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Investigation of Neurofunctional Changes Over the Course of Electroconvulsive Therapy

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Abstract

Background: Electroconvulsive therapy (ECT) is an effective treatment for patients suffering from depression. Yet the exact neurobiological mechanisms underlying the efficacy of ECT and indicators of who might respond best to it remain to be elucidated. Identifying neural markers that can inform about an individual's response to ECT would enable more optimal treatment strategies and increase clinical efficacy.
Methods: Twenty-one acutely depressed inpatients completed an emotional working memory task during functional magnetic resonance imaging before and after receiving treatment with ECT. Neural activity was assessed in 5 key regions associated with the pathophysiology of depression: bilateral dorsolateral prefrontal cortex and pregenual, subgenual, and dorsal anterior cingulate cortex. Associations between brain activation and clinical improvement, as reflected by Montgomery-Åsberg Depression Rating Scale scores, were computed using linear regression models, *t* tests, and Pearson correlational analyses.
Results: Significant neurobiological prognostic markers or changes in neural activity from pre- to post ECT did not emerge.
Conclusions: We could not confirm normalization effects and did not find significant neural markers related to treatment response. These results demonstrate that the search for reliable and clinically useful biomarkers for ECT treatment remains in its initial stages and still faces challenges.

Keywords: Electroconvulsive therapy, task-based fMRI, depression, anterior cingulate cortex

Introduction

Depression is a highly prevalent and disabling disorder affecting over 300 million people worldwide (WHO, 2017). Although several evidence-based pharmacological and psychotherapeutic treatment options are available to patients with depressive disorders, only approximately 60%–70% will eventually show a clinically significant response (Rush et al., 2006). As a result, depressed individuals may experience several ineffective treatment trials until symptom remission is achieved (Rush et al., 2009). For patients who suffer from severe depressive symptoms or who did not respond adequately to the first-line treatment options, electroconvulsive therapy (ECT) is the most effective and rapidly acting form of treatment, with estimated response rates of up to 80% (Baldinger et al., 2014; Haq et al., 2015). Yet the exact neurobiological mechanisms underlying the efficacy of ECT and

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Significance Statement

Depression is a highly prevalent disorder, and although a variety of treatments are available, at least 30%–40% of patients do not respond adequately to these interventions. Electroconvulsive therapy (ECT) is an effective treatment that has been widely used to treat these patients. Yet the exact neurobiological mechanisms behind its antidepressant effect are incompletely understood. Identifying neural markers that can inform about an individual's response to ECT would enable more optimal treatment strategies and increase clinical efficacy. Here, we investigated both neurofunctional changes over the course of treatment and neurofunctional prognostic markers of treatment outcome in depressive patients who receive ECT using task-based functional magnetic resonance imaging. There were, however, neither significant changes in neural activity between pre- and post-ECT nor an association with symptom improvement in the investigated regions of interest.

indicators of who might respond best to it remain to be elucidated. Identifying neural markers and specific neurofunctional changes that can inform about an individual's response to ECT would enable more optimal treatment strategies and increase clinical efficacy.

Functional magnetic resonance imaging (fMRI) studies have consistently revealed disturbances in neural activation patterns in acutely depressed patients. Among the most reliable findings in depression research is aberrant functional activation in the pregenual anterior cingulate cortex (pgACC; Pizzagalli, 2011; Pizzagalli and Roberts, 2022). The pgACC, a region relevant to various aspects of emotional processing, such as automatic processing of emotional cues (Pizzagalli, 2011), is part of the default mode network (DMN; Raichle et al., 2001). Functional activation in regions within the DMN is typically suppressed during goal-oriented tasks (Raichle et al., 2001). Previous studies in depressed patients have, however, found hyperactivation of or a failure to deactivate the pgACC (i.e., negative blood oxygen level dependent [BOLD] responses) during the performance of emotional tasks, suggesting that the DMN may contribute to the impairments in emotional processing in depression (Sheline et al., 2009; Grimm et al., 2011). Hyperactivity to emotional stimuli, particularly positive stimuli, has also been identified in the subgenual anterior cingulate cortex (sgACC; Fitzgerald et al., 2008). Other functional alterations in depressive disorders can be found in regions relevant for cognitive control, executive functioning, and working memory (WM). As such, fMRI studies have related attenuated activation of prefrontal and cingulate nodes (e.g., the dorsolateral prefrontal cortex [DLPFC] and the dorsal anterior cingulate cortex [dACC]) to poorer task performances, whereas individuals with depression seem to require heightened activation to perform as well as healthy controls (Rayner et al., 2016).

Growing evidence also points to a disruptive interaction between cognition and emotion (Rayner et al., 2016; Schweizer et al., 2019) resulting in, for example, affective biases during cognitively demanding tasks (Gotlib et al., 2004). Further, abnormal DLPFC and pgACC functioning has been associated with impaired WM in depression (Matsuo et al., 2007). Individuals with depression have also displayed decreased neuronal activity in the left and increased neuronal activity in the right DLPFC during emotional stimulation (Grimm et al., 2008). In keeping with the idea of lateralization effects in the DLPFC, Groenewold et al. (2013) reported in a meta-analysis including 44 fMRI studies, all of which probed emotional processing, that the left DLPFC was often less activated in depressed patients compared with healthy controls when presented with negative compared with neutral stimuli.

Current neuroimaging studies suggest that some of the identified abnormalities in functional brain activation normalize after successful treatment (Fales et al., 2009; Perrin et al., 2012; Beall et al., 2012; Abbott et al., 2013, 2014; Redlich et al., 2017). These findings were confirmed in meta-analytic investigations in which both hypo-activation in the prefrontal cortex and hyperactivation in limbic and paralimbic regions during emotional tasks normalized after pharmacological treatment (Fitzgerald et al., 2008; Delaveau et al., 2011). Similarly, in a meta-analysis by Ma (2015), functional activation in prefrontal areas (e.g., increased activity in the DLPFC during negative and positive emotions) and the emotional network normalized after successful pharmacological antidepressant treatment. In addition, cognitive behavioral therapy (CBT) normalized amygdala-hippocampal hyperactivity and dACC hypoactivity to sad faces (Fu et al., 2008). When considering normalization effects specific to ECT, fMRI studies have revealed changes in functional brain activation during emotion-processing tasks post- compared with pre-ECT (Miskowiak et al., 2017; Downey et al., 2019; Enneking et al., 2020; Loureiro et al., 2020). For instance, Enneking et al. (2020) found an increase in dACC activity after a course of ECT in depressed participants who completed a face-matching task, that was driven by treatment responders. Taken together, these findings imply that ECT, and successful treatments in general, alter activity in brain areas involved in emotional and cognitive processing. Yet the understanding of how these processes may predict response demonstrates a large challenge in research efforts.

Current investigations have highlighted the ACC as a potential biomarker for treatment response (e.g., Pizzagalli, 2011; Fu et al., 2013; Victor et al., 2013; Argyelan et al., 2016; Godlewska et al., 2018; Enneking et al., 2020). In depression research, 2 main functional subdivisions of the ACC are distinguished: whereas activity in the rostral-ventral division (i.e., sgACC and pgACC) is usually modulated by affect-related tasks, activation in the dorsal division is associated with cognitively demanding tasks (e.g., WM tasks; Jaworska et al., 2015). Indeed, in a review of 23 studies studying different antidepressant treatments and imaging methods, increased pretreatment activation in the affective subdivision, the pgACC, predicted a greater response (Pizzagalli, 2011). Regional functional activation in the sgACC has also emerged as a candidate predictor of treatment response to antidepressant medication and CBT (Fu et al., 2013). Furthermore, in a study using an implicit sad facial affect recognition task in patients receiving 16 sessions of CBT, attenuated baseline activity in the cognitive subdivision, the dACC, was associated with clinical response (Fu et al., 2008).

So far, prediction studies investigating neural markers specific to ECT response have mainly focused on neuroimaging methods such as structural MRI (e.g., Redlich et al., 2016; Wade et al., 2016; Gärtner et al., 2021) or resting-state (e.g., Perrin et al., 2012; Abbott et al., 2013), and functional connectivity analyses (e.g., Cano et al., 2016; Leaver et al., 2018). To the best of our knowledge, only a few fMRI investigations have directly linked pretreatment

task-induced regional brain activation to the improvement of depressive symptoms after ECT (Redlich et al., 2017; Enneking et al., 2020). Thus, additional task-based fMRI studies are needed to clarify the prognostic value of potential neural markers.

This investigation aims to clarify the association between functional brain activity and symptom improvement after ECT. To achieve this, we acquired task-based fMRI data before and after a course of ECT and performed region of interest (ROI) analyses. In the present investigation, we focused the analyses on the following ROIs: bilateral (left/right) DLPFC and pregenual, dorsal, and subgenual ACC (pgACC, dACC, sgACC). These regions were selected according to both their relevance in MDD pathophysiology and prediction of treatment response in prior meta-analyses and reviews (e.g., Pizzagalli, 2011; Fu et al., 2013). Further, we chose to employ an emotional WM task that includes verbal stimuli (Grimm et al., 2012), which allows studying the interaction between emotion and cognition by simultaneously activating, for instance, both the pgACC and DPLFC. Yet, the emotional WM task does not robustly activate other corticolimbic regions relevant for emotion processing, such as the amygdala, which we consequently did not select as additional ROI (Hartling et al., 2021).

First, we hypothesized that neural activity in the chosen ROIs during an emotional WM task before treatment would predict symptom improvement after ECT. We expected that increased pre-ECT activity in affective subdivisions of the ACC, and attenuated activity in the dACC and the DLPFC, would predict treatment response. Second, we compared pre-ECT and post-ECT fMRI data to identify potential ECT-evoked changes in brain activation (normalization effects). Specifically, we expected that ECT normalizes aberrant patterns of hypoactivity in brain regions for cognitive control (DLPFC and dACC) and hyperactivity (or inability to deactivate) in regions of the DMN (sgACC and pgACC) during the emotional WM task and that these changes in activation would relate to treatment response. Further, we expected a normalization of the hemispheric imbalance (right-sided hyper- and left-sided hypoactivity) in the DLPFC during emotion–cognition interaction from pre- compared with post-ECT.

Methods

Participants

The reported data were collected between 2017 and 2021 as part of the Mechanisms of Antidepressant Treatment Response (MATTER) study conducted in Berlin. In total, 21 inpatients of the Department of Psychiatry, Charité - University Medicine Berlin (Campus Benjamin Franklin) who underwent a 4-week course of ECT as antidepressant treatment agreed to participate in the study (9 women, 12 men; M = 44.05 years, SD = ± 11.03, range = 22–60 years). MRI assessments were conducted before the first (T0) and after the last (regularly 12th) ECT session (T2). There were also 2 scanning sessions not included in the analyses: 1 after the fourth session of ECT (T1), and one 6 months after the last ECT session (T3). For 2 participants, imaging data could not be collected at T2 (1 patient experienced claustrophobia in the scanner and refused a second measurement; for 1 patient, T2 was canceled due to COVID-19–related contact restrictions; also see supplementary Figure 1). However, both individuals agreed to participate in a second Montgomery-Åsberg Depression Rating Scale (MADRS) interview, which enabled us to calculate their percent change to baseline (PCB) response value. Inclusion criteria required that all participants (1) had a clinical indication for ECT, (2) fulfilled criteria of an acute MDD episode at baseline (according to DSM-5), and (3) were fluent in spoken and written German. Exclusion criteria were the presence of primary claustrophobia, MR contra-indications (e.g., cardiac pacemakers, metallic or electronic implants, etc.), previous traumatic brain injury, and other psychiatric or neurological disorders such as obsessive-compulsive disorder, alcohol, or substance abuse. The study was conducted according to the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of Charité - University Medicine Berlin. All participants provided written informed consent before participation. [Clinical Trials Registration number: NCT02871141]

Electroconvulsive Therapy

Each participant received ECT 3 times per week, mostly over the course of 4 weeks. The anesthetic agents included propofol (approximately 1.50 mg/kg) or etomidate (approximately 0.75 mg/kg). Succinylcholine (approximately 0.75 mg/kg) was used for muscular relaxation. The procedure followed the standard clinical protocols at the Department of Psychiatry that had been adapted to minimize cognitive impairment (for detailed descriptions of the ECT procedure, see Roepke et al., 2011 and Brakemeier et al., 2014). A customized MECTA spectrum 5000 Q device (MECTA Corp, Lake Oswego, OR, USA) delivered ultra-brief pulse stimuli (0.3 milliseconds) for right unilateral ECT. During the first ECT treatment, the seizure threshold was titrated, and voltage was only modified if patients did not clinically respond or showed insufficient seizures during the course of ECT (i.e., motor response <20 seconds or electroencephalogram seizure activity <30 seconds). An electroencephalogram was recorded from 2 channels using frontomastoid placements and monitored during ECT to confirm seizure activity and document seizure duration.

Functional Imaging

fMRI was conducted using a 3T Tim Trio MR scanner (Siemens, Erlangen, Germany; c.f. supplementary Table 1) with a standard 12-channel head coil at the Center for Cognitive Neuroscience Berlin (Free University Berlin). Functional scans were collected in one 12-minute run with 326 volumes and 37 oblique axial slices (TR = 2000 milliseconds, TE = 30 milliseconds, flip angle = 70, field of view = 192 mm, voxel size 3 × 3 × 3 mm). The MRI protocol also included a T1-weighted high-resolution MP-Rage scan (176 volumes, TR = 1900 milliseconds, TE = 2.52 milliseconds, flip angle = 9, field of view = 256 × 256 mm, voxel size 1 × 1 × 1 mm).

Psychological Assessment

Montgomery-Åsberg Depression Rating Scale—Symptom severity was rated by means of the German version of the MADRS (Montgomery and Asberg, 1979; German version, Neumann and Schulte, 1988). The MADRS includes 10 items rated on a 7-point (0–6) Likert scale. The score is summed for analyses and ranges from 0 to 60, with a higher score indicating greater symptom severity. The MADRS has good to excellent internal consistency, with Cronbach's alpha (α) ranging between .82 and .92 (Maier and Philipp, 1985).

Trained psychologists conducted the clinical assessment in the form of a semi-structured interview. The change in MADRS scores from baseline to post ECT was computed for each participant and estimated with the PCB response value: PCB = ([baseline – follow-up]/ baseline) * 100. Participants were classified as treatment responders if they reached a symptom reduction of ≥50% from baseline to the last ECT session (Bauer et al., 2013). Otherwise, participants were classified as treatment non-responders.

***WM Task*—**All participants completed an emotional 2-back task (EMOBACK), that is, a WM task that includes standardized emotional words. The block-designed task is composed of emotional (positive and negative) and neutral German nouns obtained from the Berlin Affective Word List (Võ et al., 2009). The nouns are matched for word length, imageability, and frequency (Grimm et al., 2012). The participants viewed the nouns in the center of a projection screen and were told to push a button whenever the presented word was identical to the one presented 2 trials back. Hence, the participants were required to monitor and remember the series of nouns to correctly respond to each target. Each condition (positive, negative, and neutral) was presented in blocks of 15 words (5 of each valence category) that were separated by fixation crosses of 10–14 seconds (see Figure 1). For each block, only 3 targets were included such that for a total of 225 words in 15 blocks, a maximum of 45 correct answers was achievable. The total task duration was 12 minutes. Parallel versions of the task were used at the 2 time points. The order in which the participants saw the parallel versions was counterbalanced.

***Procedure*—**At the beginning of each session, the MADRS interview for clinical assessment was performed. After the interview, participants received instructions on the EMOBACK task. To ensure familiarity and confirm performance accuracy during the task, participants undertook a practice trial of the task outside the scanner room. Once in the scanner, the words were generated by the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) and projected onto a screen situated at the head end of the MRI scanner bore. Participants saw the screen through a mirror placed on the head coil and were requested to respond as quickly and accurately as possible by pushing an assigned button on a standard MR response button pad.

Statistical Analysis

***Clinical, Demographic, and Behavioral Data*—**Analyses of demographic, clinical, and behavioral data were conducted using the statistical software R (version 4.1.2, R Core Team, 2021). Both accuracy and reaction times were determined for each participant. To express accuracy as a percentage with a maximum of 100, the ratio of correctly pressed responses to the total number of targets was calculated and multiplied by 100: ACCURACY = ([correctly pressed – false alarms]/ total number of targets) * 100. Mean reaction times were defined as the time between stimulus appearance and a correct response. To investigate the influence of emotional interference on WM performance (Schweizer et al., 2019), accuracy and reaction times were reported overall as well as for neutral and emotional stimuli separately. To investigate differences between pre- and post-ECT, as well as potential associations with neural activity in the chosen ROIs, *t* tests for dependent samples and Pearson correlation analyses were applied. The correlation plots were created in the *corrplot* package (version 0.84; Wei and Simko, 2017).

***fMRI Data*—**Functional images were preprocessed using MATLAB R2020b (The Mathworks, Natick, MA, USA) and SPM12 revision 7771 (Statistical Parametric Mapping, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk). Preprocessing steps included correcting for head motion by realignment according to the first volume; co-registration of the anatomical image to the mean functional image per participant; segmentation of the anatomical image; spatial normalization to the standard stereotactic space template from the Montreal Neurological Institute; and spatial smoothing with a full-width at half-maximum 6-mm Gaussian kernel. None of the participants showed excessive head movements during fMRI scanning (translational movement > 3 mm or rotation > 3°). The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. The statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors.

A fixed-effect model at a single-subject level was performed to create images of parameter estimates. For each participant, 2 contrast images were calculated: one testing the response to the WM task compared with the fixation cross (WM > fixation) and 1 testing the response to emotional stimuli relative to neutral stimuli (emotional > neutral). ROI analyses were performed using spherical ROI templates with a diameter of 10 mm that were built according to automated term-based meta-analyses on neurosynth.org and (for pgACC) previous work from our group (Grimm et al., 2012). The following ROIs were defined (Montreal Neurological Institute coordinates in parentheses; see also Figure 2): bilateral DLPFC (±40 36 32), pgACC (0 42 2), sgACC (0 28 -12), and dACC (0 32 20). The mean activity level of each ROI was extracted with the REX Toolbox (Duff et al., 2007; https://www.nitrc.org/projects/rex/).

Changes in ROI activation over the course of treatment and the association between ROI activation and change in psychometric scores were computed using the statistical software R (version 4.1.2, R Core Team, 2021). Linear regression models were utilized to test whether functional activity in the chosen ROIs at baseline was associated with changes in symptom severity. For the linear regression analyses, all participants (n = 21) were

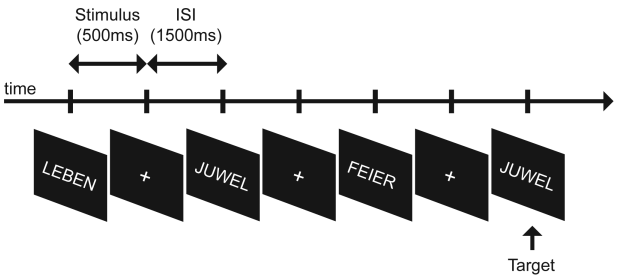

Figure 1. Experimental paradigm: schematic representation of the EMOBACK task. Word stimuli of positive, negative, or neutral valence. Participants responded whenever a word was also presented 2 trials previously. In this example, "JUWEL" is a target word. ISI, interstimulus interval.

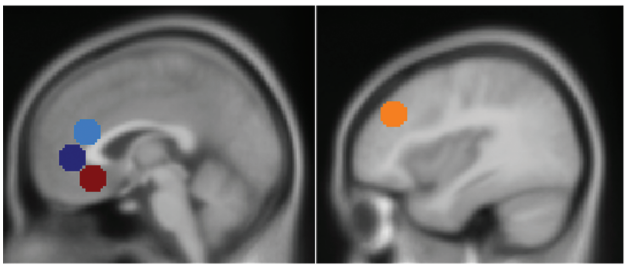

Figure 2. Region of interest templates were spheres with a 10-mm diameter. Cyan = dorsal anterior cingulate cortex (dACC), blue = pregenual anterior cingulate cortex (pgACC), red = subgenual anterior cingulate cortex (sgACC), and orange = right and left dorsolateral prefrontal cortex (DLPFC).

included. To investigate changes in functional brain activation between time points, we applied t tests for dependent samples and Pearson correlation analyses (2-tailed). Due to the drop-out of 2 participants at T2, 19 participants (n = 19) were included for the comparison of pre-ECT and post-ECT fMRI data. To account for multiple comparisons (across the 5 ROIs), Bonferroni correction was used for all analyses. Thus, the Bonferroni-corrected threshold for significance was set to $P = .05/5 = .01$.

Results

Sample Characteristics and Clinical Data

Clinical and demographic data for the entire sample (n = 21) are summarized in Table 1. The mean number of ECT sessions administered was M = 13.19 (SD = 2.62, range = 11–20). All participants were treated with antidepressant medications throughout this investigation. Psychopharmacological medication (either as monotherapy or augmentation) included selective serotonin reuptake inhibitors (SSRIs) (n = 8), atypical neuroleptics (n = 6), norepinephrine reuptake inhibitors (SNRIs) (n = 4), tri-/tetracyclic antidepressants (n = 4), norepinephrine–dopamine reuptake inhibitor (NDRI) (n = 4), monoamine oxidase inhibitors (MAOIs) (n = 1), lithium (n = 4), benzodiazepines (n = 2), and melatonin-receptor antagonists (n = 1).

The mean MADRS score at baseline was M = 32.00 (SD = 5.11, range = 24–45, n = 21). The average symptom reduction was M = 37.47% (SD = 27.88; range = −17.86 to 95.83%, n = 21). Based on our set criteria, 42.86% of the participants (9/21) could be classified as treatment responders and 57.14% (12/21) as non-responders. Within the non-responders, 41.67% of participants (5/12) showed at least partial response to the treatment (26%–49% decrease), and 58.33% of participants (7/12) showed no response (≤25% decrease; Bauer et al., 2013). None of the included patients experienced serious adverse effects that might have led to a discontinuation of the ECT treatment or an exclusion from the study. Minor, commonly occurring adverse effects such as dizziness and nausea after ECT treatment were not systematically documented.

Behavioral Results

Behavioral results are outlined in Table 2. With respect to the general accuracy on the WM task, there was no significant difference between pre- and post-treatment ($t_{(18)} = 0.214$, $P = .833$, n = 19). Likewise, neither accuracy regarding emotional stimuli ($t_{(18)} = 1.409$, $P = .176$, n = 19) nor neutral stimuli ($t_{(18)} = -1.521$, $P = .146$, n = 19) differed between pre- and post-treatment. With respect to the mean reaction time on the task, pre- and post-treatment did not differ ($t_{(18)} = -0.772$, $P = .450$, n = 19).

Table 1. Sample Characteristics at Baseline (T0)[a]

Variables	Participants (n = 21)
Age (years; M, SD)	44.05 (11.03)
Gender (women/men)	9/12
PCB value (%; M, SD)	37.47 (27.88)
MADRS Scores T0	32.00 (5.11)
MADRS Scores T2	20.38 (9.97)
Number of ECT sessions	13.19 (2.62)

Abbreviations: ECT, electroconvulsive therapy; MADRS, Montgomery Åsberg Depression Rating Scale; PCB, percent change to baseline.
[a]SDs appear in parentheses.

fMRI Results: Prediction of Treatment Outcome

The results of the regression analyses are outlined in Table 3. BOLD signals in none of the ROIs predicted significant changes in depressive symptoms. Concerning the contrast emotional > neutral, there was a nominally significant association between symptom reduction and baseline activity in the lDLPFC ($F_{(1,19)} = 4.646$, $P = .044$, n = 21). In the contrast WM > fixation, dACC activity was slightly associated with changes in depressive symptoms ($F_{(1,19)} = 3.578$, $P = .074$, n = 21), which, however, was not statistically significant. Both findings are illustrated in Figure 3. Symptom severity at baseline was not associated with baseline neural activity in the chosen ROIs (post-hoc correlational analyses; see supplementary Table 2).

fMRI Results: Change Over Course of Treatment

As there were no imaging data available for 2 participants from time point T2 (c.f. Methods section), results are reported for n = 19 participants. All demographic variables (age, gender distribution, severity) were comparable between the full sample and the participants with T2 data.

Paired t tests between ROI activity estimates from time points T0 and T2 were conducted to test whether any statistically significant changes of activity occurred over the course of treatment. Results indicated no significant changes (all $P > .05$, n = 19) over the course of treatment. Supplementary Table 3 shows all parameters for paired t tests for neural activity from all ROIs between T0 and T2. Figure 4 shows individual and group mean activation for each ROI at time point T0 and T2 for the WM > fixation and the emotional > neutral contrast.

fMRI Results: Correlation Between Changes Over Course of Treatment and Symptom Reduction

To test whether changes in neural activity in the ROIs were associated with depression symptom reduction, bivariate Pearson correlation analyses were conducted between the differences in parameter estimates of neural activation at time points T0 and T2 in the different ROIs and symptom reduction. No significant correlations emerged ($r_{(17)} = -.25$ to .40, n = 19, all $P > .05$). Supplementary Table 4 shows all parameters.

fMRI Results: Correlation Between WM Performance and Functional Activation

On a liberal threshold, we found a positive correlation between lDLPFC activity and WM accuracy prior to treatment ($r_{(19)} = .46$, $P = .038$, n = 21; contrast WM vs fixation), which implies that participants with higher activity prior to treatment showed

Table 2. Behavioral Results

Variables	Participants (T0; n = 21)	Participants (T2; n = 19)
Accuracy total (%; M, SD)	58.94 (24.14)	60.70 (20.10)
Accuracy emotional (%; M, SD)	62.38 (23.55)	59.12 (22.71)
Accuracy neutral (%; M, SD)	52.06 (28.33)	63.86 (21.12)
Reaction time (ms; M, SD)	605.31 (146.45)	630.74 (176.02)

SDs appear in parentheses.

Table 3. Regression Coefficients for Relation of Baseline Regional Function Activation to Changes in Depressive Symptoms

Variables	*B*	95% CI lower	95% CI higher	SE	*P*	R^2
Contrast: WM > fixation						
Constant	32.40	2.27	62.53	14.40		
rDLPFC	3.00	−13.09	19.10	7.69	.700	0.01
Constant	43.23	21.61	64.85	10.34		
lDLPFC	−3.93	−15.77	7.91	5.66	.495	0.03
Constant	30.53	3.84	57.21	12.75		
pgACC	−4.78	−20.84	11.29	7.67	.541	0.02
Constant	31.95	6.97	56.94	11.94		
sgACC	−5.90	−28.74	16.95	10.92	.595	0.02
Constant	31.43	17.71	45.15	6.55		
dACC	−11.07	−23.32	1.18	5.85	.074	0.16
Contrast: emotional > neutral						
Constant	39.07	26.50	51.65	6.01		
rDLPFC	23.50	−9.75	56.76	15.89	.155	0.10
Constant	39.55	27.67	51.44	5.68		
lDLPFC	37.10	1.07	73.12	17.21	.044+	0.20
Constant	37.82	25.20	50.44	6.03		
pgACC	19.41	−14.82	53.64	16.36	.250	0.07
Constant	37.53	24.70	50.36	6.13		
sgACC	16.32	−24.35	56.99	19.43	.411	0.04
Constant	37.60	24.59	50.62	6.22		
dACC	9.37	−35.31	54.06	21.35	.666	0.01

Abbreviations: dACC, dorsal anterior cingulate cortex; lDLPFC, left dorsolateral prefrontal cortex; pgACC, pregenual anterior cingulate cortex; rDLPFC, right dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulate cortex; WM, working memory.
Baseline fMRI activity was entered to predict changes in depressive symptoms. *B* represents unstandardized regression weights.
+$P < .05$.

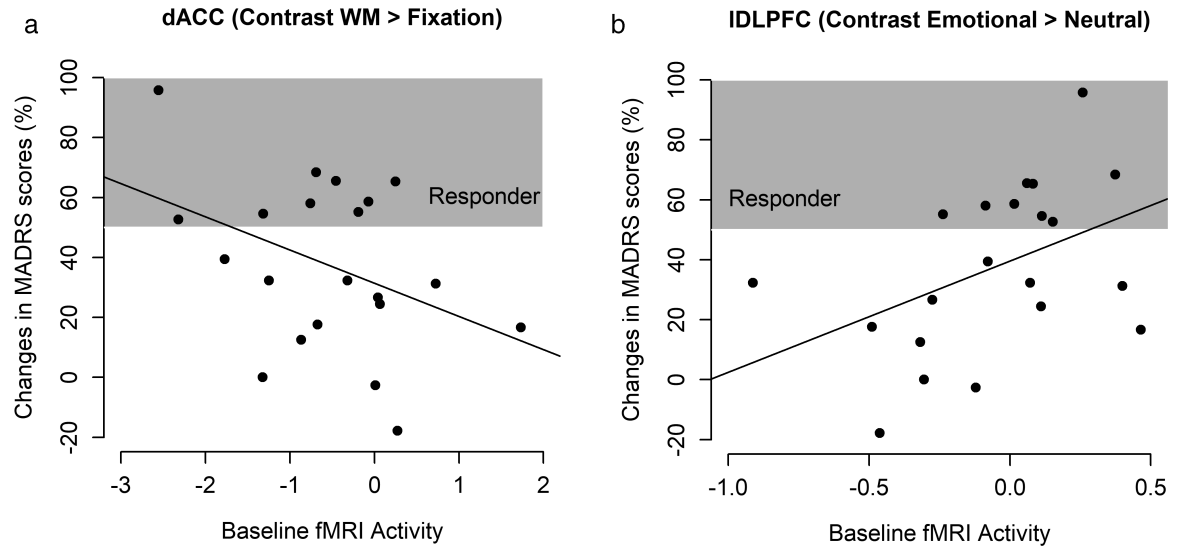

Figure 3. The scatter plots represent the patients' symptom improvement (*y*-axis; unstandardized percent change to baseline (PCB) value of each participant) with their pretreatment brain activation (*x*-axis; unstandardized mean activity level of each participant). Left: Weak association between functional activity in the dorsal anterior cingulate cortex (dACC) and the participants' percent change in the Montgomery Åsberg Depression Rating Scale (MADRS) for the WM > fixation contrast ($F_{(1,19)} = 3.578$, $P = .074$). Right: Nominally significant association between functional activity in the left dorsolateral prefrontal cortex (lDLPFC) and the participants' percent change in the MADRS for the emotional > neutral contrast ($F_{(1,19)} = 4.646$, $P = .044$). dACC, dorsal anterior cingulate cortex; lDLPFC, left dorsolateral prefrontal cortex; MADRS, Montgomery Asberg Depression Rating Scale; ROI, region of interest; WM, working memory.

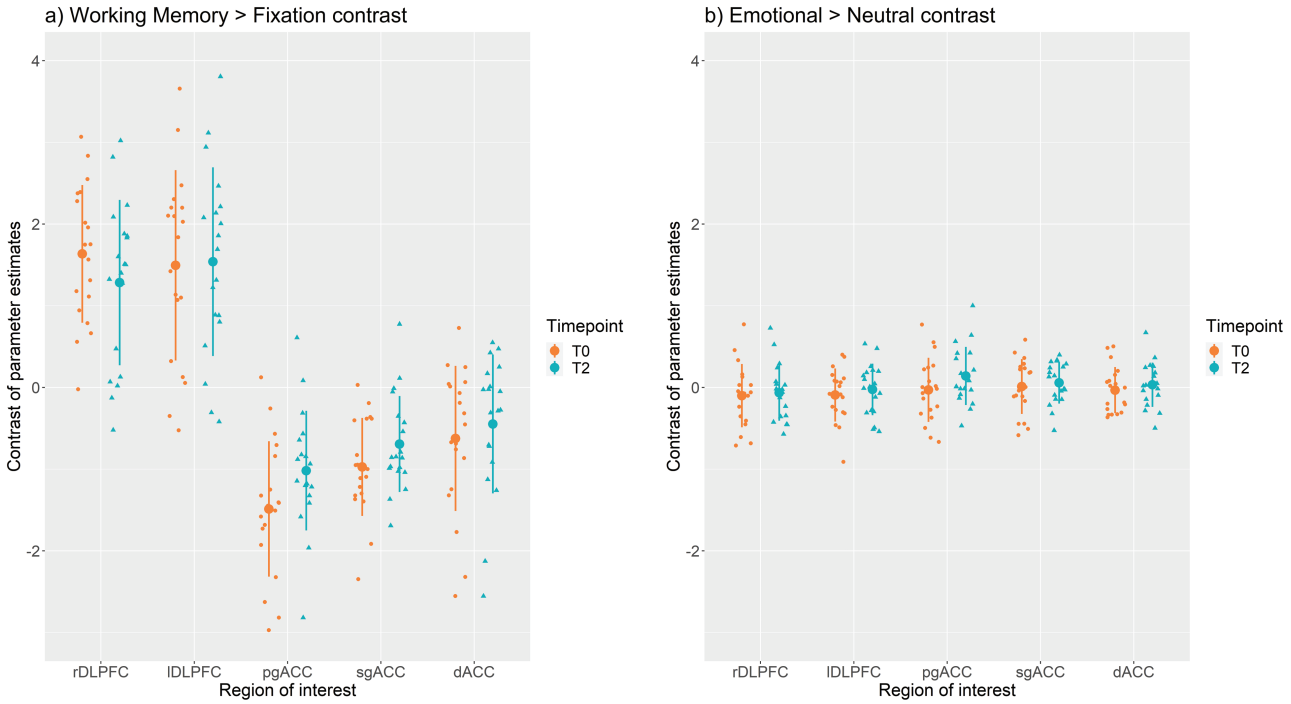

Figure 4. Contrast of mean parameter estimates of neuronal activation in the prespecified regions of interest on group (big dots) and individual (jittered dots and triangles) level for (A) WM > fixation contrast and (B) emotional > neutral contrast. Colors represent the different time points; orange: T0 (before ECT treatment), blue: T2 (after treatment with M = 12.1 ECT sessions). dACC, dorsal anterior cingulate cortex; lDLPFC, left dorsolateral prefrontal cortex; pgACC, pregenual anterior cingulate cortex; rDLPFC, right dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulated cortex; T0, before ECT treatment; T2, after ECT treatment.

higher WM accuracy (see Figure 5). When considering accuracies of emotional and neutral stimuli separately, the pattern of association with the lDLPFC was obtained only for neutral stimuli ($r_{(19)} = .48$, $P = .029$, n = 21) but not emotional stimuli ($r_{(19)} = .41$, $P = .064$, n = 21). At T2 (n = 19), no correlations between accuracy measures and activity within the chosen ROIs were detected.

Discussion

The present study was designed to identify neural predictors of treatment response and investigate neurofunctional changes over the course of ECT. To achieve this, acutely depressed individuals completed an emotional WM task before and after receiving treatment with ECT. However, inconsistent with our hypotheses, significant neural prognostic markers or changes in neural activity from pre- to post-ECT did not emerge.

Firstly, this study investigated whether pretreatment functional brain activation was associated with symptomatic improvement after ECT. In this context, neuroimaging studies have pointed to the involvement of dorsal cognitive (Fu et al., 2008; Enneking et al., 2020) and rostral-ventral affective (Pizzagalli, 2011; Fu et al., 2013; Victor et al., 2013; Godlewska et al., 2018) subdivisions of the ACC and suggested that the baseline (i.e., pretreatment) level of activity in these regions would predict response to treatment. However, inconsistent with prior literature, we did not replicate these findings. When contrasting the WM condition vs fixation, we found a weak but not statistically significant association between reduced pretreatment activity in the dACC and improvement in symptom severity. Walsh et al. (2007) reported similar association patterns in the dACC; acutely depressed patients who showed higher brain activity with increasing task difficulty in an n-back verbal WM task responded worse to fluoxetine treatment. These results might suggest that significant association patterns are more likely to emerge when the WM load increases. Enneking et al. (2020) has also identified, in a logistic regression analysis, that lower pretreatment activity in the dACC during an emotion procession task was associated with increased odds of achieving ECT response.

When testing the response of emotional stimuli relative to neutral stimuli, only at a liberal threshold, we found that increased pretreatment activity in the lDLPFC was associated with symptom improvement. This finding is in line with reported hemispheric lateralization effects: whereas the lDLPFC is thought to maintain verbal information during WM tasks, the rDLPFC has been associated with the maintenance of visual stimuli (Owen et al., 2005; Hertrich et al., 2021). Similarly, in a meta-analysis that included predominantly verbal WM conditions, individuals with depression displayed hyperactivation in the lDLPFC compared with healthy controls (Wang et al., 2015). However, the prognostic value of DLPFC activation to ECT response has mainly been identified in functional connectivity studies (Perrin et al., 2012; Abbott et al., 2013). It remains for future research, therefore, to examine whether pretreatment magnitude of DLPFC activity during cognitive and/or emotional processing predicts response to ECT.

Importantly, findings regarding the dACC and lDLPFC are not significant after correcting for multiple comparisons, which increases the chance of committing a type I error (i.e., erroneously rejecting a null hypothesis). Therefore, and in consideration of the heterogeneity in depressive disorders (e.g., in etiology and pathophysiology), the ability to interpret both findings remains limited. In addition, to the best of our knowledge, only 2 fMRI investigations have directly linked pretreatment task-induced brain activation to the improvement of depressive symptoms after ECT

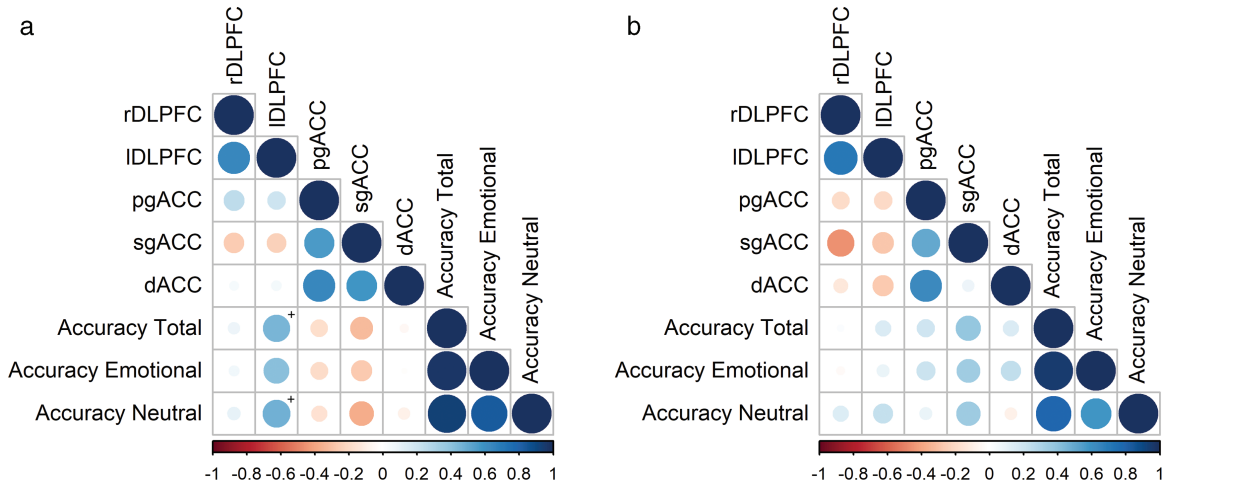

Figure 5. Left: Pearson correlation analyses between accuracy measures and functional activity in the chosen ROIs at T0 (contrast WM > fixation; n = 21). Right: Pearson correlation analyses between accuracy measures and functional activity in the chosen ROIs at T2 (contrast WM > fixation; n = 19). dACC, dorsal anterior cingulate cortex; lDLPFC, left dorsolateral prefrontal cortex; pgACC, pregenual anterior cingulate cortex; rDLPFC, right dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulate cortex. $^{+}P < .05$.

(e.g., Redlich et al., 2017; Enneking et al., 2020). However, both Redlich et al. (2017) and Enneking et al. (2020) employed face-processing tasks to investigate whether pretreatment brain activations during emotion processing were predictive of response to ECT, whereas we used a task that engages both emotional and cognitive processing. Although Redlich et al. (2017) reported that neurofunctional changes in the amygdala over the course of ECT were associated with symptom improvement, pretreatment activation had no predictive value to indicate response. Enneking et al. (2020) found that pretreatment-attenuated dACC activity was associated with increased odds of treatment response. Although the finding from the latter study is partly in line with our findings, to the best of our knowledge, it was not corrected for multiple comparisons across ROIs; therefore, additional task-based fMRI studies are needed to confirm the predictive value of this potential neural marker.

Another aim of this study was to compare pre-ECT and post-ECT fMRI data to identify potential ECT-evoked changes in brain activation. Whereas previous studies with comparable sample sizes of ECT patients (Miskowiak et al., 2017; Downey et al., 2019; Enneking et al., 2020; Loureiro et al., 2020) have reported changes in functional brain activation over the course of treatment, the present study failed to find any significant effects. For example, Enneking et al. (2020) found an increase in dACC activity post- compared with pre-ECT. Although our ROI (0 32 20) was located slightly further dorsal than the reported cluster (2 36 16), we could not replicate this finding. Another recent fMRI study (Loureiro et al., 2020) reported reduced amygdalar activation towards emotional stimuli but no change in dACC activity. This is a notable inconsistency between the 2 studies, because both used similar emotional face-matching tasks, which could suggest similar activation patterns and changes therein over time. Although ECT effects on neural activation during emotion processing are hence still partly unclear, it should also be noted that the EMOBACK task is rather aimed at investigating emotion–cognition interaction than sheer emotion effects (Hartling et al., 2021). Thus, it is possible that ECT may have an effect primarily on the processing of emotional information and less on the (higher-order) mechanism of integrating emotional information with executive tasks.

We further hypothesized that ECT would modulate prefrontal hemispheric imbalance of right-sided hyper- and left-sided hypoactivity, because this differential neuropsychological characterization was found by other fMRI studies using tasks probing emotion stimulation or emotion–cognition interaction (Grimm et al., 2008; Diener et al., 2012). Although we observed a numerical reduction of activity in the right DLPFC and a slight increase of activity in the left DLPFC ROI over the course of ECT, these changes were not significant. Speculatively, neurofunctional changes induced by ECT may not be best grasped directly after the acute treatment phase. Brain functional changes induced by ECT might be mediated by a re-wiring process during a time window of ECT-induced neuroplasticity (Ousdal et al., 2021). This process might not be completed after the last ECT session but rather occur over the course of several months (Kohler et al., 2011).

Surprisingly, we did not detect restored deactivation in the 2 affective subareas of the ACC (i.e., pgACC and sgACC) after ECT, as has been reported after pharmacological interventions (Delaveau et al., 2011). Also, both ROIs did not emerge as predictors of treatment response. PgACC activity has been a well-replicated neuroimaging marker of depressive symptom improvement (Pizzagalli, 2011; Fu et al., 2013; Victor et al., 2013; Godlewska et al., 2018), and the absence of effects may suggest pgACC activity as an indicator of response specific to pharmacological or psychotherapeutic treatments. It could also point to a difference in the neurobiological mechanisms of change, where ECT may not (directly) modulate deactivation in the DMN. However, it is also possible that ECT effects on activation in both ROIs were too small to be detected by our study due to its limited statistical power. The present results may also differ from previous studies because of the used task because hyperactivity in the sgACC and pgACC (or inability to deactivate them) is often detected by neuroimaging tasks eliciting negative processing biases (Pizzagalli and Roberts, 2022). Most studies probing emotional processing or the modulatory effects of emotional stimuli on WM utilize visual—but not verbal—task stimuli (Hertrich et al., 2021), with 1-word stimuli eliciting weaker emotional brain responses (Schlochtermeier et al., 2013).

Lastly, we investigated whether regional brain activity was associated with performance levels in the WM task. When contrasting the WM condition against fixation, we found a nominally

significant correlation between higher activity in the lDLPFC and more accurate responses during the task (overall accuracy and accuracy regarding neutral stimuli). Indeed, prefrontal hyperactivation in MDD patients has been associated with intact performances during WM tasks (Rayner et al., 2016). This pattern of association is also consistent with data reported by Gärtner et al. (2018), who found that although acutely depressed patients had similar behavioral performances to healthy controls in the EMOBACK-task, they exhibited increased reactivity in the lDLPFC. However, the overall mean accuracy level in this sample was 55.83%, which is lower than the means reported by Gärtner et al. (2018; 73.60% accuracy for depressed patients). Both samples also differed in depression severity, with our sample having slightly higher depression severity scores. We propose that task demands may have been too high for this sample, which may have led to non-significant effects. In keeping with this idea, a review by Pizzagalli (2011) inferred that reduced behavioral performance is generally accompanied by blunted DLPFC and dACC activation.

Another possibility for the null results in this study could be the comparably low proportion of treatment responders. Although most participants had a reduction in symptoms after ECT, fewer than one-half of the participants could be classified as responders, suggesting that there was a more heterogeneous antidepressant response to ECT than the previous literature suggests (Rush et al., 2006; Brakemeier et al., 2014). This may have been caused by the low representation of patients with psychotic symptoms or schizoaffective disorders, because these variables have been identified as a clinical predictors of treatment response (van Diermen et al., 2018). Another tentative explanation could be the younger age representation in our sample or lower symptom severity scores compared with other clinical trials (e.g., Brakemeier et al., 2014). Future studies could examine specified subgroups (e.g., depressive episodes with vs without psychotic symptoms or younger vs older age groups), which would clarify the differences in responses to ECT. In addition, this is the first time, to our knowledge, the EMOBACK task was used for interventional research, and although the task reliably elicits BOLD responses in both cognition and emotion-related regions (Grimm et al., 2012; Scheidegger et al., 2016; Gärtner et al., 2018), it is unclear whether it is sensitive to change (pre- to post-ECT). Although it is always harder to interpret non-significant than significant findings, our results demonstrate that any relationships between neurofunctional activation patterns and antidepressant response to ECT are likely specific to the task used and/or the sample characteristics. Further, it might suggest that such effects are less robust than would be needed for biomarkers with clinical utility.

The current study has several strengths, such as the use of a regression-based prediction analysis on continuous symptom reductions. Several patients only partially responded to the treatment, and the dichotomization into ECT responders and non-responders may limit the informative value of the results (Royston et al., 2006; Carstens et al., 2021; Gärtner et al., 2021). Also, we investigated a naturalistic sample of depressed patients in a clinical setting, which makes the sample more representative for depressed patients receiving ECT (Carstens et al., 2021). Lastly, this publication reports non-significant results, which aids in the understanding of ECT effects. If publication bias is present (i.e., selective publication of studies reporting statistically significant results), guidelines recommending the employment of certain interventions may be mistakenly deducted from meta-analyses. Psychotherapists and physicians would employ interventions in routine care that may be less efficacious than previously assumed. Still, methodological limitations and clinical implications of the present findings warrant discussion.

The sample size was modest, and we did not correct for multiple confounders, which could have affected the power of our study. The sample size represents general difficulties in the recruitment of the target group itself, that is, severely depressed patients receiving ECT. If a prediction of treatment response with neural markers is feasible, multi-center collaborations make it more likely to recruit enough participants to provide clinically reliable and valuable results (van Horn and Toga, 2009; Ousdal et al., 2021). Another limitation reflects the use of sum scores. Depression is a highly heterogeneous disorder with divergent responses to treatment (Fried and Nesse, 2015; Drysdale et al., 2017). The use of sum scores may therefore be insufficient to identify evidence-based neural predictors of symptom improvement (Carstens et al., 2021). Future studies should rely on more nuanced categorization systems to reduce diagnostic heterogeneity (e.g., clustering participants into subgroups defined by shared neurobiological or clinical substrates) because this could improve the precision of predictive neuroimaging models of ECT effects (Wade et al., 2021). Finally, although this is due to the naturalistic study set-up, the participants in this study were all medicated, which raises the question of possible medication effects on the behavioral and functional results. The different types of antidepressant medication might have posed an additional variance or might have blunted the statistical signal of a possible ECT effect. It is also conceivable that we were unable to detect interhemispheric differences due to the masking effects of the different types of antidepressant medication (Bajbouj et al., 2006).

In conclusion, we did not confirm our hypothesis that ECT normalizes aberrant patterns of hypoactivity in brain regions for cognitive control (DLPFC and dACC) and hyperactivity in regions of the DMN (sgACC and pgACC). Depressive symptom improvement was also not associated with pretreatment functional activation during the EMOBACK task. Therefore, our results demonstrate that the search for reliable and clinically useful biomarkers for ECT treatment is still facing challenges.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

Simone Grimm has served as a consultant to and received research support from Boehringer Ingelheim Pharma. Malek Bajbouj has served as a consultant to GH Research, Janssen, Bayer, and Boehringer Ingelheim.

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