a ventromedial corticostriatal target that is a target of its downstream influence. Together, these findings point towards a prominent, selective effect of exposure therapy on a cortical substrate that is anatomically and functionally distinct (31).
from other prefrontal cortical regions widely held to convey the efficacy of psychotherapy (18, 35).

In contrast to prefrontal cortical regions implicated in executive control or salience (36), the frontopolar cortex (a.k.a. anterior prefrontal cortex (31) or rostral prefrontal cortex (29)) is believed to control the balance of stimulus-dependent (e.g., to the external environment) and stimulus-independent attention (e.g., attention towards the internal milieu) (29). The lateral frontopolar region identified here has been implicated in higher-order processes requiring a continual integration of inner mental phenomena with outward attention to “keep something in mind” while performing concurrent tasks (29). The frontopolar cortex is composed primarily of Brodmann area 10, a substrate with unique cytoarchitecture (31). Substantially enlarged in humans, it is one of the last regions to mature developmentally and is almost exclusively interconnected with higher-order associative cortices involved in cross-modal information integration (31). Hemodynamic changes in this region occur across many paradigms (29), consistent with its proposed role as a coordinator of multiple component cognitive functions processed by more posterior prefrontal areas (31). Meta-analytic data indicates this region is activated by reappraisal (37), particularly in the later temporal phases (38), and is hypoactive in PTSD (39), suggesting the effects observed here may indicate normalization of an abnormality.

Increased activation in this region was concomitant with increased ventromedial prefrontal (Brodmann Areas 25 and 32)/ventral striatal connectivity. Activation of this ventromedial (Brodmann area 25)/ventral striatal region moderated treatment response during emotional conflict regulation at baseline (34), illustrating a potential connection between these processes and a common substrate. Brodmann area 25, i.e. subgenual cingulate has been implicated in parasympathetic modulation of internal state (40), while the nucleus accumbens/ventral striatum have been shown to mediate relationships between successful reappraisal and both ventromedial prefrontal and frontopolar function (41). That greater activation in this region at baseline predicted more favorable psychotherapy outcomes in this sample was interpreted in the context of emotional conflict regulation as an enhanced capacity to attenuate arousal/vigilance following perturbation by a salient stimulus (34). Consistent with the proposed role of the lateral frontopolar cortex in switching between stimulus-dependent and stimulus-independent attention (42), this convergence suggests that psychotherapy may train the lateral frontopolar cortex to better evoke or amplify attention towards an internal regulatory process that mediates successful emotion regulation and marks cessation of reappraisal (41). Clinically, this may manifest as less engagement in avoidance strategies to regulate emotional state and more moderate, less excessive responses to emotionally salient stimuli.

It is noteworthy that Brodmann area 10 has demonstrated psychotherapy-related changes in two PTSD imaging studies, one showing increased left hemisphere recruitment during script-driven imagery in police officers (10), and the other showing attenuated right hemisphere activation during anticipation of negative vs. positive images in assaulted women (12). Thus, our findings add to accumulating evidence that frontopolar cortical function conveys at least some of the beneficial effects of PTSD psychotherapy. We expand upon initial findings through demonstrating change in lateral frontopolar reappraisal-related
activation, connectivity with the ventromedial prefrontal cortex/ventral striatum, frontopolar resting entropy, as well as demonstrating that lateral frontopolar cortex stimulation can modulate ventromedial prefrontal/ventral striatal function. Additional studies in social anxiety disorder have also demonstrated functional changes in Brodmann area 10 following treatment, e.g., during social evaluation following nefazodone (43) and during threat processing following cognitive-behavioral therapy (44). The frontopolar cortex is also an efficacious TMS site for the treatment of major depression (45), and frontopolar cerebral blood flow indexes treatment response after exposure with response prevention for obsessive-compulsive disorder (46). Thus, the frontopolar cortex may be a transdiagnostic therapeutic target across disorders characterized by diminished positive affect and exaggerated fear, anxiety, and threat reactivity.

We demonstrate the capacity for lateral frontopolar stimulation to influence ventromedial prefrontal/striatal signal in healthy individuals, which provides initial evidence for an integrated communication pathway operating in multiple contexts. This communication may therefore reflect a process of general relevance, consistent with the interactions of these regions during a range of behaviors (28, 30) and the proposed role of the frontopolar cortex as an attentional gate (29). Specifically, transient lateral frontopolar activations are also thought to support bi-directional switching between stimulus-independent and stimulus-dependent processing modes (29), which may underlie TMS-induced deactivation of ventromedial prefrontal cortex. As this region is implicated in control and awareness of one’s internal state (40), attenuation of regional activity here by frontopolar stimulation may signal a shift away from a stimulus-independent state of rest (47). Likewise, increased resting entropy in the lateral frontopolar cortex following psychotherapy suggests this region is able to function more flexibly and assume a more varied repertoire of configurations, which may reflect a wider range of mental states. Here, we utilized TMS/fMRI and resting state data only to follow up on primary analyses of task findings, and we did not undertake an extensive investigation of these metrics. Therefore, findings should be considered initial supporting evidence to better contextualize the results of task effects, while future investigations focused specifically on TMS/fMRI and resting state metrics in PTSD will provide further insights.

This study’s primary limitation is the lack of a traumatized healthy comparison sample to determine whether functional changes reflect normalization of abnormalities or compensatory adaptations. Second, we did not collect frontopolar TMS/fMRI data in patients, which would have been most informative for this investigation. We note that the TMS/fMRI findings reported here may not necessarily apply to individuals with PTSD. Third, we did not counterbalance task order across participants, as it was not possible to ensure balanced administrations across randomized groups. However, this could also reduce generalizability of brain change effects if the task administration order exerted habituation effects on the brain dynamics in a given task that showed a differential change over time between treatment arms. It is notable that we did not detect hypothesized treatment-related changes in limbic regions, e.g. amygdala and insula, previously demonstrated to be hyperactive in PTSD and to display changes following therapy (14–16). This may reflect a lack of power to detect effects of smaller magnitude. However, it is also noteworthy that amongst randomized controlled PTSD imaging studies, changes in prefrontal function in the
absence of limbic changes are observed with equivalent frequency (10, 11) as limbic changes (14, 16), perhaps related to variation in the experimental task, study sample characteristics, or other factors. Future studies are needed to understand these sources of variation. Additionally, that effects were observed only during the reappraisal task could relate to differences in evoked arousal related to the complex affective picture stimuli utilized in that task vs. emotional faces utilized in other tasks. However, that lateral frontopolar entropy changes were observed in the immediate treatment group at rest, a low-arousal state, suggests this is not the case. Future studies examining peripheral arousal measures during task completion, e.g., skin conductance response, will be helpful in delineating whether selective effects during one task are related to evoked arousal, the mental process engaged, or both.

Regardless, our findings have import for understanding the mechanism of exposure therapy by demonstrating that the most prominent functional brain change during the processing and regulation of non-traumatic emotional stimuli occurs in an anatomically distinct, higher-order frontal structure (31). This region may also be responsible for the instantiation of a conceptually-distinct process: a gating mechanism dictating the balance of awareness of the internal and external world (29). Future studies are needed to further elaborate on the functional significance of the frontopolar cortex in PTSD and its change following exposure therapy, but these findings nevertheless identify an underexplored anatomical brain target and pathway of influence to the ventromedial prefrontal cortex with promise for stimulation-based therapeutics and augmentation of psychotherapy effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


differences in trait anxiety predict the response of the basolateral amygdala to unconsciously
20. Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during
implicit regulation of emotional processing in generalized anxiety and major depressive disorders.
22. Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM, Glover GH, Deisseroth K,
Etkin A. Causal interactions between fronto-parietal central executive and default-mode networks
9:e89948. [PubMed: 24657999]
25. Shuiabi E, Thomson V, Bhuian N. Entropy as a measure of operational flexibility. European
psychophysiological interactions (gPPI): a comparison to standard approaches. Neuroimage. 2012;
29. Burgess PW, Dunmontheil I, Gilbert SJ. The gateway hypothesis of rostral prefrontal cortex (area
30. Turner MS, Simons JS, Gilbert SJ, Frith CD, Burgess PW. Distinct roles for lateral and medial
rostral prefrontal cortex in source monitoring of perceived and imagined events.
31. Ramnani N, Owen AM. Anterior prefrontal cortex: insights into function from anatomy and
32. Milad MR, Rosenbaum BL, Simon NM. Neuroscience of fear extinction: implications for
34. Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, Weiss ME, Thompson AL,
Zack SE, Lindley SE, Arnow BA, Jo B, Gross JJ, Rothbaum BO, Etkin A. Brain activation during
emotional reactivity and regulation predicts psychotherapy outcome in posttraumatic stress
35. Messina I, Sambin M, Palmieri A, Viviani R. Neural correlates of psychotherapy in anxiety and
36. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD.
Dissociable intrinsic connectivity networks for salience processing and executive control. J
37. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis


Figure 1. Prolonged exposure increases left frontopolar cortex activation during cognitive reappraisal

A schematic of the task contrast is displayed at the top of the figure, which compares brain activation while individuals deliberately and consciously reduce negative emotion in response to an affectively charged picture relative to when they simply look at the picture and experience their natural emotional response. The line graph depicts the mean individual mixed model-derived predicted values for activation within each treatment arm and at each timepoint. The interaction effect of time and treatment arm is rendered on a template surface, in which individuals in the prolonged exposure group ($N=36$) displayed significantly greater increase in activation over time relative to those in waitlist ($N=30$). Pre= pre-treatment; Post = post-treatment; $** = p < 0.01$. 
Figure 2. Prolonged exposure increases connectivity between the left frontopolar cortex and the ventromedial prefrontal cortex/ventral striatum: A circuit conveying downstream influence in healthy individuals

Panel A depicts the treatment arm × time interaction effect in which individuals in the prolonged exposure group (N=36) displayed significantly greater increases in connectivity from the left frontopolar cortex to the ventromedial prefrontal cortex/ventral striatum during cognitive reappraisal relative to individuals in waitlist (N=30). The line graph depicts the mean individual mixed model-derived predicted values for connectivity within each treatment arm and at each timepoint. The activation change and its connectivity target are rendered on average surfaces. Panel B depicts the causal effect of left frontopolar stimulation in healthy individuals (N=14) on blood oxygenation-level dependent signal change in this same ventromedial prefrontal/striatal region relative to right motor cortex stimulation, which was used as a comparison site. The bar graph depicts the mean individual ventromedial prefrontal/ventral striatal activation values for each stimulation site. The top left brain depicts frontopolar stimulation site, and the top right brain depicts right motor cortex stimulation site, both rendered on an average surface. fMRI = functional magnetic resonance imaging; Fp = frontopolar cortex; M1 = primary motor cortex; PFC = prefrontal cortex; Pre = pre-treatment; Post = post-treatment; TMS = transcranial magnetic stimulation; ** = p < 0.01, *** = p < 0.001.
Figure 3. Treatment-related changes in left frontopolar activation during reappraisal relate to improvements in PTSD hyperarousal symptoms and psychological well-being

Diagram at the top depicts the reappraisal contrast from the task, and the treatment arm \times time interaction effect in the left frontopolar cortex is rendered on an average brain surface below. Scatterplots depict relationships between average within-subject activation increases over time in left frontopolar cortex during reappraisal (pre-treatment subtracted from post-treatment) and within-subject changes (post-treatment subtracted from pre-treatment) in:

Panel A) hyperarousal symptoms assessed by the Clinician-Administered PTSD Scale; and

Panel B) Psychological Health subscale from the WHO Quality of Life BREF measure.

CAPS = Clinician-Administered PTSD Scale; Psych = psychological; WHO-QoL = WHO-Quality of Life BREF.
Figure 4. Prolonged exposure increases resting regional brain entropy of the same lateral frontopolar region displaying treatment-related change in functional activation during cognitive reappraisal.
Panel A depicts a brain map of the mean regional brain entropy distribution across the entire PTSD sample at baseline, with regions displaying regional entropy values greater than the whole brain mean displayed in red and those displaying regional entropy values lower than the whole brain mean displayed in blue. Image is overlaid on the Montreal Neurological Institute 152-person average T1 structural. Panel B depicts the reappraisal frontopolar activation effect rendered on an average brain surface. The line graph depicts the mean individual mixed model-derived predicted entropy values within each treatment arm and timepoint. Pre= pre-treatment; Post = post-treatment; ** = p < 0.01; *** = p < 0.001.
Table 1

Participant demographics and treatment outcome.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Immediate Treatment (N=36)</th>
<th>Patient Waitlist (N=30)</th>
<th>F/χ² (p value)</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean or N and % of Group (SD)</td>
<td>Mean or N and % of Group (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34.42 (10.23)</td>
<td>39.03 (10.35)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>14.72 (2.17)</td>
<td>15.17 (2.78)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (N=13; 36%)</td>
<td>Male (N=10; 33%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Female (N=23; 64%)</td>
<td>Female (N=20; 66%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WASI Full Scale IQ</td>
<td>109.03 (9.09)</td>
<td>112.81 (11.57)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SSRI/SNRI Meds</td>
<td>Sertraline (N=1; 3%)</td>
<td>Duloxetine (N=1; 3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Citalopram (N=2; 5%)</td>
<td>Sertraline (N=1; 3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MDD Diagnosis at Intake</td>
<td>Yes (N=18; 50%)</td>
<td>Yes (N=17; 57%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>No (N=18; 50%)</td>
<td>No (N=13; 43%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dropout</td>
<td>Completed (N=25; 69%)</td>
<td>Completed (N=26; 87%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Did not complete (N=11; 31%)</td>
<td>Did not complete (N=4; 13%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAPS Index Trauma</td>
<td>Natural disaster (N=3; 8%)</td>
<td>Natural disaster (N=1; 3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Physical Assault (N=9; 25%)</td>
<td>Physical assault (N=7; 23%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Assault w/ weapon (N=3; 8%)</td>
<td>Assault w/ weapon (N=2; 7%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Sexual assault (N=1; 3%)</td>
<td>Sexual assault (N=1; 3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Combat exposure (N=4; 11%)</td>
<td>Combat exposure (N=4; 13%)</td>
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<tr>
<td></td>
<td>Injury/illness/suffering (N=5; 14%)</td>
<td>Injury/illness/suffering (N=7; 23%)</td>
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<td>–</td>
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<tr>
<td>CAPS: Developmental Stage at Time of Index Trauma</td>
<td>Adult (N=20; 56%)</td>
<td>Adult (N=14; 47%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Teen (N=8; 22%)</td>
<td>Teen (N=11; 37%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Child (N=8; 22%)</td>
<td>Child (N=5; 17%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAPS: How Exposed to Index Trauma</td>
<td>Experienced (N=27; 75%)</td>
<td>Experienced (N=17; 57%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Witnessed (N=9; 25%)</td>
<td>Witnessed (N=13; 43%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAPS: Index Trauma Repeated?</td>
<td>No (N=25; 69%)</td>
<td>No (N=20; 66%)</td>
<td>–</td>
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</tr>
<tr>
<td></td>
<td>Yes (N=11; 31%)</td>
<td>Yes (N=10; 33%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAPS: Multiple Criterion A Events?</td>
<td>No (N=24; 66%)</td>
<td>No (N=20; 66%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes (N=12; 33%)</td>
<td>Yes (N=10; 33%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAPS Total</td>
<td>66.33 (15.17)</td>
<td>71.37 (14.99)</td>
<td>–</td>
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<tr>
<td>CAPS ReExp</td>
<td>17.53 (6.40)</td>
<td>18.73 (6.02)</td>
<td>–</td>
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</tr>
<tr>
<td>CAPS Avd</td>
<td>26.94 (7.86)</td>
<td>28.77 (8.89)</td>
<td>–</td>
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<tr>
<td>CAPS Hyper</td>
<td>21.86 (6.28)</td>
<td>23.87 (4.91)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BDI-II Total</td>
<td>23.69 (8.68)</td>
<td>23.17 (8.60)</td>
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<tr>
<td>PCL-C Total</td>
<td>56.16 (10.61)</td>
<td>57.36 (12.04)</td>
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<tr>
<td>PCL-C ReExp</td>
<td>16.47 (3.83)</td>
<td>16.29 (3.98)</td>
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<tr>
<td>PCL-C Avd</td>
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<td>18.04 (4.19)</td>
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<tr>
<td>WHO-QoL Physical</td>
<td>12.46 (2.99)</td>
<td>12.43 (3.11)</td>
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<tr>
<td>WHO-QoL Psych</td>
<td>10.04 (2.29)</td>
<td>10.83 (2.34)</td>
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<td>WHO-QoL SocRx</td>
<td>9.71 (4.06)</td>
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<td>WHO-QoL Envir</td>
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<td>12.79 (3.37)</td>
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<td>Post-Treatment Symptom/Quality of Life Measures</td>
<td>CAPS Total</td>
<td>29.60 (21.26)</td>
<td>64.23 (21.77)</td>
<td>32.99 (&lt; 0.001)***</td>
</tr>
<tr>
<td>Measure</td>
<td>Immediate Treatment (N=36)</td>
<td>Patient Waitlist (N=30)</td>
<td>F/χ² (p value)</td>
<td>Cohen's d</td>
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<td>Mean or N and % of Group (SD)</td>
<td>Mean or N and % of Group (SD)</td>
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<tr>
<td>CAPS ReExp</td>
<td>6.20 (6.49)</td>
<td>16.92 (7.97)</td>
<td>27.62 (&lt; 0.001) ***</td>
<td>1.48</td>
</tr>
<tr>
<td>CAPS Avd</td>
<td>10.60 (9.50)</td>
<td>24.50 (11.30)</td>
<td>22.51 (&lt; 0.001) ***</td>
<td>1.33</td>
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<tr>
<td>CAPS Hyper</td>
<td>12.80 (8.75)</td>
<td>22.81 (7.00)</td>
<td>20.43 (&lt; 0.001) ***</td>
<td>1.26</td>
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<tr>
<td>BDI-II Total</td>
<td>9.69 (7.77)</td>
<td>17.87 (9.27)</td>
<td>11.23 (0.002) **</td>
<td>0.96</td>
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<tr>
<td>PCL-C Total</td>
<td>26.13 (7.80)</td>
<td>49.00 (13.35)</td>
<td>45.55 (&lt; 0.001) ***</td>
<td>2.09</td>
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<tr>
<td>PCL-C ReExp</td>
<td>7.41 (2.63)</td>
<td>14.38 (5.14)</td>
<td>31.76 (&lt; 0.001) ***</td>
<td>1.71</td>
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<tr>
<td>PCL-C Avd</td>
<td>10.36 (3.36)</td>
<td>19.24 (6.32)</td>
<td>33.46 (&lt; 0.001) ***</td>
<td>1.75</td>
</tr>
<tr>
<td>PCL-C Hyper</td>
<td>8.41 (3.11)</td>
<td>15.38 (4.15)</td>
<td>39.05 (&lt; 0.001) ***</td>
<td>1.90</td>
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<tr>
<td>WHO-QoL Physical</td>
<td>14.63 (3.29)</td>
<td>12.65 (3.19)</td>
<td>4.09 (0.049) *</td>
<td>0.61</td>
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<tr>
<td>WHO-QoL Psych</td>
<td>13.19 (2.59)</td>
<td>11.94 (2.52)</td>
<td>2.63 (0.11)</td>
<td>0.49</td>
</tr>
<tr>
<td>WHO-QoL SocRx</td>
<td>11.83 (3.20)</td>
<td>10.73 (3.20)</td>
<td>1.29 (0.26)</td>
<td>0.34</td>
</tr>
<tr>
<td>WHO-QoL Environ</td>
<td>14.59 (2.42)</td>
<td>13.57 (2.99)</td>
<td>1.55 (0.22)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Avd = avoidance/numbing subscale; BDI-II = Beck Depression Inventory-II; CAPS = Clinician-Administered PTSD Scale for DSM-IV; Hyper = hyperarousal subscale; MDD = major depressive disorder; PCL = PTSD Checklist for DSM-IV Civilian Version; ReExp = reexperiencing subscale; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor; WASI = Wechsler Abbreviated Scale of Intelligence; WHO-QoL = WHO Quality of Life BREF Scale; WHO-QoL Physical = physical health subscale; WHO-QoL Psych = psychological health subscale; WHO-QoL SocRx = social relationships subscale; WHO-QoL Environ = environment subscale.

* p < 0.05;  
** p < 0.01;  
*** p < 0.001.