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Altered effective connectivity during cognitive distancing in cognitive behavioral therapy nonresponders with depression

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Abstract

Background. Approximately half of individuals with major depressive disorder (MDD) do not respond to cognitive behavioral therapy (CBT). Cognitive distancing is a reappraisal tactic central to CBT, and neural responses during reappraisal have been linked to psychotherapy outcome. We examined whether pretreatment effective connectivity during cognitive distancing was associated with CBT response in adults with MDD.

Methods. Seventy-seven outpatients with MDD (31 women) completed fMRI during a distancing task before 25 CBT sessions as part of the SPeED trial, which included a pre-CBT phase of exercise or waiting list. Dynamic causal modeling estimated effective connectivity within a 10-region network. Group differences were assessed with parametric empirical Bayes, and predictive utility was evaluated with leave-one-out cross-validation.

Results. Responders (n = 39) showed greater relative modulation along a dorsomedial-to-ventrolateral prefrontal-to-superior frontal/pre-supplementary motor area cascade during distancing, whereas nonresponders exhibited greater relative modulation of amygdala-to-ventrolateral prefrontal cortex connectivity. Nonresponders showed decreased dorsolateral prefrontal self-inhibition during negative picture processing, consistent with heightened local excitability. Distancing-related effects exceeded 99% posterior probability and predicted treatment response in cross-validation (r = .21–.31, p < .05).

Conclusions. Effective connectivity during distancing robustly differentiated responders from nonresponders, with nonresponders showing weaker intra-prefrontal control and stronger amygdala-to-prefrontal influence. These neural patterns contribute to insight into CBT nonresponse and suggest a mechanism associated with lowered symptom improvement through cognitive interventions. However, incremental predictive value beyond baseline clinical measures was modest. If replicated prospectively, such measures may contribute to multimodal prediction models and adjunctive treatment strategies.

Clinical trials registration name. Neurobiological correlates and mechanisms of the augmentation of psychotherapy with endurance exercise in mild to moderate depression – SPeED, http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00008869, DRKS00008869.

Introduction

Worldwide, ~280 million people suffer from major depression, representing about 5% of adults (National Survey on Drug Use and Health [NSDUH], 2022). Cognitive Behavioral Therapy (CBT) is an efficient first-line treatment for depression (Berger & Adli, 2022; Bundesärztekammer [BÄK] et al., 2022), yet ~50% of patients do not show meaningful improvement (Cuijpers et al., 2021). Predicting nonresponse to CBT for depression using clinical and demographic measures alone has mostly proven not sufficient, highlighting the need to incorporate additional data, such as early treatment progress or neuroimaging biomarkers, to improve accuracy (Hammelrath et al., 2024; Rozental, Andersson, & Carlbring, 2019). Understanding the neural mechanisms driving nonresponse is therefore essential to better understand who does not benefit from CBT and to more effectively allocate patients to appropriate treatment.

One promising direction is examining cognitive distancing. Cognitive distancing is a type of reappraisal (next to reinterpretation), in which individuals adopt a detached observer perspective to create psychological distance from stimuli. Whereas reinterpretation modifies the meaning of the emotional situation, distancing changes the perspective from which the stimulus is

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represented – here, by adopting the viewpoint of a neutral observer – without changing the stimulus content itself. Accordingly, distancing may rely on slightly different psychological and neural mechanisms relating to perspective taking and creating psychological distance (Denny et al., 2023; Powers & LaBar, 2019).

As a key strategy in CBT, reappraisal has been linked to treatment response in both anxiety and depression (Lueken et al., 2016; Sloan et al., 2017). Brain activity during reappraisal has been linked to psychotherapy response in social anxiety and major depression, indicating that neural mechanisms underlying cognitive reappraisal may influence treatment outcomes (Feurer et al., 2024; Goldin et al., 2012). Cognitive distancing is considered an important component of CBT interventions. In the present paradigm, we aimed to assess cognitive distancing by instructing participants to use distancing while viewing stimuli during fMRI. Additionally, participants provided subjective valence ratings after the scanning session. Recent meta-analyses describe the critical role of a prefrontal control system in modulating subcortical affective systems in distancing, particularly the amygdala. Within the prefrontal control system, most involved domain-general cognitive control regions include the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC), and superior frontal gyrus (SFG) extending into the pre-supplementary motor area (pre-SMA) (Buhle et al., 2014; Denny et al., 2023; Diekhof, Geier, Falkai, & Gruber, 2011; Kalisch, 2009; Kohn et al., 2014; Messina, Bianco, Sambin, & Viviani, 2015; Morawetz, Bode, Derntl, & Heekeren, 2017). Perspective taking and monitoring distancing outcome been associated with SFG/pre-SMA (Denny et al., 2023; Powers & LaBar, 2019). The involvement of the ventromedial prefrontal cortex (VMPFC) remains less clear, with some meta-analyses reporting its recruitment (Diekhof et al., 2011) while others do not (Buhle et al., 2014; Denny et al., 2023). Additional regions, such as the inferior parietal lobule (IPL), posterior cingulate cortex (PCC), middle cingulate cortex (MCC), and precuneus, have also been implicated (Buhle et al., 2014; Denny et al., 2023; Diekhof et al., 2011; Kalisch, 2009; Kohn et al., 2014; Messina et al., 2015; Morawetz et al., 2017). The VLPFC has additionally been highlighted in a recent fMRI–TMS study demonstrating that distancing critically depends on this region as a central regulatory hub (He et al., 2023), a finding further supported by a recent clinical trial (Feurer et al., 2024). Although individuals with MDD recruit similar networks as healthy controls during distancing, some studies have observed attenuated activation in prefrontal control regions and heightened amygdala reactivity (for review/meta-analysis, see Picó-Pérez et al., 2023; Zilverstand, Parvaz, & Goldstein, 2017). Reduced engagement of the VLPFC and DLPFC, in particular, has been described across internalizing disorders (Zilverstand et al., 2017).

Initial studies have examined neurobiological markers of reappraisal (including distancing) to approach a better understanding of nonresponse to CBT (Bomyea et al., 2020; Bryant et al., 2021; Marwood, Wise, Perkins, & Cleare, 2018). However, studies in adult depression are rare and have largely focused on regional activation patterns, with mixed findings. In a randomized trial including patients with MDD and SAD assigned to CBT or supportive therapy, Feurer et al. (2024) reported treatment-specific associations between baseline reappraisal-related activation and symptom trajectories: greater symptom improvement was associated with lower VLPFC engagement in CBT, whereas greater improvement was associated with higher VLPFC engagement in supportive therapy. This pattern suggests that VLPFC recruitment during reappraisal may not reflect a uniformly 'beneficial' marker across psychotherapies, but may instead index processes that interact with specific treatment mechanisms (e.g. reduced reliance on effortful semantic/selection processes in CBT, or greater engagement of such processes aligning with supportive therapy, conferring with meta-analytic evidence implicating VLPFC in implementing reappraisal-related control processes). Work by Rubin-Falcone et al. (2018); see corrigendum Rubin-Falcone et al. (2021) found that pre-treatment emotion regulation-related BOLD activation was not associated with CBT outcome in adults with MDD, whereas other neural signals (e.g. emotional reactivity measures) or longitudinal changes in regulation-related activation over the course of CBT tracked improvement. Together, these studies indicate that baseline activation during reappraisal may be an inconsistent prognostic marker in adult depression and motivates approaches that examine directed network interactions during reappraisal. Supporting this, Kung et al. (2023) applied DCM in depressed youth and reported that baseline fronto-amygdalar effective connectivity during reappraisal related to diagnosis and remission (e.g. altered VLPFC to amygdala modulation and baseline VMPFC to amygdala coupling), illustrating the promise of effective connectivity for characterizing outcome-relevant circuitry beyond regional activation.

Most authors assume that network-level interactions are a crucial prerequisite for emotion processing and reappraisal (Morawetz et al., 2020). However, the role of these network interactions in therapeutic success has rarely been tested directly. To our knowledge, no study has examined changes in effective connectivity during cognitive distancing that may underlie CBT nonresponse in adult depression. Therefore, it remains unclear which specific neural pathways are critical for a significant response to CBT. To address these questions, we employed Dynamic Causal Modeling (DCM) of emotion regulation during fMRI before CBT to identify which dynamic neural connections of the neural network underlying cognitive distancing may play a role in distinguishing individuals who respond significantly to CBT from those who do not. DCM offers a powerful framework for analyzing effective connectivity, capturing causal relationships between brain regions and behavior, while accounting for latent dynamics (Ashburner & Friston, 2005; Zeidman, Jafarian, Corbin, et al., 2019; Zeidman, Jafarian, Seghier, et al., 2019). The present study is a secondary analysis of the SPeED randomized controlled trial (Heinzel et al., 2022), in which participants completed baseline fMRI (T1), subsequently underwent high-intensity exercise, low-intensity exercise, or a waiting period (T1–T2), and then received CBT (T2–T3). In the parent trial report, exercise-arm assignment did not yield differential post-CBT symptom change; however, individual fitness improvement during the pre-CBT phase predicted subsequent CBT response. We therefore examined the robustness of the present effective connectivity findings by additionally accounting for fitness change in sensitivity analyses.

We hypothesized that, before CBT, future nonresponders would show altered context-dependent effective connectivity within fronto-limbic circuits during distancing, particularly involving VLPFC-centered modulatory interactions. This hypothesis was motivated by evidence implicating VLPFC as a key node in voluntary emotion regulation, including causal perturbation work suggesting that prefrontal regulation involves coordinated VLPFC-to-VMPFC-to-subcortical circuitry (He et al., 2023). Given the bidirectional nature of regulation networks and mixed prior prognostic findings in cognitive distancing based on regional activation, we did not specify a single edge-level direction a priori. Rather, we expected a less adaptive 'gain-control' configuration in nonresponders that could be expressed as reduced prefrontal modulation and/or increased relative influence of bottom-up salience inputs.

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Methods and materials

Participants

One hundred and twenty German middle-aged outpatients with MDD (mild or moderate) from a larger clinical trial on the augmentation of CBT response by physical exercise (SPeED): Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients (Heinzel et al., 2018) were included in the current study. A depressive episode was diagnosed with the German version of the Structured Clinical Interview for DSM-IV TR (SCID; First, 1997) by trained clinical psychologists. In short, patients completed a baseline fMRI scan assessing cognitive distancing (T1). Afterwards, participants were randomly assigned to a low (LEX), intermediate exercise intervention (HEX), or no physical exercise intervention (wait list, WL), followed by a second assessment (T2). Finally, all participants received 25 sessions of CBT, and psychiatric symptoms were assessed again (T3). Symptom severity was assessed using the Global Severity Index (GSI) of the Brief Symptom Inventory (BSI). Results of the physical exercise intervention were previously published (Heinzel et al., 2022). CBT response was defined as a statistically meaningful change based on the Reliable Change Index (RCI) (Jacobson & Truax, 1991), which determines whether symptom improvement from baseline (T1) to post-treatment (T3) exceeds the threshold of measurement error. The calculation used a test–retest reliability of r=.90, derived from Hiller, Schindler, Andor, and Rist (2011), and the baseline standard deviation of the full study sample (N = 120, SD = 0.434). Using a conservative 99% confidence criterion yielded a critical change threshold of 0.50 BSI-GSI points. Participants showing a pre (T1)- to post (T3)-CBT decrease of <0.50 points were classified as nonresponders. The reliability coefficient for the RCI was derived from prior studies in comparable outpatient samples in Germany (Hiller et al., 2011). This RCI-based response definition was specified a priori as part of the FOR5187 harmonized analysis strategy across retrospective datasets (OSF preregistration: 10.17605/OSF.IO/W327J), to ensure comparability of outcome definitions across studies. Mean duration from baseline to post-CBT was m = 48.5 (±21.96) weeks. Data acquisition took place between July 2015 and April 2020.

At baseline, the sample comprised 120 patients, of whom 87 completed the study and 33 discontinued. Baseline characteristics of completers and noncompleters are compared in Supplementary Table S1. Ten completers were excluded because of insufficient fMRI data quality, resulting in a final analysis sample of 77 patients (see Table 1 for demographic and clinical characteristics).

A full list of inclusion and exclusion criteria can be found in the Supplementary Materials; participant flow is reported in Heinzel et al. (2018, 2022). The study was approved by the local ethics committees of Charité – Universitätsmedizin Berlin, Germany (No EA1/113/15), and of the Freie Universität Berlin, Germany (No 133/2016) and conducted in accordance with the Declaration of Helsinki. The trial was registered at the International Clinical Trials Registry Platform of the World Health Organization

Table 1. Demographic, clinical, and fitness characteristics of CBT responders and nonresponders

	Nonresponder N = 38	Responder N = 39	Group comparison	
			Statistics	p-value
Age (years)	40.29 ± 10.38	39.26 ± 10.66	t_{75} = .431	.668
Gender (female)	14	17	χ^2 = .361	.546
Education (years)	15.75 ± 3.90	15.93 ± 2.92	t_{68} = .246	.806
Pre-CBT BSI-GSI	.93 ± .42	1.20 ± .36	t_{75} = −2.946	.004
Post-CBT BSI-GSI	.86 ± .54	.37 ± .29	t_{75} = 4.926	<.0001
Mean BSI-GSI change (T3-T1)	−.08 ± .30	−.83 ± .31	t_{75} = 10.75	<.0001
Antidepressants				
With any vs. without any (n)	14 vs. 24	14 vs.25	χ^2 = .573	.333
SSRI (n)	7	8		
SSNRI (n)	3	0		
SNDRI (n)	1	2		
Tricyclic (n)	0	2		
Tetracyclic (n)	1	1		
Other (n)	2	1		
Exercise training group (HEX/ LEX/WL)	(17/11/10)	(9/18/12)	X^2 = 4.32	.115
Fitness (W/kg bodyweight)				
Pre	2.33 ± .50	2.29 ± .50	t_{75} = .45	.653
Post[a]	2.30 ± .47	2.33 ± .54	t_{75} = .24	.808
Relative change (%)	−.63 ± 9.82	2.09 ± 11.12	t_{75} = 1.11	.270

Notes: If not stated otherwise, values represent means and standard deviations. Physical fitness is indicated by maximum achieved Watt per kg bodyweight during ergometry.
HEX, high-intensity exercise group; LEX, low-intensity exercise group; WL, waiting list group.
[a]Value was missing for two participants.

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(http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00008869). Written informed consent was obtained from all participants.

fMRI cognitive distancing task

Participants received training on cognitive distancing before fMRI scanning. The block-design task comprised the following four conditions: 'permit neutral', 'permit negative', 'distance neutral', and 'distance negative' in a 2 × 2 design. The task was adapted from Erk et al. (2010). See Supplementary Material for details.

fMRI data analysis

Only fMRI data from T1 (pre-treatment measurement time point) were analyzed for the current study. Details regarding fMRI sequences, preprocessing steps, and whole-brain activation analyses can be found in the Supplementary Material.

Dynamic causal modeling (DCM)

Overview

DCM is a generative effective connectivity model that fits fMRI time series in a network of interconnected nodes. Alternative models, corresponding to distinct effective connectivity network structures, are compared within a Bayesian framework (Friston, Harrison, & Penny, 2003; Zeidman, Jafarian, Seghier, et al., 2019). Here, DCM was used to select the model that best explains the pre-treatment fMRI time series during an experimental task. At the first level (for each participant), a variational model inversion scheme was used to fit a fully interconnected model between 10 brain regions (see below) to each participant's data, resulting in the free-energy approximation to model (log-) evidence and the posterior parameter estimates (effective connectivity weights between nodes). Bayesian model reduction was used to prune the parameters of the full model that did not increase model evidence, yielding a parsimonious set of connections between brain regions. These are interpreted as directed connectivity weights that can be modulated by psychological processes of interest (i.e. emotion processing and distancing). At the second level (across participants), hierarchical Bayesian modeling (i.e. Parametric Empirical Bayes, or PEB) was used to contrast connection strengths (i.e. their probability density) between groups of interest (here, CBT nonresponders vs. responders). This allows estimation of the effective connectivity differences between groups while considering within-participants variability on connectivity parameters. These parameters were then subjected to leave-one-out cross-validation to predict CBT response at a single-participant level.

Model space and time-series extraction

Candidate model space selection was guided by previous investigations of the emotion regulation network. Based on reviews on the distancing network (Buhle et al., 2014; Denny et al., 2023; Diekhof et al., 2011; Kalisch, 2009; Kohn et al., 2014; Messina et al., 2015; Morawetz et al., 2017; Ochsner, Silvers, & Buhle, 2012; Powers & LaBar, 2019), we identified the following regions of interest for this network: dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), superior frontal gyrus (SFG) reaching into the preSMA, dorsomedial prefrontal cortex (DMPFC), ventromedial prefrontal cortex (VMPFC), inferior parietal lobule (IPL), posterior cingulate cortex (PCC), precuneus, and amygdala. See Supplemental Information for details on ROI definition procedure.

Model specification, estimation, and parametric empirical Bayes

The connectivity weights consist of three sets of parameters: condition nonspecific estimates ('A matrix'), modulatory parameters denoting connectivity changes due to experimental conditions ('B matrix'), and input parameters ('C matrix') defining nodes receiving experimental inputs. Our initial model consisted of a fully interconnected A matrix, three B matrices corresponding to the two task conditions and their interaction (i.e. *negative*, *distancing*, *negative x distancing*), and a C matrix defining two driving inputs into the right and left amygdala. After fitting this DCM model for each participant, we defined and estimated group-level Bayesian hierarchical models (PEB) of the A matrix and used Bayesian Model Reduction to prune those connection parameters that did not contribute to model evidence (<99% posterior probability [PP]). The remaining connections were included in our final DCM model that we used to investigate the experimental effects. Specifically, we used PEB to examine whether CBT response groups differed in how their condition-specific connectivity parameters ('B matrix') are modulated by negative emotions, cognitive distancing, or their interaction. A group effect was considered significant for parameters that showed >99% posterior probability relative to 0 (two-tailed) (see Supplementary Materials for technical details).

Leave-one-out cross-validation

We employed leave-one-out cross-validation to test whether effect sizes of differences in connectivity parameters between CBT responders and nonresponders were large enough to predict individual group membership. This process involves iteratively estimating a group-level PEB model with all participants but one (train set) and then utilizing this model to predict the omitted participant's CBT response status (test set). Prediction accuracy was quantified by correlating predicted and observed values.

Results

Demographic and behavioral results

N = 39 participants showed a reliable change in BSI-GSI values from baseline to post-CBT (responders). Whereas responders showed significantly higher BSI-GSI scores pre-CBT than nonresponders, the pattern was reversed after CBT, with nonresponders showing significantly higher BSI-GSI values. Both groups did not differ with respect to age, gender, level of education, exercise condition, or fitness change (Table 1). Fitness change was not significantly associated with symptom change in our outcome metric (Pearson $r = -.140$, $p = .235$).

Whole brain activations

Whole sample

The principal contrasts examined activation and deactivation associated with distancing (distance vs. permit). Results showed that distancing was associated with robust activation of prefrontal and parietal (primarily right-lateralized) areas, in addition to the posterior cingulate reaching into the precuneus. Decreased activation during distancing (vs. permit) was observed mainly in the ventromedial prefrontal cortex (VMPFC) and bilateral occipital areas. Furthermore, contrasting negative > neutral yielded widespread activation in cortical midline structures and limbic areas in addition to bilateral occipital areas (Figure 1). The statistical parametric

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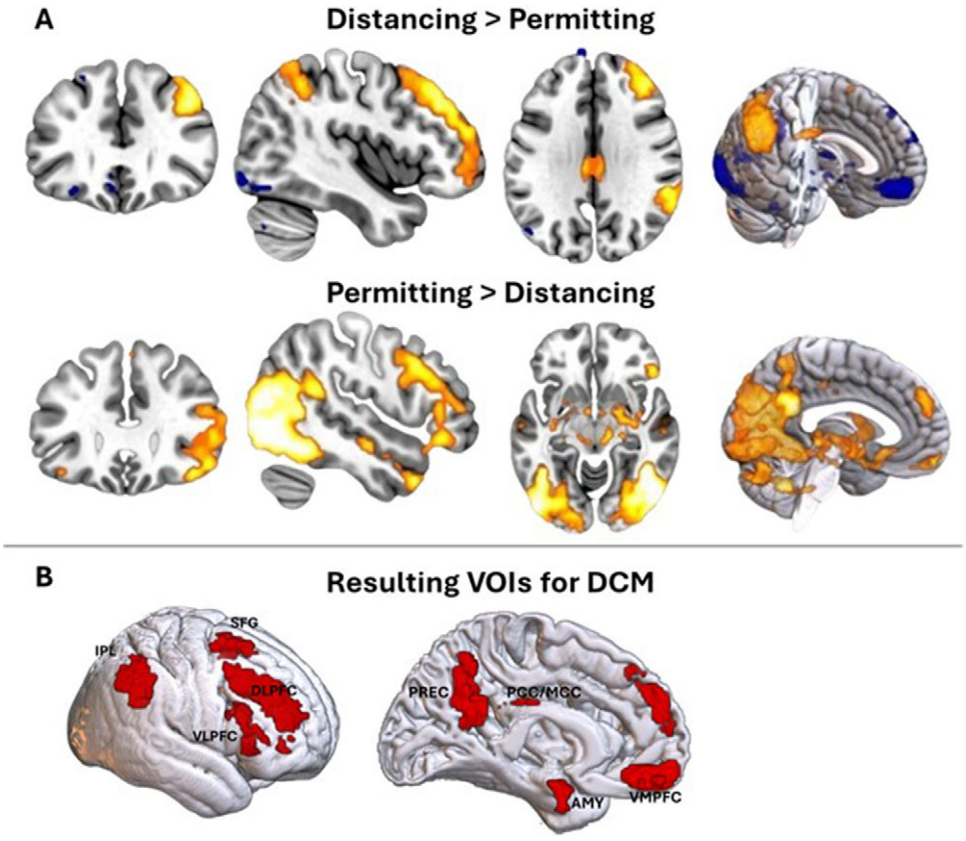


Figure 1. (a) Whole-brain task activation comparing distancing and permitting conditions in flexible factorial design, thresholded at $p < .05$ (family-wise error corrected). Yellow indicates increased, and blue decreased activation. (b) Volumes-of-interest (VOIs) used for DCM analysis. AMY, amygdala; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; IPL, inferior parietal lobule; PCC/MCC, posterior and middle cingulate cortex; PREC, precuneus; SFG, superior frontal gyrus; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex.

maps were employed to determine peak values within the volumes of interest incorporated into our model space. The interaction contrast (responders vs. nonresponders × distance vs. permit) did not reveal any significant activation clusters at the whole-brain level (voxel-wise FWE-corrected).

Results of DCM and leave-one-out cross-validation

Pruning of condition nonspecific connections (A matrix) resulted in retaining 54 out of 100 connections of the full model. Three pruned self-connections were added again to the model space to ensure stability (see Supplementary Materials for details), and the resulting 57 connections were incorporated into the final DCM model space used to analyze the effects of distancing.

The main aim of the study was to test if cognitive distancing modulates brain connectivity differently in CBT responders compared to nonresponders. PEB analysis revealed that a highly selective subset of condition-specific connections (B matrix) related to distancing was subject to a different degree of modulation in responders than nonresponders. Specifically, the connection from DMPFC to VLPFC was found to be 35.39% more strongly modulated by distancing in responders than nonresponders (0.303 log Hz posterior estimate, PP = 1.0). Moreover, the connectivity from VLPFC to SFG was found to be 23.12% more strongly modulated by distancing in responders than nonresponders (0.208 log Hz posterior estimate, PP = 1.0). Finally, the modulation of the connectivity from the right amygdala to VLPFC by distancing was found to be 42.76% weaker (0.356 log Hz posterior estimate, PP = 1.0) in responders than nonresponders. These results were confirmed by leave-one-out cross-validation, which showed significant prediction of group membership by all three connections modulated by distancing (amygdala to VLPFC: $r = .21$, $p = .03$; DMPFC to VLPFC: $r = .31$, $p = .03$; VLPFC to SFG: $r = .23$, $p = .02$). See Table 2 for details regarding connections differentially modulated by distancing in responders versus nonresponders.

Moreover, PEB results based on the B matrix related to the negative condition showed that in responders, negative stimuli modulated the DLPFC self-connection 33.91% more than in nonresponders (0.292 log Hz posterior estimate, PP = 1.0). However, this effect did not significantly predict individual group membership according to the cross-validation. Finally, no group differences were observed in the B matrix related to the interaction effect (Figure 2).

Because responders and nonresponders differed in baseline symptom severity, we additionally conducted a sensitivity analysis reestimating the PEB model with baseline BSI-GSI at T1 as an additional covariate (see Supplementary Materials for details). After adjustment for baseline symptom severity, the distancing-related DMPFC to VLPFC and right amygdala-to-VLPFC effects remained above the predefined posterior-probability threshold, whereas the VLPFC to SFG/pre-SMA effect no longer did. An additional distancing-related effect emerged from the left amygdala to the SFG/pre-SMA, with stronger modulation in nonresponders. All three significant distancing-related effects predicted group

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Table 2. DCM results showing connections differentially modulated by distancing in CBT responders versus nonresponders

Connection	Direction of intrinsic connection[a] (A-matrix)	Modulation by distancing[a]	Difference in modulation by distancing (responders vs. nonresponders)	Posterior estimate (log Hz)	PP	Cross-validation *r*	Cross-validation *p*
DMPFC → VLPFC	Excitatory	Inhibitory	35.39% weaker in nonresponders	.303	1.0	.31	.03
VLPFC → SFG	Excitatory	Inhibitory	23.12% weaker in nonresponders	.208	1.0	.23	.02
Amy (R) → VLPFC	Excitatory	Excitatory	42.76% stronger in nonresponders	.356	1.0	.21	.03

Notes: Shown are intrinsic connection types, modulation effects, group differences, posterior estimates (log Hz), posterior probability (PP), and cross-validation metrics (r, p).
[a]Modulation of intrinsic connection and modulation (i.e. excitatory/inhibitory) reflect the sign of the group-level posterior estimate but does not reflect significant commonalities across all participants. This information is provided for interpretive purposes only. See Supplementary Table S3 for significant commonalities between responders and nonresponders. Differences between responders and nonresponders were significant (posterior probability > .99). AMY (R), right amygdala; DMPFC, dorsomedial prefrontal cortex, PP, posterior probability; SFG, superior frontal gyrus; VLPFC, ventrolateral prefrontal cortex.

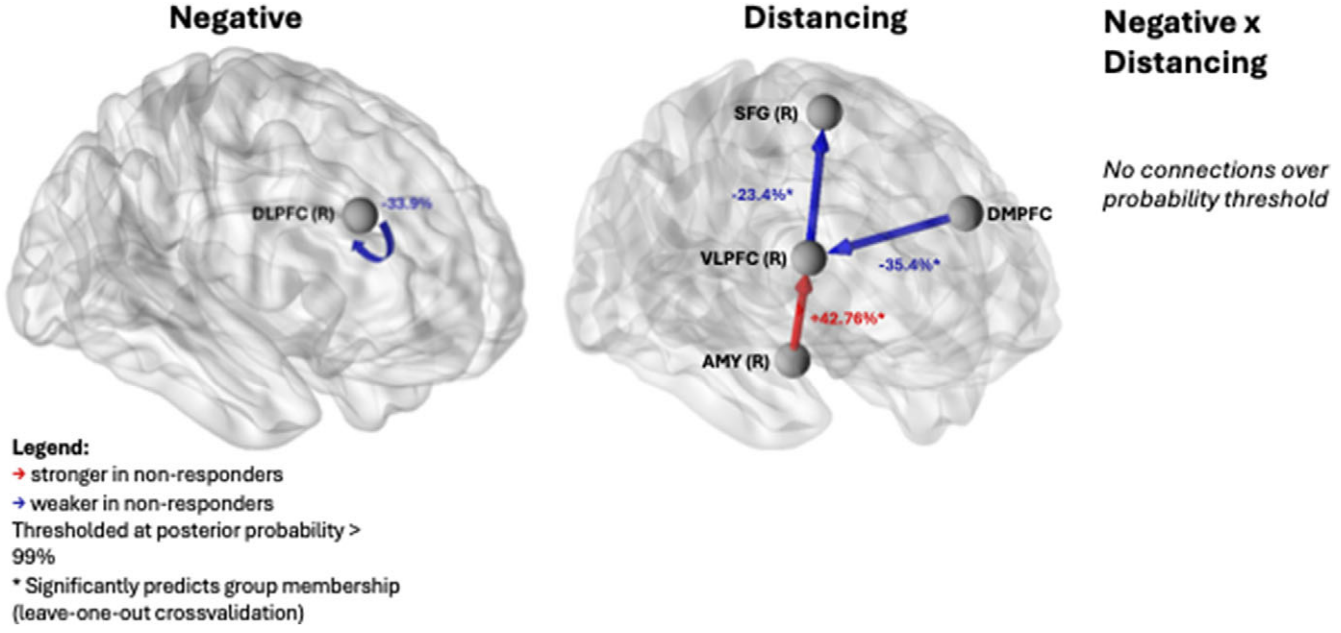


Figure 2. Effective connectivity results from Dynamic Causal Modeling (DCM) analysis using Parametric Empirical Bayes (PEB) and Bayesian Model Averaging (BMA) for the contrasts negative, distancing, and their interaction. The figure shows significant modulatory connections that differ between CBT responders and nonresponders. Blue arrows indicate weaker, and red arrows indicate stronger, connections in nonresponders. Only connections with a posterior probability >99% are shown.

membership in leave-one-out cross-validation. The DLPFC self-connection remained significant in the PEB-model but did not predict group membership, consistent with the unadjusted model. An additional precuneus-to-VLPFC effect emerged but was not significant in leave-one-out cross-validation.

To test whether modulatory connectivity during distancing predicted changes in symptom severity, we conducted a hierarchical regression analysis. Baseline symptom levels were entered in the first step, followed by the three significant modulatory connections (DMPFC→VLPFC, VLPFC→SFG, and Amygdala→VLPFC) in the second step.

Baseline symptom levels (BSI-GSI T1) explained 15.7% of the variance (R^2 = .157), $F(1,75)$ = 13.998, p < .001. Adding three modulatory connections (DMPFC → VLPFC, VLPFC → SFG, Amygdala → VLPFC) improved the model (ΔR^2 = .035, overall model: $F(3,72)$ = 4.279, p = .004), but the increase in explained variance to 19.2% (R^2 = .192) only was modest and not significant.

Because a subset of participants underwent a physical exercise intervention as part of the original trial, we additionally conducted two sensitivity analyses. In the first, we reestimated the second-level PEB model, including physical fitness change (maximum achieved watts per kg on the cycle ergometer at T1 vs. T2) as a covariate. In the second, we controlled for antidepressant medication status. The overall pattern of effects remained broadly consistent, while additional covariate-adjusted effects emerged during the negative condition (see Supplementary Materials for details).

Discussion

Despite advancements in CBT, approximately half of patients with major depression still do not respond, underscoring the need to understand neural mechanisms that differentiate responders from nonresponders. Adopting a detached, observer perspective ('distancing') is a core skill needed in CBT. Using DCM during

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distancing, we found that responders exhibit stronger modulation in effective connectivity along a DMPFC-to-VLPFC-to-SFG/pre-SMA cascade, whereas nonresponders show weaker modulation of these intra-prefrontal influences and stronger amygdala-to-VLPFC modulation by distancing. Our results converge with recent meta-analyses and reviews that implicate these regions in distancing and broader prefrontal control functions (Buhle et al., 2014; Denny et al., 2023; Diekhof et al., 2011; Kohn et al., 2014; Morawetz et al., 2017; Powers et al., 2020) and support weaker context-dependent modulations of these intra-prefrontal pathways in non-responders. The VLPFC may support selecting and implementing the detached observer perspective, including suppressing competing self-relevant appraisals. The SFG/pre-SMA may be particularly relevant to the monitoring and coordination of distancing. Maintaining a detached perspective requires participants to keep the regulatory goal active, monitor changes in their emotional response, and adjust regulatory efforts when needed. SFG/pre-SMA and adjacent medial frontal regions have been implicated in these monitoring and control processes and may contribute to maintaining the distanced stance and monitoring whether it is sustained (Denny et al., 2023; Powers & LaBar, 2019). We speculate that lowered attenuation of the VLPFC to SFG/pre-SMA connectivity during distancing in nonresponders may indicate that SFG/pre-SMA stays more dependent on reactive selection and updating processes in the VLPFC and is less efficiently coordinating and maintaining distancing goals. In nonresponders, modulation of both DMPFC to VLPFC and VLPFC to SFG/pre-SMA influences was weaker, and VLPFC was, relative to the other group, more strongly driven by amygdala input, altogether possibly pointing to a regulatory network that is less flexible and more dominated by bottom-up salience signals during distancing. The weaker context-dependent modulation of these intra-prefrontal pathways together with stronger limbic-to-prefrontal coupling is consistent with a regulatory configuration that is less flexibly reconfigured by distancing and more strongly influenced by stimulus-driven salience signals. In line with this, reappraisal meta-analyses converge on prefrontal control (including VLPFC) as an implementer of inhibitory/selection processes and semantic updating rather than the locus of sustained perspective maintenance (Buhle et al., 2014; Kohn et al., 2014; Morawetz et al., 2017) and findings that show VLPFC more involved in reinterpretation than distancing (Denny et al., 2023) dovetailing with our interpretation that a larger reduction of VLPFC's coupling on SFG/pre-SMA may be adaptive once the distanced stance is established.

During distancing, nonresponders showed greater modulation of the right amygdala-to-VLPFC connection than responders. Quantitative connectivity syntheses indicate robust amygdala-to-VLPFC coupling during regulation (Morawetz et al., 2020). Importantly, the amygdala not only generates emotional responses but also supports stimulus-driven attention (Peck & Salzman, 2014), signaling the need for control (Paret et al., 2018). Together, elevated modulation of the connectivity from amygdala to VLPFC during distancing may reflect compensatory bottom-up recruitment of prefrontal regions in individuals with depression who exhibit deficits in adaptive prefrontal regulation. More specifically, we speculate that intrusive salience input may keep VLPFC engaged in reactive updates, preventing a clean shift into the autonomously sustained distancing mode. While interpreting increased amygdala-to-VLPFC modulation in nonresponders as compensatory recruitment is plausible, the present data do not allow us to distinguish compensatory/adaptive versus inefficient or maladaptive accounts. An alternative interpretation is that stronger amygdala-to-VLPFC coupling reflects inefficient gating of bottom-up salience signals, such that stimulus-driven input persistently drives VLPFC engagement and interferes with the establishment or maintenance of a stable distanced stance.

More broadly, although the present findings can be described in terms of top-down prefrontal control and bottom-up amygdala signaling, contemporary models conceptualize emotion regulation as the flexible coordination of multiple interacting networks involved in cognitive control, appraisal, salience detection and emotion generation (Morawetz et al., 2020). From this perspective, the combination of stronger amygdala-to-VLPFC modulation and weaker intra-prefrontal modulation in nonresponders may reflect an imbalance in the reciprocal coordination or interaction of large-scale affective and control networks, rather than a unitary failure of top-down regulation.

Using DCM, the present study extends prior work by highlighting altered bottom-up amygdala-to-VLPFC connectivity as a prominent component of dysregulation, rather than focusing exclusively on changes in top-down interpretation typically emphasized in earlier studies (e.g. Johnstone et al., 2007; Zilverstand et al., 2017), underscoring the importance of modeling directed interactions. However, we regard this as a gain-control imbalance (excess bottom-up weighting plus insufficient intra-prefrontal down-weighting), not as definitive evidence for a single directional mechanism.

An important consideration is that responders and nonresponders differed in symptom severity at baseline. In a covariate-adjusted sensitivity analysis controlling for baseline BSI-GSI, the overall pattern remained broadly consistent, but some effects changed: the differential modulation of VLPFC to SFG connectivity by distancing was no longer evident, whereas a stronger modulation of left amygdala to SFG/pre-SMA connectivity in nonresponders by distancing emerged. This suggests that part of the original intra-prefrontal effect pattern may have been shared with baseline symptom burden, while the main finding of altered amygdala to ventrolateral prefrontal coupling in nonresponders remained. At the same time, baseline severity is not only a potential confound but may itself be clinically linked to later treatment outcome. By controlling for this variance, we might therefore eliminate important information. Higher baseline symptom levels may provide greater scope for symptom reduction and may therefore also contribute to response classification through regression-to-the-mean effects. Accordingly, the unadjusted and covariate-adjusted models address related but not identical questions: the former captures overall baseline brain differences associated with later response status, whereas the latter isolates response-related effects over and above baseline severity.

Because the present study is a secondary analysis of the SPeED trial, which included a pre-CBT phase of high-/low-intensity exercise or waiting (T1–T2) before CBT (T2–T3), exercise-related physiological changes could in principle influence fMRI-based estimates of effective connectivity. In the present imaging completer sample, responders and nonresponders did not differ in baseline physical fitness or fitness change, and fitness change was not associated with symptom change in our outcome metric. We reestimated the second-level PEB model, including fitness change as a covariate (Supplementary Materials). The overall pattern remained broadly consistent, while additional covariate-adjusted amygdala-related effects emerged (increased left amygdala-to-DMPFC modulation during negative picture processing and increased inhibitory self-connection of the left amygdala in responders; the latter did not predict group membership in leave-one-out cross-validation). Even though fitness change did not differ

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between groups and was not associated with symptom change, modeling it may reduce residual physiological variability in BOLD-based connectivity estimates and thereby reveal additional conditional group effects, without implying a causal role of fitness change. Considering all results related to the effect of fitness, we interpret these as exploratory sensitivity findings, which need to be replicated in future studies rather than evidence that fitness change drives the main response-related effective connectivity pattern.

To our knowledge, this is the first study to use DCM to examine causal interactions within distancing networks associated with CBT response in adults with depression. Kung et al. (2023) investigated prefrontal-to-amygdala connectivity during distancing in adolescents with MDD and found that weaker excitatory coupling from the ventromedial prefrontal cortex to the amygdala at baseline was associated with remission (Kung et al., 2023). While both studies implicate prefrontal-limbic interactions in treatment outcome, the approaches differed. Kung et al. focused narrowly on prefrontal outputs to the amygdala, whereas we modeled a broader bidirectional network of 10 prefrontal, limbic, and parietal regions, enabling detection of intra-prefrontal differences, afferent inputs into lateral and medial prefrontal areas, and local dorsolateral prefrontal excitability. Developmental stage may also contribute, as adolescents show ongoing maturation of fronto-limbic circuitry (Gee et al., 2013; Tang et al., 2018), which can influence both baseline connectivity and responsiveness to CBT. Differences from Kung et al. (2023) may additionally reflect differences in reappraisal tactics examined. Our task specifically assessed cognitive distancing, whereas Kung et al. (2023) used a broader reappraisal paradigm mixing reinterpretation and distancing strategies. Although both tactics engage overlapping prefrontal control and fronto-limbic networks, studies based on neural activation indicate that distancing might be linked more strongly to dorsolateral prefrontal and parietal regions and to amygdala attenuation, whereas reinterpretation appears to rely more on VLPFC mechanisms supporting semantic selection and meaning change (Denny et al., 2023).

Finally, decreased DLPFC self-inhibition was observed in non-responders relative to responders during negative picture processing. In DCM, self-connections represent local inhibitory gain within a region; reduced self-inhibition reflects greater excitability or disinhibition of the local neuronal population, rather than greater BOLD activation per se (Friston, Zeidman, & Litvak, 2015; Zeidman, Jafarian, Corbin, et al., 2019). This pattern may indicate that the DLPFC in nonresponders is more readily engaged by negative stimuli but recruited inefficiently. Although this finding remains exploratory, it aligns with models of impaired prefrontal control in depression. Prior studies have linked better outcomes to increased DLPFC activation during emotional face processing (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008; Jamieson, Harrison, & Davey, 2021; Ritchey et al., 2011) and modulation of DLPFC connectivity by negative facial expressions has also been associated with treatment response (Jamieson et al., 2021). The current findings, however, concern local excitability rather than long-range coupling and contrast with studies emphasizing altered amygdala–prefrontal pathways (Jamieson et al., 2021; Kung et al., 2023). Such discrepancies may reflect differences in task demands, analytic approaches, or sample characteristics. It is important to note that this finding did not significantly predict group membership in the leave-one-out cross-validation; however, it highlights another potential mechanism of inefficient prefrontal recruitment in nonresponders that warrants replication in larger samples.

At the behavioral level, CBT benefits when patients can adaptively shift between engagement and self-distancing (Barbosa et al., 2021). Our DCM results point to a possible circuit-level mechanism for this adaptive regulation: responders showed stronger intra-prefrontal regulation alongside reduced amygdala→VLPFC influence. This pattern aligns with broader evidence that depression is characterized by impairments in goal-adaptive regulation (Gao et al., 2025; Joormann & Stanton, 2016).

Process-based CBT emphasizes targeting dysfunctional processes and strengthening flexible skill repertoires rather than applying a one-size-fits-all protocol (Hayes & Hofmann, 2017). In this framework, the present pattern in nonresponders – stronger limbic-to-prefrontal coupling alongside weaker context-dependent modulation within intra-prefrontal pathways during distancing – may reflect reduced flexibility in implementing distancing. Clinically, this could translate into slower learning, poorer generalization, or less reliable retrieval of distancing skills, potentially increasing the need for therapist-guided scaffolding (e.g. graded practice, feedback, and support in shifting between engagement and distancing).

Evidence from standard interventions suggests that emotion regulation processes and related neural markers can shift with treatment. For example, exposure-based CBT has been reported to produce early changes in neural responses during an emotion regulation task in panic disorder (Reinecke, Thilo, Croft, & Harmer, 2018) and antidepressant pharmacotherapy has been associated with more adaptive emotion regulation strategies, with larger improvements linked to better clinical outcomes (McRae et al., 2014).

Against this background, our findings do not imply that CBT should be modified as a uniform protocol. Rather, they motivate prospective testing of individualized, process-targeted augmentation for individuals showing a pronounced imbalance between limbic salience drive and context-dependent modulation within intra-prefrontal pathways during distancing (Cohen & DeRubeis, 2018). This could include intensified therapist-guided scaffolding and flexibility training, and – more speculatively – adjunctive emotion-focused methods, neuromodulation, or pharmacological approaches (e.g. ketamine) aimed at facilitating prefrontal engagement and/or reducing excessive salience drive. These clinical implications remain hypothesis-generating for future research and require stratified prospective trials. The present data do not specify which therapeutic micro-interventions or augmentations would be optimal for a given connectivity profile.

Limitations

While leave-one-out cross-validation demonstrated predictive utility, the incremental variance explained by connectivity parameters beyond pre-CBT clinical measures was modest (from 15.7% to 19.2%) and not significant. Given the cost and complexity of fMRI, these neural markers are therefore unlikely to be sufficient for clinically useful prediction on their own and should currently be considered primarily informative at a mechanistic rather than a translational level. Further research with larger and more diverse samples is needed to determine whether such measures add meaningful value within multimodal prediction frameworks. While responders had significantly higher BSI-GSI scores than nonresponders before CBT, this pattern reversed after treatment, with nonresponders exhibiting significantly higher BSI-GSI values. This is likely explained by the fact that higher baseline symptom severity provided more room for improvement (regression to the mean).

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Patients with higher initial symptom distress may also be more motivated to engage with therapy. However, this makes it difficult to disentangle whether pre-treatment connectivity differences reflect eventual treatment response, baseline clinical state, or both. Although a sensitivity analysis controlling for baseline severity yielded overall a similar picture of decreased intra-prefrontal modulation in nonresponders and increased amygdala-to-prefrontal modulation by distancing in nonresponders, some effects changed, indicating that part of the observed connectivity pattern overlapped with initial symptom burden. Furthermore, because the original design of the trial included a pre-CBT phase (exercise or waiting) between T1 and T2 and CBT between T2 and T3 (Heinzel et al., 2018, 2022), our primary outcome (T1–T3 change) reflects improvement across the full study sequence rather than a CBT-only effect; some of the effects might have been due to physical exercise rather than CBT in part of the participants. Responders and nonresponders did not differ in their allocation to the respective fitness groups nor in their fitness increase. However, exercise and changes in physical fitness can influence cerebrovascular/hemodynamic properties that may contribute to the BOLD signal and could therefore, in principle, affect fMRI-derived connectivity estimates. Although DCM includes an explicit hemodynamic model, we addressed this concern by conducting a sensitivity analysis reestimating the second-level PEB model including fitness change as a covariate (Supplementary Materials), which yielded a broadly consistent overall pattern. Nevertheless, vascular contributions to the main findings cannot be fully excluded in the absence of direct physiological measures. Although our DCM model included a broad set of prefrontal and limbic regions, the number of trials per condition was limited, potentially reducing the sensitivity to detect interaction effects. A further limitation concerns behavioral verification of emotion regulation success. Participants provided post-scan affect ratings for all stimuli (reported in the Supplementary Materials), but responders and nonresponders did not differ in these subjective ratings. Importantly, these ratings were collected after scanning and were not obtained during active regulation. Future studies should include online trial-wise ratings (or other behavioral indices) of regulation success to more directly relate connectivity patterns to subjective distancing efficacy. Finally, the present analyses were restricted to CBT completers from the initial sample (n = 120). Comparison between completers and non-completers did not show significant differences, but this approach might still reduce generalizability. The full sample may be informative for future analyses examining predictors of treatment adherence and study dropout. These questions were beyond the scope of the current study but represent an important avenue for future research.

Conclusion

Our findings reveal distinct connectivity patterns in individuals who did not respond to CBT, characterized by weaker intra-prefrontal modulation and stronger bottom-up amygdala-to-VLPFC signaling during cognitive distancing. This suggests that nonresponders may be less able to recruit prefrontal control mechanisms to sustain a detached perspective, thereby limiting the effectiveness of cognitive interventions in CBT. These results underscore the potential utility of adjunctive strategies – such as neuromodulation, reinforcement-based, or emotion-focused approaches – for patients with reduced prefrontal regulatory capacity. Future work should test these mechanisms in prospective cohorts and evaluate targeted interventions that address deficits in cognitive distancing before, or alongside, standard CBT.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291726106138.

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Competing interests. The authors declare none.

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