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Trying to name what doesn't change: Neural nonresponse to Cognitive Therapy for depression

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Original Article

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Abstract

Background. Theoretical models of neural mechanisms underlying Cognitive Behavior Therapy (CBT) for major depressive disorder (MDD) propose that psychotherapy changes neural functioning of prefrontal cortical structures associated with cognitive-control processes (DeRubeis, Siegle, & Hollon, 2008); however, MDD is persistent and characterized by long-lasting vulnerabilities to recurrence after intervention, suggesting that underlying neural mechanisms of MDD remain despite treatment. It follows that identification of treatment-resistant aberrant neural processes in MDD may inform clinical and research efforts targeting sustained remission. Thus, we sought to identify brain regions showing aberrant neural functioning in MDD that either (1) fail to exhibit substantive change (nonresponse) or (2) exhibit functional changes (response) following CBT.

Methods. To identify treatment-resistant neural processes (as well as neural processes exhibiting change after treatment), we collected functional magnetic resonance imaging (fMRI) data of MDD patients ($n = 58$) before and after CBT as well as never-depressed controls ($n = 35$) before and after a similar amount of time. We evaluated fMRI data using conjunction analyses, which utilized several contrast-based criteria to characterize brain regions showing both differences between patients and controls at baseline and nonresponse or response to CBT.

Results. Findings revealed nonresponse in a cerebellar region and response in prefrontal and parietal regions.

Conclusions. Results are consistent with prior theoretical models of CBT's direct effect on cortical regulatory processes but expand on them with identification of additional regions (and associated neural systems) of response and nonresponse to CBT.

Introduction

Psychotherapy is associated with neural changes in major depressive disorder (MDD) (Franklin, Carson, & Welch, 2016; Frewen, Dozois, & Lanius, 2008; Marwood, Wise, Perkins, & Cleare, 2018; Sankar et al., 2018); however, despite observed neural changes, the course of treated MDD remains chronic and impairing, featuring persistent symptoms and vulnerability to future depressive experiences (Judd et al., 1998; Kennedy, Abbott, & Paykel, 2004; Strege, Richey, & Siegle, 2022). The observation of neural changes does not inform potential neural disease-relevant mechanisms that are resistant to change (i.e. neural markers distinct to depressed individuals that persist despite intervention). Complementary knowledge of treatment-resistant processes could speed progress toward interventions that provide sustained remission, as these markers may equally represent plausible targets for intervention to the extent that they are both pathognomonic of depression and treatment-resistant. Accordingly, our objective was to identify brain regions (and related neural systems) of nonresponse as well as treatment change. We conducted functional magnetic resonance imaging (fMRI) whole-brain conjunction analyses in MDD patients before and after Cognitive Behavior Therapy (CBT) and never-depressed individuals at two time points equal in duration to MDD patients, in order to characterize brain regions that were both divergent from controls at baseline and either responsive to treatment or remained measurably stable.

Several theoretical models of CBT's influence on neural functioning suggest CBT targets cognitive-control processes and related cortical regions, that may relate to depressive symptomatology via regulatory influence of structures involved in more automatic threat- or salience-related reactivity (Clark & Beck, 2010; DeRubeis, Siegle, & Hollon, 2008; Goldapple et al., 2004; Mayberg, 2003). The proposed interactions between cognitive-control and salience-related neural systems are consistent with CBT theory and practice. According to cognitive theory, depression involves recurrent maladaptive information processing tendencies, such as prioritized attention for negative stimuli. CBT targets maladaptive cognitive biases

with therapeutic exercises, during which the individual practices examining the accuracy and utility of their thoughts and generating more realistic and adaptive thoughts (Beck, 2008; Clark & Beck, 2010). Through repeated exercises, one develops skills at recognizing, challenging, and reducing reactivity to negative thinking patterns, thus strengthening cognitive-control abilities during negative emotional states. The theorized cognitive-control neural systems affected by CBT involve prefrontal regions (e.g. lateral/dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex, and orbitofrontal cortex), and may also involve subregions of the anterior cingulate cortex (ACC), such as the subgenual ACC (sgACC); however, theories differ in interpretation of ACC involvement, with some potential for salience-related or salience-moderating properties (Clark & Beck, 2010). Subcortical structures in these models primarily include the amygdala and/or hippocampus, viewed as salience-related and associated with strong emotional experiences. Thus, theoretical frameworks suggest CBT may affect subcortical salience functioning as an indirect effect of increased cortical regulation.

Research on neural effects of CBT in depression provides only partial support for cortical regulation models. One review observed CBT and interpersonal psychotherapy for depression primarily affected prefrontal (dorsolateral, ventrolateral, and medial) and cingulate (anterior and posterior) cortical functioning (Frewen et al., 2008), whereas a more recent review of pre- *v.* post-CBT neuroimaging studies in depression found that the ACC (multiple subregions) most consistently showed change, instead of the DLPFC or other prefrontal regions. They also reported change (although less frequently) of subcortical regions associated with salience-related processes [e.g. amygdala and hippocampus (Franklin et al., 2016; Zheng et al., 2017)]. Functional change of the ACC (rostral) after psychotherapy (CBT, behavioral activation, and psychodynamic) for depression was also reported by a recent meta-analysis (Sankar et al., 2018). Another recent meta-analysis that also collapsed across psychotherapy types in depression and anxiety similarly found only partial support for prior theories, reporting most robust changes in anterior cingulate and prefrontal cortical regions as well as the insula (Marwood et al., 2018). Mixed findings in the literature may reflect heterogeneous study methodologies (e.g. task type, neuroimaging modality, and sample characteristics) as well as heterogeneous review methodologies (e.g. treatment and sample inclusion criteria), suggesting CBT changes neural functioning, but its effects may be more nuanced than indicated by prior theoretical models.

Despite observed neural changes, depressive symptoms and vulnerabilities persist in MDD after treatment. Long-term intervention follow-up research suggests that the course of MDD involves persistent (most often low-grade) depressive symptoms (Judd et al., 1998; Kennedy et al., 2004; Strege et al., 2022). Even individuals considered 'remitted' often exhibit at least one residual symptom, with some estimates indicating over 90% of remitted patients (Nierenberg et al., 2010). Common residual depressive symptoms after treatment consist of sleep disturbance and fatigue (Conradi, Ormel, & de Jonge, 2011; McClintock et al., 2011; Nierenberg et al., 2010; Romera et al., 2013; Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010), sad mood (McClintock et al., 2011; Romera et al., 2013; Taylor et al., 2010), and concentration difficulties (Conradi et al., 2011; McClintock et al., 2011). Individuals with MDD also experience high rates of relapse and recurrence, with some estimates over 90% when followed for 25 years (Gotlib & Hammen, 2008), suggesting that even during periods of reduced symptoms, vulnerability for more severe psychopathology persists throughout the lifespan. The persistence of symptoms as well as risk of relapse/recurrence suggests underlying neurobiological mechanisms of depression maintenance may continue to persist despite treatment.

In consideration of prior theory and supporting research on CBT's effects on cognitive-control and salience-related neural systems (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003), we used a task with salient negative emotional words and prompts asking participants to rate the self-relevance of words, to encourage elaborative processing of emotional stimuli (Siegle, Granholm, Ingram, & Matt, 2001). We examined indices of sustained neural reactivity to capture disturbances in cognitive control (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). We hypothesized functional changes of the DLPFC following CBT, as it is the most consistently referenced cognitive control prefrontal region of prior theories (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003) and because it is considered a major hub of a brain network commonly associated with cognitive control, the executive network (Menon, 2011); however, with mixed findings in the literature, we may not observe DLPFC functional change. The literature also suggests that we may observe functional changes in other regions as well, e.g. ACC subregions. Given the novelty of our approach for identifying nonresponse, it is unclear from theory and literature which regions will show functional nonresponse. With theory stating CBT affects cognitive control and cortical regulation, we anticipate that nonresponse will not include prefrontal cortical regions. Nonresponse may include salience-related subcortical regions, as CBT is theorized not to directly affect subcortical reactivity (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003); however, findings of subcortical functional changes in the literature also suggest the potential for this to not be the case (Franklin et al., 2016).

Although the study focus was on processing of negative emotional stimuli, examining reactivity to other valence types would inform whether observed neural changes and nonresponse findings are specific to negative emotions or more generalized. Thus, to assess valence specificity, we conducted exploratory analyses on positive and neutral word trials also included in the task.

To identify neural systems of nonresponse to therapy and therapy-related change mechanisms, we assessed individuals with MDD ($n = 58$) and never-depressed controls ($n = 35$) at two time points, before and after CBT for individuals with MDD and before and after a comparable amount of time for never-depressed controls. We used conjunction analyses to characterize areas of nonresponse (showing differences between MDD patients and never-depressed controls prior to treatment and also showing no practical change with treatment). In an additional exploratory analysis for biomarkers, we assessed whether any of the nonresponse regions were also prognostic of treatment outcome. For assessing change mechanisms, we considered remediation of existing aberrant functioning as well as novel compensatory developments. As an exploratory aim, we assessed areas showing remediation-based change for normalization, comparing post-treatment MDD patients and never-depressed controls.

Consistent with the aim of examining nonresponse and response to therapy in the brain, we also conducted region-of-interest (ROI) analyses with regions associated with cognitive-control and salience-related neural systems. We chose

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the DLPFC (cognitive control), amygdala (salience related), and sgACC (potential moderator of neural processes) as representative of these brain systems because they were consistently referenced across theoretical models (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003), and they were also associated with related neural networks (e.g. executive, (Menon, 2011); salience, (Zheng et al., 2017)) or have shown functional connections with regions of these networks (Disner, Beevers, Haigh, & Beck, 2011; Drevets, Savitz, & Trimble, 2008). However, other ROIs (e.g. other prefrontal or anterior cingulate subregions, the insula, and the hippocampus) also could have been included as representative of networks. Our objective was not to test all empirically-supported regions but rather to get a supplementary estimate of neural processes of interest (cognitive control and salience related).

Method

Participants

Participants were adults ($n = 58$) with MDD who received CBT as part of prior clinical trials (MH58356; PI: Thase, MH58397; PI: Jarrett; MH074807; PI: Siegle) and underwent fMRI tasks before and after treatment. Participants also included never-depressed controls ($n = 35$) from MH074807, assessed at two timepoints of comparable duration to those of the MDD group. The CBT participants completed Cognitive Therapy (Beck, 1979) protocols that consisted of 16–20 sessions. See our prior publication (Siegle et al., 2012) for additional information regarding the therapy protocol. Participants met MDD DSM-IV diagnostic criteria via a structured clinical interview (SCID-IV; First, Spitzer, Gibbon, & Williams, 1996) and also scored at least 14 on the Hamilton Rating Scale for Depression (Hamilton, 1960) prior to the start of treatment. In interest of contrasting pre- and post-assessments, analyses were restricted to participants who had fMRI task data for both timepoints (Consort diagram, Supplement 1). Sample demographics and clinical characteristics (Supplement 2) show that depressed individuals and never-depressed controls did not differ on demographic variables but differed on self-reported depression symptoms.

fMRI task and data preparation

We used a modified personal relevance rating task (PRRT) (Siegle, Carter, & Thase, 2006; Siegle et al., 2007; Siegle et al., 2012), during which trials ($N = 60$) began with a fixation cue (row of X's with prongs around center X), presented for one second. A word (normed or idiographic) of positive, negative, or neutral valence appeared after the fixation cue for 200 ms. Analyses were of negative word trials. After each word, a row of X's appeared and stayed on the screen for 10.8 s. Each trial contained prompt asking participants to push a button indicating perceived self-relevance (relevant, somewhat relevant, not relevant) of the word.

Our fMRI processing methods were consistent with our prior publication (Siegle et al., 2012). Processing was done with locally developed NeuroImaging Software and AFNI. We applied slice-time correction, motion correction (AFNI 3dVolReg), linear detrending to eliminate scanner drift, and voxelwise winsorization of outliers. We converted data to percent-change from that voxel's median within the run. Data were additionally temporally smoothed (7-point Gaussian filter), cross-registered to the Colin-27 MNI with AIR's 32-parameter non-linear warp (Woods, Mazziotta, & Cherry, 1993), and spatially smoothed (6-mm full width half maximum), and we normalized time series across scanners.

Contrast images were sustained neural reactivity to negative words, calculated as the difference between the mean of later (4th–7th) images for each negative-word trial and that trial's first image, acquired during the presentation of the trial's fixation cue (prior to the negative word). We did not use neutral or positive words for contrasts due to prior research showing that neutral and positive stimuli may not actually be neutral and positive for depressed individuals (Epstein et al., 2006). For example, a study looking at neural reactivity to emotional words in depressed individuals found that depressed individuals do not show neural reactivity of the ventral striatum, a reward-related region, in response to positive words. In the same study, depressed individuals actually showed greater neural reactivity of the left amygdala to neutral words than negative words (Epstein et al., 2006). These neuroimaging findings are consistent with clinical observations and behavioral data, e.g. negative interpretations of neutral experiences when depressed (Hindash & Amir, 2012), as well as prior self-report research, e.g. difficulty sustaining positive affect in response to positive scripts (Horner et al., 2014).

Conjunction analyses

To identify brain areas and related neural systems of treatment nonresponse and change mechanisms, we conducted several voxelwise whole-brain conjunction analyses (Friston 1999; Friston 2005) in which we interpreted our hypotheses as supported when all a priori criteria were met across participants. One set of contrasts probed differences between the MDD group and never-depressed controls (voxels showing aberrant neural functioning). Other contrasts probed the effect of time, such as pre- and post-treatment for the MDD group (voxels showing change or absence of change after treatment). We calculated voxelwise Cohen's d (henceforth, d; details in Supplement 3) for each contrast image and used these effect size estimates to test the a priori criteria for establishing conjunction between images at a given voxel. Reliance on clinically significant or demonstrably null effects across all tests within the conjunction obviates common concerns regarding the interpretability of conjunction analyses in fMRI (Nichols, Brett, Andersson, Wager, & Poline, 2005) without requiring significance thresholds suggested to be overly conservative (Friston, 2005).

To test a priori criteria, we used effect size cutoffs to determine a practical absence of effect (nonresponse) or a minimum treatment effect that was still clinically-relevant (response). In light of fMRI effect size literature and supporting Human Connectome Project data reporting smaller effect size estimates (Cremers, Wager, & Yarkoni, 2017; Poldrack et al., 2017), we anticipated 'response' to be a modest effect at best, a minimal yet clinically relevant effect ($d > 0.24$) (Cuijpers, Turner, Koole, van Dijke, & Smit, 2014), whereas we viewed nonresponse as a practical absence of effect ($d < 0.05$), a threshold considered to reflect approximately 98% overlap between samples (Grice & Barrett, 2014). A practical absence of effect ($d < 0.05$) is represented as '$=$' below. A clinically relevant effect ($d > 0.24$) is represented as '$\neq$' below. Pre/post represents prior to or after treatment for depressed participants or a comparable amount of time for control participants. Conjunction 'and' operations are represented

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Table 1. Defining change mechanism and nonresponse

Voxel characteristic	Group and time comparisons		
	Pre-treatment depressed sample and control sample at time 1	Depressed sample before and after treatment	Depressed sample (difference between pre and post) and control sample (difference between time 1 and 2) (i.e. Group × Time interaction)
Change mechanism			
Remediation	✓	✓	✓
Compensatory	**X**	✓	✓
Nonresponse	✓	**X**	

Note. Check mark indicates samples differed ($d > 0.24$) at the voxel; X indicates a practical absence of effect between samples ($d < 0.05$) at the voxel.

as '*' below (tabular presentation of formulae for change mechanisms and nonresponse, Table 1).

Formulae

Defining nonresponse. We calculated nonresponse as: (pre-control ≠ pre-depressed) * (pre-depressed = post-depressed).

Defining biomarker. Biomarkers were areas of nonresponse that also were prognostic of treatment outcome, calculated as voxelwise R^2 change from adding depression symptoms (Beck Depression Inventory (BDI-II) residuals) to a scanner-only whole-brain regression.

Defining change mechanisms. We considered two potential change mechanisms, (1) remediation-based and (2) compensatory. We defined remediation-based change as: (pre-control ≠ pre-depressed) * (pre-depressed ≠ post-depressed) * (pre-post control ≠ pre-post depressed). We defined compensatory change as: (pre-control = pre-depressed) * (pre-control ≠ post-depressed) * (pre-post control ≠ pre-post depressed).

Defining normalization. We considered normalization regions to be areas that exhibited change mechanism qualities (defined above) and also showed comparable neural reactivity between post-treatment depressed patients and never-depressed controls, as suggested by voxelwise d estimates for the post-control *v.* post-depressed contrast.

Cluster thresholding

To control for Type I error, AFNI's 3dFWHMx and 3dClustSim's ACF model provided cluster size for cluster thresholding. 3dFWHMx's spatial autocorrelation function provided the noise smoothness values for 3dClustSim (post 2015 smoothing correction). We used the conjunctive p for the voxel p values (<0.005 for change mechanism and <0.02 for nonresponse), and we set the significance threshold to $p < 0.05$. We defined conjunctive p as the product of p values for each contrast in the conjunction analysis, e.g. change mechanism conjunctive p corresponds to: (p value for d1 > 0.24) * (p value for d2 > 0.24) * (p value for d3 > 0.24). 3dClustSim's ACF model provided cluster thresholds of >93 voxels for change mechanisms and >297 voxels for nonresponse for whole brain results.

A priori regions of interest

For assessing whether a priori ROIs (bilateral DLPFC, sgACC, and amygdala), representative of cognitive-control and salience-related neural systems, met criteria for change mechanism or nonresponse, we applied region masks to the results of the whole-brain voxelwise conjunction analyses. To determine appropriate cluster thresholds, we submitted each region mask to the 3dclustim function and followed the aforementioned cluster thresholding approach.

Results

Nonresponse

One vermis-centered cluster comprising primarily cerebellar regions met contrast criteria for nonresponse and survived cluster-thresholding (Table 2; Fig. 1). MDD patients showed reduced activation of the nonresponse cluster relative to control participants, which did not increase after CBT (Fig. 2*a*).

Biomarkers

R^2 changes from incorporating depression symptom residuals (BDI-II) to a whole-brain regression (neural reactivity regressed on site) ranged from 0 to 0.15 in the non-response cluster, suggesting minimal prognostic value (Fig. 1).

Change mechanisms

Three clusters met a priori contrast criteria for a remediation-based change mechanism and survived cluster-thresholding (Table 2; Fig. 3). MDD patients exhibited less reactivity to negative stimuli in prefrontal and parietal cortical change mechanism clusters relative to controls, which increased after CBT for the MDD group (Fig. 2*b*). No areas that met contrast criteria for a compensatory change mechanism survived cluster-thresholding.

Table 2. Coordinates for clusters of non-response and change mechanisms

Centroid location	Size (mm^3)	*x*	*y*	*z*
Non-response				
Cerebellar vermis	38 031.25	2	−63	−19
Change mechanism				
Right superior frontal gyrus	22 312.50	15	30	39
Right precuneus	7937.50	5	−69	36
Right angular gyrus	5250	47	−64	43

Note. Coordinates are cluster centroids reported in MNI space.

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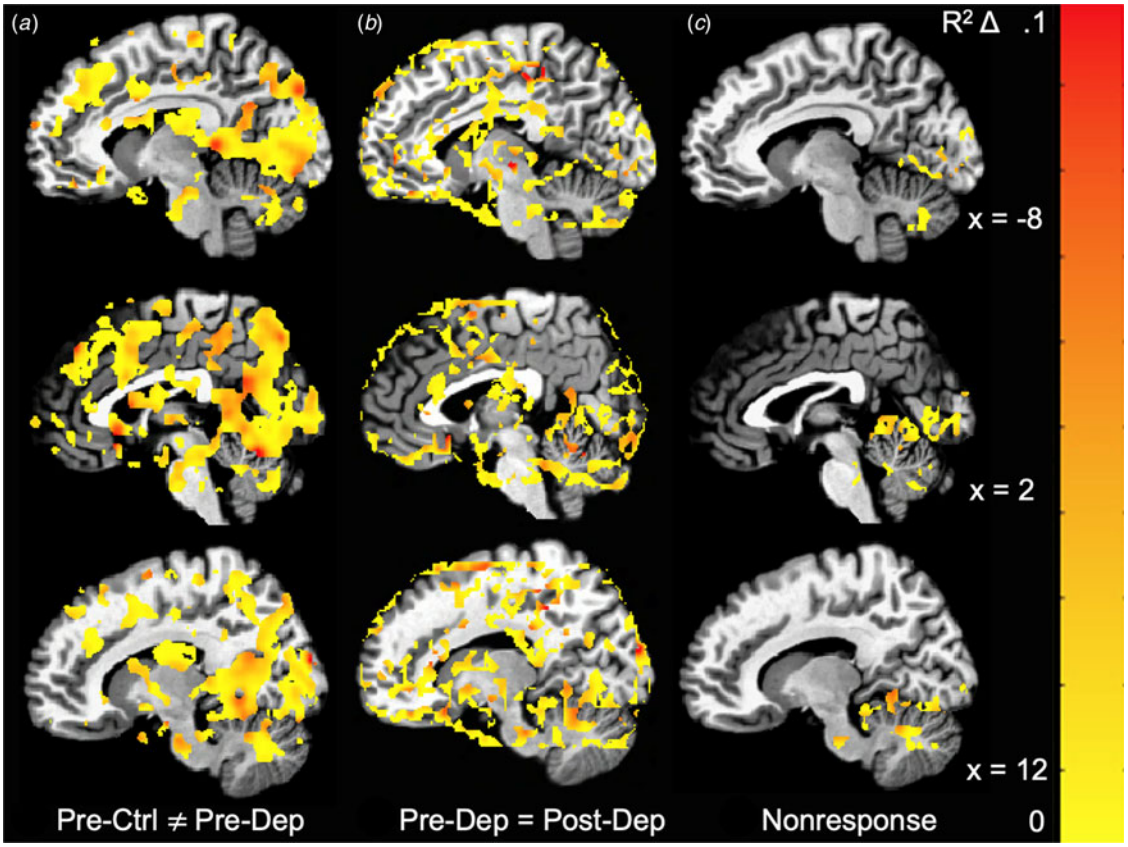

Fig. 1. Treatment nonresponse cluster.
Note. (a) Pre-Ctrl ≠ Pre-Dep represents brain areas where control participants differed ($d > 0.24$) from depressed patients prior to treatment. (b) Pre-Dep = Post-Dep represents brain areas where a practical absence of effect ($d < 0.05$) was observed when comparing depressed patients prior to and after treatment. (c) Nonresponse represents areas that met both A and B effect size criteria and survived cluster thresholding [>297 voxels (AFNI's NN3, 2-sided)].
Coloring represents whole-brain regression R2 Δ values on neural reactivity to negative words at the pre-treatment scan as predicted by residual BDI-II scores above and beyond scanner (i.e. extent to which the region acts as a predictor of treatment response); the overall low values suggest non-response regions are not associated with either clinical change or change in activity in association with treatment.

Normalization

For brain regions suggesting a remediation-based change mechanism, some portions of clusters exhibited normalization following CBT; effect sizes (d) ranged from 0 to 0.5 for differences between post-treatment depressed patients (Fig. 3).

A priori regions of interest

The application of nonresponse and change mechanism a priori criteria to the bilateral, functionally defined DLPFC (Siegle et al., 2012) resulted in separate clusters within the DLPFC that exhibit change mechanism or nonresponse qualities (Fig. 4). The change mechanism cluster (3187.50 mm^3) within the DLPFC was centered at 33, 24, 39 (MNI), and the nonresponse cluster (1718.75 mm^3) within the DLPFC was centered at 45, 26, 31 (MNI). Both cluster centroids were in the middle frontal gyrus. The application of nonresponse and change mechanism criteria to the bilateral sgACC and amygdala resulted in small clusters (~2 voxels) within a priori regions that did not survive cluster correction.

Discussion

The study objective was to identify brain areas (in context of related neural systems) resistant to as well as responsive to change following CBT. Exploratory aims were to evaluate the extent to which identified nonresponse regions acted as biomarkers (prognostic of treatment outcome) and the extent to which change mechanism regions normalized (comparable after treatment to never-depressed controls). Conjunction analyses resulted in one vermis-centered cluster that differed between depressed and control participants and did not change following CBT, as well as three prefrontal and parietal clusters that changed after treatment. Smaller observed biomarker and normalization effect sizes suggest the cerebellar nonresponse region shows minimal prognostic potential for CBT, and subregions of prefrontal and parietal change mechanism regions appear to normalize after CBT. Analyses specific to regions often-cited in related theoretical models and associated with neural systems of interest (e.g. DLPFC, sgACC, amygdala) yielded subregions of the DLPFC meeting criteria for nonresponse or change mechanism.

Study findings were largely consistent with prior theoretical models of cognitive regulatory processes (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003), yet expanded on prior work with consideration of additional regions/subregions. We found functional DLPFC subregions that showed different responses (change mechanism *v.* nonresponse) to CBT. This observation could be considered consistent with prior work suggesting functional subdivisions of the DLPFC exist (Cieslik et al., 2012) and may be differentially associated with

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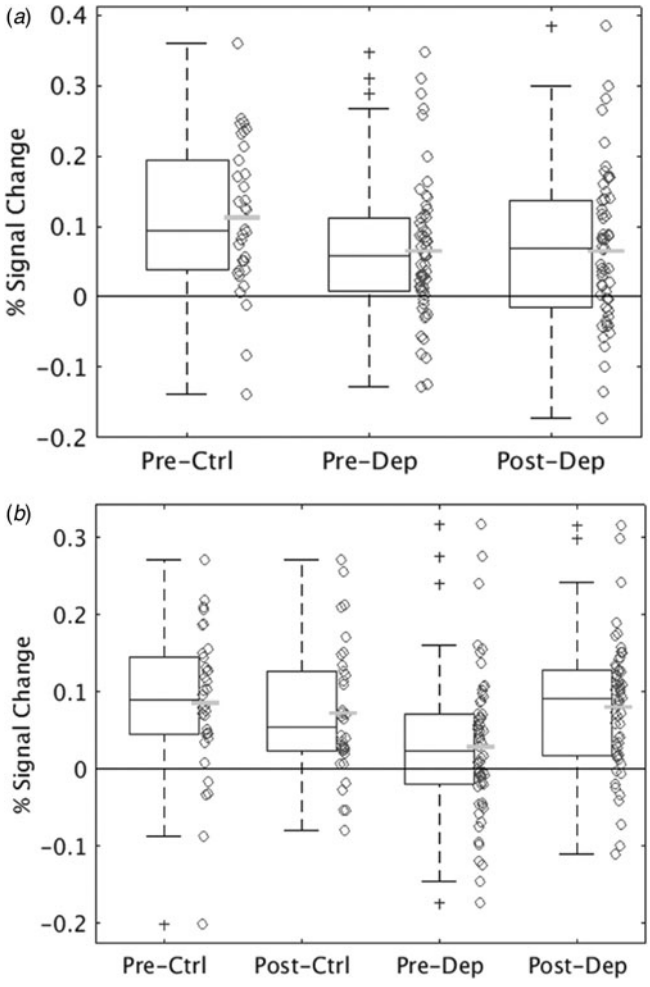

Fig. 2. Box and scatter plots for individual averages of nonresponse and response clusters.
Note. (a) Individual mean reactivity averages of the nonresponse cluster for control participants (Pre-Ctrl) and MDD patients prior to and after CBT (Pre-Dep, Post-Dep); (b) Individual mean reactivity averages of the change mechanism regions (all clusters) for pre and post assessments for both control participants (Pre-Ctrl, Post-Ctrl) and MDD patients (Pre-Dep, Post-Dep). Gray lines represent mean, and black lines represent median.

treatment (Rosen et al., 2021), or it could be consistent with a partial response model in which DLPFC functioning was somewhat, but incompletely affected by CBT. The change mechanism DLPFC subregion was more ventral than the nonresponse region and had a portion of the cluster extending farther in the anterior direction, thus appearing more consistent with the meta-analytically derived anterior-ventral subregion (Cieslik et al., 2012). The anterior-ventral subregion has shown stronger association with the ACC (Cieslik et al., 2012), subregions of which have shown strong connections with subcortical salience-related structures (Disner et al., 2011; Drevets et al., 2008), suggesting this DLPFC subregion's potential influence of salience-driven processes. In support of this division, targeting the DLPFC subregion showing greater connectivity to the sgACC is associated with better depression response to transcranial magnetic stimulation (TMS) (Rosen et al., 2021).

Additional change mechanism findings of increased activation of the precuneus and angular gyrus suggest that the cognitive-control regulation processes of CBT may also involve functional changes of default mode network (DMN) regions (Raichle, 2015). A wealth of research suggests aberrant DMN functioning in MDD (Hamilton et al., 2015; Scalabrini et al., 2020; Williams, 2016), as it is believed to contribute to depression symptoms and disease maintenance features, e.g. rumination (Zhou et al., 2020). Often-observed inverse correlations of DMN regions with the task network would not predict this observation, but it is consistent with more nuanced conceptions of DMN and prefrontal interactions, with region activity and functional connectivity contingent on task requirement and stimulus type (Beaty, Benedek, Silvia, & Schacter, 2016; Bluhm et al., 2011; Hearne, Cocchi, Zalesky, & Mattingley, 2015; Mayer, Roebroeck, Maurer, & Linden, 2010; Piccoli et al., 2015; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Sreenivas, Boehm, & Linden, 2012). For example, goal-directed tasks that involve internally focused processes (e.g. self-referential), show activity of and positive functional associations between DMN and prefrontal regions, with greater functional coupling of DMN and prefrontal regions associated with optimal performance (Beaty et al., 2016; Konishi, McLaren, Engen, & Smallwood, 2015; Straub et al., 2015). The finding of increased activity of key DMN regions and the task network during a self-relevance rating task suggests that CBT's proposed mechanisms of enhanced cognitive control may also involve dynamic cooperation of neural systems (task-based and default mode), necessary for flexible allocation of cognitive resources (Cocchi, Zalesky, Fornito, & Mattingley, 2013; Zabelina & Andrews-Hanna, 2016).

Areas that did not show change in response to CBT, but were different in depressed and never-depressed individuals before treatment, may give particular insight into why depression symptoms return, despite remission in therapy, as they could represent ongoing vulnerabilities to recurrence. In particular, the vermis (and cerebellum more broadly) is largely not referenced in popular theoretical models of CBT (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003); however, there is substantial literature on its involvement in emotion processes (Adamaszek et al., 2017; Pierce & Péron, 2020; Sacchetti, Scelfo, & Strata, 2009; Schmahmann, 2010; Strata, 2015) and MDD (Villanueva, 2012). The vermis, is specifically referred to as a key region of cerebellar affective processing (Baumann & Mattingley, 2012; Pierce & Péron, 2020), the 'limbic cerebellum' (Stoodley & Schmahmann, 2010). It is theorized to contribute to the detection of a stimulus' emotional relevance by modulating reactivity of limbic structures within the salience network (Habas et al., 2009), potentially suggesting that while CBT targets cortical regulators of the salience network, it may not address other regulators.

The vermis is also implicated in a wide variety of body-relevant processing such as postural control (Colnaghi, Honeine, Sozzi, & Schieppati, 2017) and expression of emotion in the body (Sokolov et al., 2020). Increasing data suggests profound roles for how people relate to their body in emotional information processing (Colombetti, 2014; Damasio, 1999; De Gelder, 2016; van der Kolk, 1994; Wassmann, 2010), particularly with regard to posture (Dael, Mortillaro, & Scherer, 2012; Gilbert, Martin, & Coulson, 2011; Strata, 2015). Potentially, CBT, especially CT focuses on cognitions (the mind), leaving vulnerabilities to continued symptomatology in the arena of mind/body relationships, and the body's role in emotion. This theory would suggest that mind-body interventions such as yoga, which affect the cerebellum (van Aalst et al., 2020, 2021), could be of interest as adjuncts to CBT.

Other potentially adjunctive interventions (e.g. antidepressant medications, exercise, neuromodulation) also demonstrate functional

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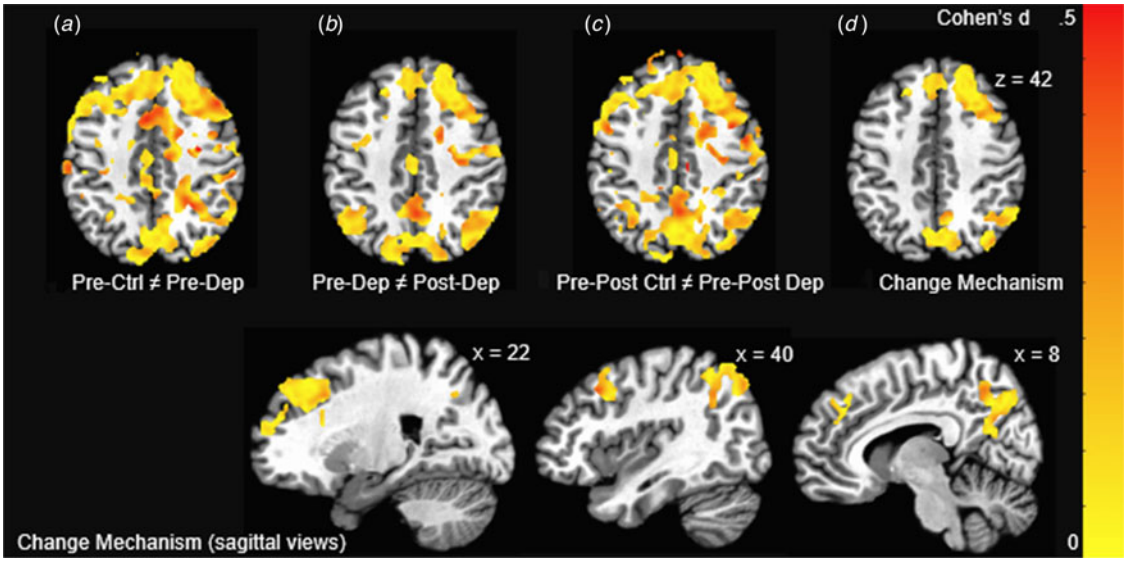

Fig. 3. Treatment response (change mechanism) clusters.
Note. (a) Pre-Ctrl ≠ Pre-Dep represents brain areas where control participants differed ($d > 0.24$) from depressed patients prior to treatment. (b) Pre-Dep ≠ Post-Dep represents brain areas where depressed patients prior to and after treatment differed ($d > 0.24$). (c) Pre-Post Ctrl ≠ Pre-Post Dep represents brain areas where pre-post estimates differed ($d > 0.24$) between control participants and depressed patients. (d) Change Mechanism represents brain areas that met all prior criteria (a, b, c) and survived cluster thresholding (>93 voxels [AFNI's NN3, 2-sided]). Coloring represents d estimates (contrast of post-treatment depressed patients and never-depressed control participants), showing some instances in which effect sizes suggest normalization occurs

cerebellar change. In an MDD intervention study, increased cerebellar activity was identified as a unique effect of paroxetine, an effect absent from the CBT comparison group (Goldapple et al., 2004). Several imaging studies examining antidepressant medication effects in MDD samples have also found functional changes of the cerebellum (Cullen et al., 2016; Delaveau et al., 2011; Frodl et al., 2011; Fu et al., 2004, 2007; Mayberg et al., 2000). In addition to antidepressant medication, there is preliminary support of repeated aerobic exercise altering cerebellar functioning (Leddy et al., 2013; Won et al., 2021). A more targeted cerebellar intervention may involve neuromodulation via electrical or magnetic stimulation. For an early example of cerebellar stimulation, patients of heterogeneous treatment-resistant psychiatric conditions saw symptom improvements following implantation of a vermis pacemaker (Heath, 1977). Less-invasive options for modulating cerebellar functioning include TMS and transcranial direct current stimulation (tDCS). For example, repetitive TMS of the vermis has been found to improve depressive symptoms in schizophrenia relative to a sham condition (Garg, Sinha, Tikka, Mishra, & Goyal, 2016), and tDCS of the cerebellum has been shown to enhance emotion recognition and improve symptoms of treatment-resistant obsessive-compulsive disorder when combined with SSRIs (Ferrucci et al., 2012).

Study findings were regarding negative emotional stimuli, but task design allowed for exploratory analyses of valence type. With a negative emotion emphasis of prior theoretical frameworks (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003), as well as a study Cognitive Therapy protocol consisting primarily of cognitive restructuring of beliefs around negative information (instead of focusing on savoring, behavioral activation, or other techniques for increasing positive affect), our primary questions regarded neural reactivity to negative words. That said, the task's positive and neutral word trials provided the ability to examine valence specificity. Thus, we conducted exploratory parallel analyses for positive and neutral trials (Supplements 4 and 5, respectively) as well as a mixed-effects analysis including all trial types (Supplement 6). Parallel analyses for positive and neutral words showed that some effects may be unique to negative emotional stimuli (e.g. prefrontal change mechanism cluster), whereas other effects show some similarities between valence types (e.g. negative and neutral words for the nonresponse region). The absence of any change mechanism cluster for positive words may reflect the negative emotion focus of the treatment protocol or the complicated nature of assessing positive emotion processing in depression (e.g. positive stimuli being interpreted as negative or neutral for some depressed individuals (Horner et al., 2014)). The partial overlap between negative and neutral trials for nonresponse is consistent with literature showing neutral stimuli may actually be processed as negative by depressed individuals (Epstein et al., 2006). The more widespread nonresponse findings for neutral words could be due to neutral words having more interpretative variability in association with depression, in contrast to negative words, which are thought to be 'negative' for all people, thus perhaps processed more similarly. Valence-related general linear tests within a mixed-effects analysis illustrate other potential valence specific and general effects, e.g. some overlapping regions and some specific regions within the medial and lateral prefrontal cortex for positive *v.* negative words for related conjunction criteria (online Supplementary Fig. S6.2). These regions are not functionally distinct enough in the literature to allow easy functional interpretation, but they support the potential usefulness of using multiple types of stimuli in future work that aims to elucidate nonresponse. This perspective is bolstered by the substantial literature on positive emotions in depression (Carl, Soskin, Kerns, & Barlow, 2013; Keren et al., 2018; Vanderlind, Millgram, Baskin-Sommers, Clark, & Joormann, 2020), including prior neuroimaging studies examining neural reactivity to rewarding/positive stimuli within the context of CBT for depression (Chuang et al., 2016; Dichter et al., 2009; Forbes et al., 2010; Hanuka et al., 2022; Ritchey, Dolcos,

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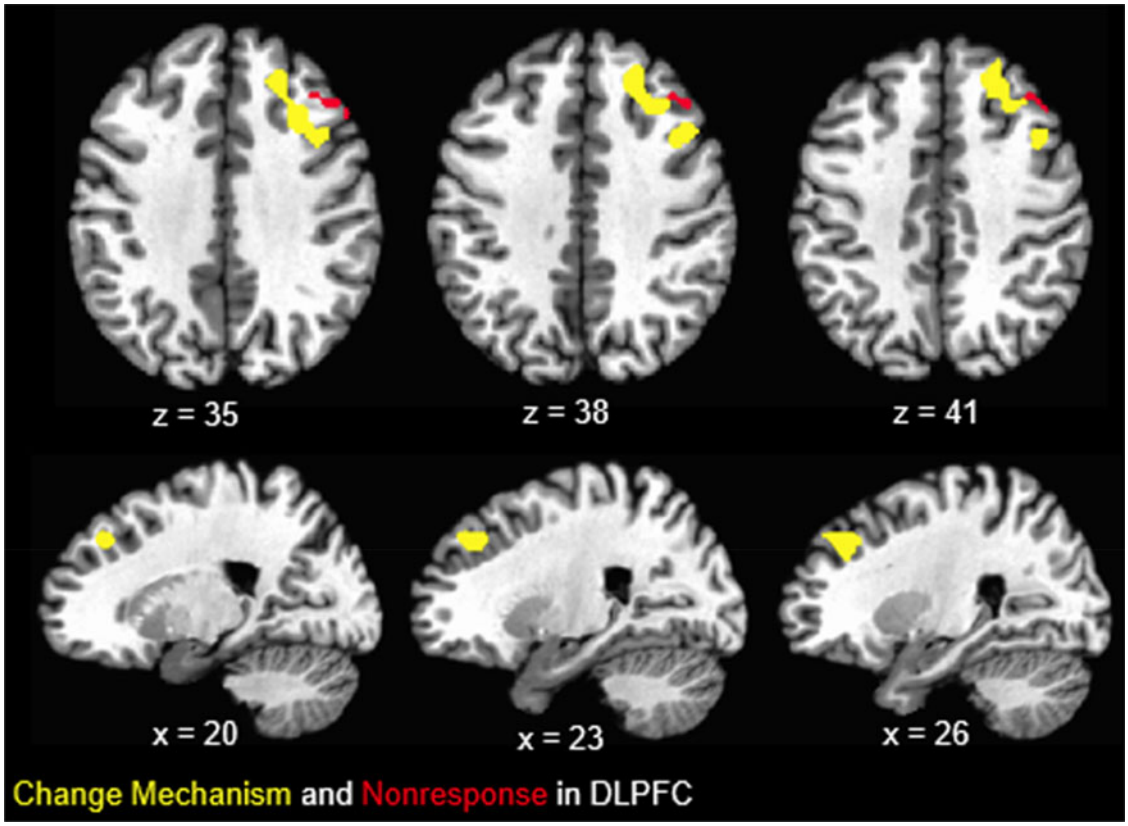

Fig. 4. Clusters within the dorsolateral prefrontal cortex.
Note. The yellow cluster represents a subregion within the dorsolateral prefrontal cortex that met criteria for a change mechanism [pre-depressed ≠ pre-control * pre-depressed ≠ post-depressed * pre-post depressed ≠ pre-post control (≠ corresponds to $d > 0.24$)] and survived cluster correction (>19 voxels). The red cluster represents a subregion within the dorsolateral prefrontal cortex that met criteria for nonresponse [pre-depressed ≠ pre-control * pre-depressed = post-depressed (≠ corresponds to $d > 0.24$ and = corresponds to $d < 0.05$)] and met cluster correction (>43 voxels).

Eddington, Strauman, & Cabeza, 2011; Straub et al., 2015). These studies show some overlapping regions with negative emotion research (e.g. prefrontal and anterior cingulate cortical regions), but they also show distinct regions related to reward processing in the brain, e.g. ventral striatum.

The current study has multiple methodological limitations. Results are contingent on a priori effect size thresholds for 'response' and 'nonresponse,' and it is unclear whether the thresholds selected are optimal. Thresholds were defined with the intent of representing a minimal effect that was still clinically-relevant (Cuijpers et al., 2014) and a practical absence of effect (~98% group overlap (Grice & Barrett, 2014)); however, there is a literature lacuna regarding appropriate effect size thresholds for neural changes following MDD treatment, making the decision of optimal thresholds particularly challenging. In addition, despite the study's relatively large sample for task-based neuroimaging and treatment studies, a larger replication sample would allow confidence in the replicability of findings, with differentiation of potentially responsive subtypes (Beijers, Wardenaar, van Loo, & Schoevers, 2019; Price et al., 2017), and potentially better generalization to the larger depressed population. Neural reactivity was measured in response to negative words and prompts of self-relevance, which may not capture the complexities of real-world stressors of living with MDD; replication of the observed associations with other tasks may help to address issues of generalization.

Study limitations notwithstanding, findings provide additional support for and expand upon prior theory of neural mechanisms associated with CBT (Clark & Beck, 2010; DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003). The direct effect of CBT on cortical regulatory processes was largely supported. Study results added to the literature with the suggestion of different effects of CBT on functional subdivisions of the DLPFC (DeRubeis et al., 2008). Increased DMN reactivity could highlight the role of CBT in changing the nature of self-relevant processing, e.g. allowing more functional task-related self-awareness. The vermis (and cerebellum more broadly) exhibited aberrant neural reactivity to negative emotional stimuli in MDD and did not respond to CBT, potentially suggesting that CBT's direct effects on neural reactivity are specific to cortical regulatory regions. Accordingly, aberrant cerebellar functioning may serve as a target for future depression intervention research aimed at addressing neurobiological vulnerabilities that persist in treated MDD.

The study finding of nonresponse of the vermis to CBT also speaks to a broader concerning message, that aberrant neural functioning persists in treated-MDD, even when symptoms improve, making a person with a history of MDD neurally vulnerable for a return to depressive experiences. Persistent vulnerability to depression is also supported by clinical long-term (9–14 years) follow-up data that we collected on a subset of this sample. When assessing cross-year, cross-severity depression symptom estimates in the years after CBT, every individual eventually experienced a return to symptoms. Moreover, the near-universal trajectory was persistent symptoms for several years with persistent quality of life deficits across multiple life domains, which is consistent

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with other depressed samples and similar follow-up methods (Judd et al., 1998; Kennedy et al., 2004). The neuroimaging nonresponse finding from this study, within the context of bleak clinical outcomes, supports a conceptualization of MDD that is truly chronic, even with rigorously-implemented, gold-standard evidence-based treatment.

In consideration of persistent neural vulnerabilities in MDD, several avenues for future research and clinical applications follow. Further exploring nonresponse in the brain following CBT, with different tasks and/or neuroimaging measures, would be helpful to better understand neural vulnerabilities that remain. In addition, expanding this research to examine nonresponse following other treatment modalities, such as antidepressant medications, other forms of psychotherapy, or recent alternative interventions (e.g. ketamine), would be important. We anticipate that there may be at least some differences in nonresponse among modalities, given suggested differences in neural mechanisms of treatment (DeRubeis et al., 2008; Goldapple et al., 2004; Mayberg, 2003). Moreover, with regular combined use of psychotherapy and pharmacotherapy being commonplace, examining neural nonresponse differences between combined and monotherapy approaches would also be beneficial. Clinically, better understanding of neural nonresponse following treatment provides opportunities to improve existing interventions, adjusting our treatment modalities to now address previously unaddressed vulnerabilities. There's the additional opportunity to combine different treatment modalities to treat remaining vulnerabilities. More immediate clinical recommendations involve treating MDD as the chronic condition (with persistent vulnerabilities) that it is, thus we advise continued assessment after completing treatment and receipt of mental health services upon symptom return. Moreover, it may be beneficial to engage in discussion with the patient about MDD's chronicity, to stress the importance of continued symptom monitoring and also to normalize the persistence of symptoms and persistence of maladaptive affective responses to depressive stressors.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723000727.

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Conflict of interest. Author GJS receives royalty payments on a patent regarding a novel depression intervention licensed to Apollo Neurosciences, which is not relevant to this article, and consults for Johnson and Johnson on novel pharmacology unrelated to this project. The other authors report nothing to disclose.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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