

Frontoparietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients With Major Depression

Anett Gyurak, Brian Patenaude, Mayuresh S. Korgaonkar, Stuart M. Grieve, Leanne M. Williams, and Amit Etkin

ABSTRACT

BACKGROUND: Despite cognitive function impairment in depression, its relationship to treatment outcome is not well understood. Here, we examined whether pretreatment activation of cortical circuitry during test of cognitive functions predicts outcomes for three commonly used antidepressants.

METHODS: Eighty medication-free outpatients with major depression and 34 matched healthy controls were included as participants in the International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial. During functional magnetic resonance imaging, participants completed three tasks that assessed core domains of cognitive functions: response inhibition (Go/NoGo), selective attention (oddball), and selective working memory updating (1-back). Participants were randomized to 1 of 3 arms: escitalopram, sertraline (serotonin-specific reuptake inhibitors [SSRI]), or venlafaxine-extended release (serotonin and norepinephrine reuptake inhibitor [SNRI]) therapy. Functional magnetic resonance imaging scans were repeated after 8 weeks of treatment, and remission was assessed using the Hamilton Rating Scale for Depression.

RESULTS: Dorsolateral prefrontal cortex activation during inhibitory “no go” responses was a general predictor of remission, with remitters having the same pretreatment activation as control participants and nonremitters hypoactivating relative to controls. Posttreatment dorsolateral prefrontal cortex activation was reduced in both remitters and controls but not in nonremitters. By contrast, inferior parietal activation differentially predicted remission between SSRI and SNRI medications, with SSRI remitters showing greater pretreatment activation than SSRI nonremitters and the SNRI group showing the opposite pattern.

CONCLUSIONS: Intact activation in the frontoparietal network during response inhibition, a core cognitive function, predicts remission with antidepressant treatment, particularly for SSRIs, and may be a potential substrate of the clinical effect of treatment.

Keywords: Cognition, Continuous performance, Executive function, Go/NoGo, Major depressive disorder, Remission, Response inhibition, Selective-serotonin reuptake inhibitor, Serotonin-norepinephrine reuptake inhibitor, Sustained attention, Treatment prediction antidepressant

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The past 2 decades have brought a wealth of neuroimaging studies of depression and have provided a general understanding of brain network dysfunctions in this disorder. These studies highlight biased engagement of frontoparietal regulatory network, as well as alterations in the reciprocal relationship between regulatory and limbic reactivity networks (1–3). Although most imaging studies of depression examine the role of regulatory circuitry in the context of affective provocation or at rest, there is robust evidence that network dysfunction is also evident during cognitive function probes (4–6). Cognitive function and related constructs such as executive function are broadly defined as psychological processes that underlie the ability to carry out goal-directed behaviors and modify

prepotent responses (7,8). These abilities in turn enable the individual to fine tune their behavior across a variety of domains (9–11). Deficit in depression has been documented behaviorally across working memory/continuous performance (12,13) and response inhibition (14); for a review see (4). A relationship has also been demonstrated between poor pretreatment cognitive functioning and poor treatment outcomes in adult (15) as well as in older adult populations (16). In line with this, neuroimaging studies also show that, compared to healthy controls, depressed patients show altered activation of cognitive function circuitry across a range of tasks that tap into working memory/continuous performance (2,17), planning (18), and inhibition (2).

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Antidepressant medications represent the most common treatment option for major depressive disorder (MDD) (19–21), yet little is presently known about how differences in brain activity predict who will respond and whether prediction of response differs among medications. This is particularly true with respect to the neural systems underlying cognitive functions. To our knowledge, the only functional imaging study that has examined treatment response as a function of pretreatment cognitive function was reported by Langenecker *et al.* (22), who studied neural activation during response inhibition using a Go/No-Go task. They found that elevated pretreatment activation in the right lateral and medial prefrontal cortices and in limbic regions predicted lower depression after treatment with escitalopram therapy. That work guides our primary hypothesis regarding the relationship of cognitive function-related activation to treatment outcome. Here we also expanded on those previous findings by including multiple cognitive function tasks that assessed different aspects of cognitive functions and examined outcomes across multiple medication types.

Specifically, building on those previous studies, our goal was to examine whether neural activation in response to multiple probes of cognitive functions prior to treatment could predict remission and response with different types of antidepressant medications. The International Study to Predict Optimized Treatment in Depression (iSPOT-D) collected neuroimaging data before and after randomized treatment with 1 of 3 commonly prescribed antidepressants: escitalopram, sertraline, and venlafaxine-extended release (venlafaxine-XR) (2,23). We hypothesized that 1) neural activation as assessed by functional magnetic resonance imaging (fMRI) scans during 1 or all 3 cognitive task probes (response inhibition [Go/NoGo task], selective attention [oddball task], and working memory updating [n-back continuous performance task]) in medication-free pretreatment in depressed patients would predict antidepressant outcome. We also conducted exploratory analyses to test the hypothesis that 2) the predictive neural signal(s) would interact with medication type (serotonin-specific reuptake inhibitors [SSRI]: escitalopram, sertraline, or serotonin and norepinephrine reuptake inhibitor [SNRI]: venlafaxine-XR). Additionally, we hypothesized that 3) neural activation in treatment-predictive regions would be different at baseline between participants with depression, as a function of remission, and healthy control participants; and finally that 4) treatment predictive regions' activation will change with treatment as a function of remission.

METHODS AND MATERIALS

Participants and Procedure

The methods and protocol for the study have been reported in detail elsewhere (2,23). The current analyses focused on 80 previously nonmedicated participants with MDD and 34 (age-, sex-, and education-matched) healthy control participants who provided MRI data both before and after treatment at Westmead Hospital (Sydney Medical School, University of Sydney) as part of the iSPOT-D study. Participants, 18–65 years of age, were fluent in English and were recruited from clinics and through flyers and advertisements in the

community. Healthy control participants were recruited through the same channels and were screened for current Axis I and II disorders using the Mini-International Neuropsychiatric Interview (MINI), and they were additionally required to have a 17-item Hamilton Rating Scale for Depression (HRSD₁₇) score of ≤ 7 . Standard MRI exclusion criteria were applied (pregnancy, metal in body, neurological disorders, 20/20 or corrected vision). Inclusion criteria for MDD included a primary Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR) diagnosis of nonpsychotic MDD using the MINI (24) and a score of ≥ 16 on the HRSD₁₇ (25). All MDD participants were either antidepressant medication naïve or, if previously prescribed an antidepressant medication, had undergone a wash-out period of at least 5 half-lives. Patients who had taken any of the study medications during their current episode or previously had an adverse reaction to any of the study medications were excluded. Both MDD and control participants returned for a repeat scan and clinical assessments following the 8-week treatment phase (Figure S1 in Supplement 1). Imaging data were not available for 1 major depressive disorder participant on 1 of the cognitive tasks, resulting in 79 participants for the Go/NoGo task and 80 for the other 2 tasks.

The study received approval by the institutional review board. After the study procedures were explained to the participants, they provided written informed consent according to National Health and Medical Research Council of Australia guidelines.

Criteria for Outcomes: Remission and Response

Our outcome variables were 1) remission, defined as a score of ≤ 7 on the HRSD₁₇ (using clinician-determined scores at week 8 posttreatment), and 2) treatment response, defined as a $\geq 50\%$ decrease from the baseline HRSD₁₇ (25).

Illness Burden

Our statistical analyses covaried for an “illness burden” baseline severity index (26) to ensure that this did not confound the identification of neural predictors. To create this severity index, we calculated for each participant the first principal component across the five established depression severity scales, which captured multiple aspects of illness severity (26): the Depression, Anxiety and Stress Scales (27), the World Health Organization Quality of Life-BREF (http://www.who.int/substance_abuse/research_tools/whoqolbref/en/) (28), the Social and Occupational Functioning Assessment Scale (29), the 16-item Quick Inventory of Depressive Symptomatology (30), and the HRSD₁₇.

fMRI Activation Tasks

Details of the activation tasks and their rationale for design and inclusion have been documented previously, and the utility of these tasks for investigation of MDD has been reported (2,23,31). Briefly, we chose three canonical cognitive tasks to map the diversity of cognitive functions (32), among those that have been used in research of depression (4). To optimize the engagement of the process of interest, following recommendations, tasks were designed to minimize behavioral differences in accuracy and reaction time because our a priori goal was to compare groups with documented

differences in cognition (33). Tasks were administered via goggles and head coil setup, and participants listened to tones via an MRI-compatible headset and submitted keypress responses using a custom-made button box. All participants completed three tasks designed to measure fundamental aspects of cognitive function. In addition, they completed two tasks designed to measure emotion function that are not discussed here.

Response inhibition was assessed using the Go/NoGo task in which participants had to press the green stimulus (“Go” trials) and to inhibit responses to the red stimulus (“No Go” trials). The stimulus was the word “press.” There were 120 trials in total, of which 30 were No/Go inhibition trials. The critical contrast reflecting response inhibition was No/Go minus Go.

Selective attention was assessed using an auditory oddball task in which participants had to selectively respond (via button press) to higher-pitched “target” tones presented infrequently among a series of lower pitched “nontarget” tones. There were 20 target and 100 nontarget tones. The critical contrast reflecting oddball detection was target minus nontarget trials.

Selective working memory updates were assessed using the continuous performance task in which participants had to determine whether the current letter they saw on the screen was the same as one letter prior (1-back), but they were only to respond if the repeated letter was displayed in yellow color. Intermixed with the yellow letters (66%) were white letters (33%), for which no response was required, and these served as perceptual baseline trials. There were a total of 120 trials with 30 of them being targets. The critical contrast that reflected working memory updating was 1-back minus perceptual baseline trials.

For all tasks, reaction time and button box responses were recorded using custom-designed software and hardware. Due to software errors, behavioral responses during the scan were lost for 29 healthy controls and 19 major depressive disorder participants. The button box malfunctioned for an additional 15 participants. However, participants also completed the tasks outside the scanner behaviorally during the recording of event-related brain potentials. Analyses of these data confirmed that, as intended (33), there were no accuracy differences between healthy controls and those with MDD, nor between remitters and nonremitters (all p values $> .22$). Reaction times were not different between healthy controls and patients with MDD on the Go/NoGo task ($F_{1,102} = 1.70$, $p = .20$) but were different on the oddball ($F_{1,104} = 4.37$, $p = .03$) and n-back ($F_{1,111} = 11.30$, $p = .001$) tasks. Importantly, there were no reaction time differences among MDD patients between remitters and nonremitters (all p values $> .20$) on either of the three tasks.

Details of MRI acquisition were published previously (2,23,34) and also can be found in the [Supplement 1](#).

Analyses

Preprocessing of fMRI data can be found in the [Supplement 1](#). The following analyses were undertaken to address the four hypotheses outlined above:

1) Whether pretreatment neural activation in the cognitive tasks generally predicted outcome across medication

types. We conducted a second-level random effects analysis using fixed factorial general linear models, using SPM8 software (Statistical Parametric Mapping version 8; Wellcome Department of Cognitive Neurology, London, United Kingdom) for each task separately. Remission on the HRSD₁₇ (binary variable for week-8 score ≤ 7) and response ($\geq 50\%$ improvement on the HRSD₁₇ scale) were dependent variables in separate models. Pretreatment severity was included as covariate in these analyses.

Voxel significance was determined using a small volume correction (SVC) for multiple comparisons (35) in SPM8 software at a familywise error of $p \leq .05$ (cluster-forming threshold, $p = .001$, uncorrected) in a set of a priori-defined regions. Regions of interest (ROIs) were selected from a meta-analysis of cognitive functions by Dosenbach *et al.* (36). We identified 19 regions that together represent the two primary networks that support cognitive functions: the cingulo-opercular network (dorsal anterior-cingulate, and bilateral anterior prefrontal cortex, bilateral anterior insula/frontal operculum, bilateral anterior thalamus) and the frontoparietal attention network (bilateral prefrontal cortex, bilateral intraparietal sulcus, bilateral frontal cortex, bilateral dorsolateral prefrontal cortex [DLPFC], bilateral inferior parietal lobule, bilateral precuneus, and the midcingulate area). Individual ROIs were generated as 10-mm-radius gray matter-corrected spheres around each peak voxel coordinate specified in the meta-analysis (36). We combined these into a single mask that encompassed all regions and networks and determined significance in this mask. We then extracted beta values for visualization purposes from areas that survived SVC (37). Finally, we also undertook an exploratory voxel analysis of the whole brain to identify any nonhypothesized regions of activation involved in the prediction of remission, reported at an uncorrected p level of .001.

2) Whether activation in the cognitive tasks differentially predicts remission between medication types. As an exploratory analysis, we created a model with regressors for medication type (SSRI vs. SNRI) and interaction of remission/response outcome with medication type in the second-level fixed factorial SPM8 model, correcting for multiple comparisons as above for each task. Pretreatment severity was included as covariate in these analyses. We also used SAS software (SAS/STAT software 9.2; Cary, North Carolina) to test whether moderation across medication types was observed for extracted activity in the treatment predictive cluster identified in the general prediction analysis (a medication type by brain activation interaction on remission and response outcomes).

3) Whether depressed participants differed as a function of remission from healthy controls at the pretreatment baseline in regions that predicted treatment outcomes. We examined whether pretreatment activation in regions identified under Hypothesis 1 and Exploratory Hypothesis 2 differed as a function of diagnosis, as a function of subsequent remission status, using regression on extracted beta values in SAS software (SAS/STAT software).

4) Whether regions that predicted remission also changed with treatment, as a function of remission or response status. We extracted beta values from the clusters identified under Hypothesis 1 and Exploratory Hypothesis 2

Table 1. Demographic and Clinical Characteristics of Remitters vs. Nonremitters

Characteristic	Major Depressive Disorder			Healthy Comparison	
	Remitters Mean (±SD)	Nonremitters Mean (±SD)	Statistics	Mean (±SD)	Statistics
Age	28.35 (7.10)	36.65 (14.65)	$t_{78} = -3.15, p = .002$	31.48 (12.43)	$t_{112} = -.522, p = .603$
Years of Education	14.59 (2.44)	13.88 (3.12)	$t_{78} = 1.12, p = .27$	NA	NA
Males/Females	20/17	20/23	$F_{1,80} = .44, p = .51$ $\chi^2 = .57, p = .45$	22/22	$F_{1,114} = .08, p = .78$ $\chi^2 = .08, p = .77$
Age at Onset	19.54 (7.71)	21.33 (13.21)	$t_{78} = -.72, p = .47$	NA	NA
Major Depressive Episode Duration	8.30 (6.49)	14.84 (14.19)	$t_{78} = -2.58, p = .01$	NA	NA
Clinician-rated Severity-Hamilton Depression Rating Scales	21.78 (4.34)	20.58 (3.45)	$t_{78} = -1.38, p = .17$	NA	NA
Self-rated Severity-Quick Inventory of Depressive Symptomatology	14.08 (4.02)	13.48 (3.32)	$t_{78} = -.73, p = .46$	NA	NA
Average Dose at Week 8 (mg)	Escitalopram: 9.71 (3.73)	Escitalopram: 14.00 (9.66)	Escitalopram: $t_{26} = -1.35, p = .22$	NA	NA
	Sertraline: 57.81 (28.46)	Sertraline: 61.36 (25.89)	Sertraline $t_{26} = -.33, p = .74$		
	Venlafaxine-XR: 80.00 (19.36)	Venlafaxine-XR: 109.10 (39.16)	Venlafaxine-XR: $t_{25} = -2.28, p = .03$		
Number of Participants	Escitalopram: 12 Sertraline: 13 Venlafaxine-XR: 12	Escitalopram: 14 Sertraline: 14 Venlafaxine-XR: 14	$F_{2,76} = .01, NS$		

NA, not applicable; NS, not significant.

from posttreatment scans among depressed participants. We then used repeated measures analyses with planned contrasts to compare change over the eight weeks in those who remitted.

RESULTS

Demographic and clinical characteristics of remitting and non-remitting participants with major depressive disorder are shown in Table 1, with data for healthy controls shown for comparison. As shown in Table 1, remitters and nonremitters were different in age but not in gender or years of education. Table 1 also shows duration, severity, age of onset, and dose for each antidepressant group. As an additional control, we report results with and without controlling for age.

Pretreatment Neural Activation in Cognitive Tasks Predicts Outcomes

Significant prediction of remission, after correction for multiple comparisons, was achieved in the Go/NoGo task, which assessed the response inhibition aspect of cognitive function. Specifically, remitters to treatment were distinguished from nonremitters by greater pretreatment right dorsolateral prefrontal activation in the NoGo-minus-Go contrast (response inhibition) (Figure 1A and 1B; peak voxel x, y, z = 44, 30, 38, respectively; z = 3.90; $p_{familywise\ error\ (FWE)} = .039$). To estimate effect sizes, we conducted a generalized linear model analysis between beta values extracted from this site and remission status, partial $\eta^2 = 0.17$, 95% confidence interval: .04–.31. The relationship between remission status and DLPFC activation remained significant after age was

entered as an additional covariate; partial $\eta^2 = 0.12$, 95% CI .01–.25. The sensitivity of the beta values extracted from DLPFC activation in prediction remission is 48.9, and the specificity is 64.3. We used a probability cutpoint of .5 (see Table S1 in Supplement 1 for uncorrected results for all tasks). No regions significantly predicted the response outcome after SVC. Given the lack of findings for response, we focused subsequent analyses on the remission finding (see Table S1 in Supplement 1 for uncorrected results for prediction of response on all tasks).

Exploratory Analysis: Activation in the Cognitive Tasks Differentially Predicts Remission Between Medication Type or Medication Class

We found a significant interaction between remission status and medication type in the right inferior parietal cortex (peak voxel x, y, z = 56, -44, 46, respectively; z = 4.60; $p_{FWE} = .01$) (Figure 2A and 2B), also only in the Go/NoGo task. This interaction was driven by greater parietal activation during inhibition in SSRI remitters than in SSRI nonremitters at baseline ($t_{51} = 4.78, p < .01, d = 1.11$) but less parietal activation in the same contrast for SNRI remitters than for SNRI nonremitters ($t_{24} = 2.91, p < .05, d = .67$ at baseline, partial $\eta^2 = .22$, 95% CI 8.72–52.15). The sensitivity of the beta values extracted from the parietal activation in predicting remission is 45.9, and the specificity is 69.0, using a probability cutpoint of .5. We also tested whether the DLPFC cluster identified as a general predictor of remission outcome was also a differential predictor by medication type, but this interaction for the DLPFC was not significant ($F_{1,72} < 1$, not significant).

Depressed Participants Differ as a Function of Remission From Healthy Controls at the Pretreatment Baseline

Next, we compared extracted beta values for the NoGo-minus-Go contrast at pretreatment data for remitters and nonremitters to that of healthy controls for the DLPFC cluster (general predictor) and inferior parietal cluster (differential predictor) identified above. Although nonremitters showed DLPFC hypoactivation compared to healthy controls ($t_{93} = 2.91, p = .004, d = .60$) (Figure 3), the relatively normal level of activation in remitters was not different from controls ($t_{69} < 1, p = .23$).

Similarly, MDD participants who did not remit on SSRI treatment showed pretreatment inferior parietal hypoactivation compared to controls ($t_{44} = -2.22, p = .03$), whereas the relatively normal parietal activation in remitters to SSRIs did not differ from healthy controls ($t_{57} < 1, ns$).

Regions That Predicted Remission Also Changed With Treatment, as a Function of Remission Status

We used a repeated measures analysis of variance to examine the effect of treatment (baseline vs. posttreatment at week 8)

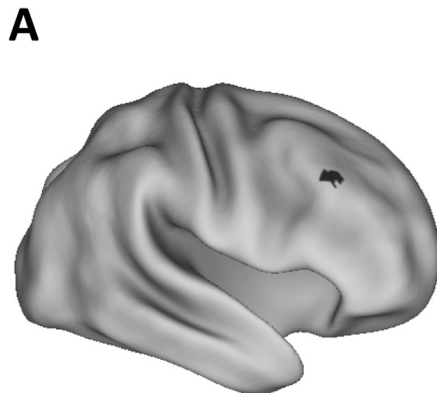


Figure 1. Prediction of remission by baseline brain activation. (A) Region in the dorsolateral prefrontal cortex in the [NoGo – Go] contrast that predicts HRSD₁₇ remission, visualized as extracted beta values (B). Error bars are standard errors. HRSD₁₇, 17-item Hamilton Rating Scale for Depression.

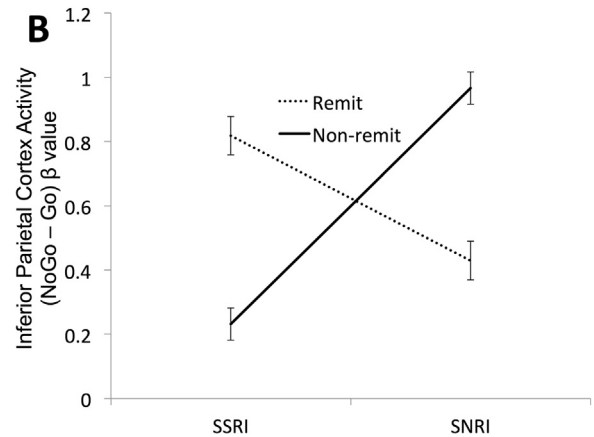
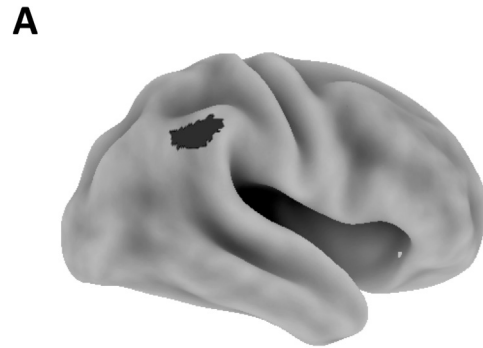
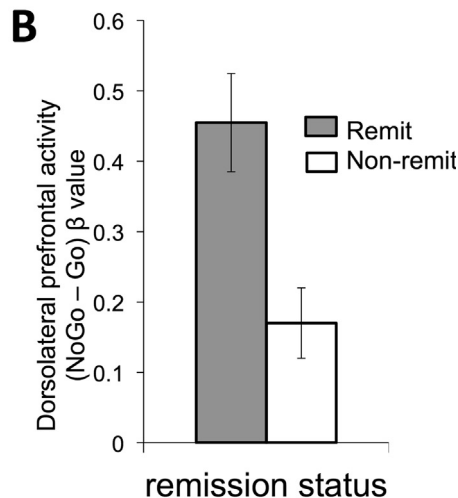


Figure 2. Moderation of prediction of remission by medication type. (A) Region in the right inferior parietal cortex in the [NoGo – Go] contrast that predicts HRSD₁₇ remission differentially by selective-serotonin reuptake inhibitors compared to serotonin-norepinephrine reuptake inhibitor, visualized as extracted beta values (B). Error bars are standard errors. HRSD₁₇, 17-item Hamilton Rating Scale for Depression.

and remission on change in the treatment-predictive DLPFC, including baseline severity scores as covariates. Results showed a significant interaction between remission status and pre- and posttreatment changes in activation ($F_{1,76} = 4.35, p < .05$) (Figure 3). Planned comparisons showed that remitters had a reduction in DLPFC activation from pre- to posttreatment ($t_{38} = 2.87, p < .05$), whereas there was no change in nonremitters ($t_{43} < 1, p = .61$). Parallel analyses using paired t tests in healthy participants showed a trend-level reduction of DLPFC activation from baseline to 8 weeks posttest ($t_{33} = 1.55, p = .06$).

For the inferior parietal cortex, the focal three-way interaction between remission status, type of treatment, and pre- and posttreatment changes in activation was significant ($F_{1,74} = 10.41, p = .002$). This interaction was driven by the baseline differences documented above as none of the post-treatment pairwise comparisons among MDD patients was significant (Figure 4). The t test comparisons between remitters and healthy participants at 8 weeks revealed the same pattern as at pretreatment baseline, indicating that there were no differences between participants who remitted on SSRIs and healthy controls ($t_{57} < 1$) (Figure 4), but those who remitted on SNRI were different from healthy participants at the trend level ($t_{44} = -1.57, p = .06$) (Figure 4).

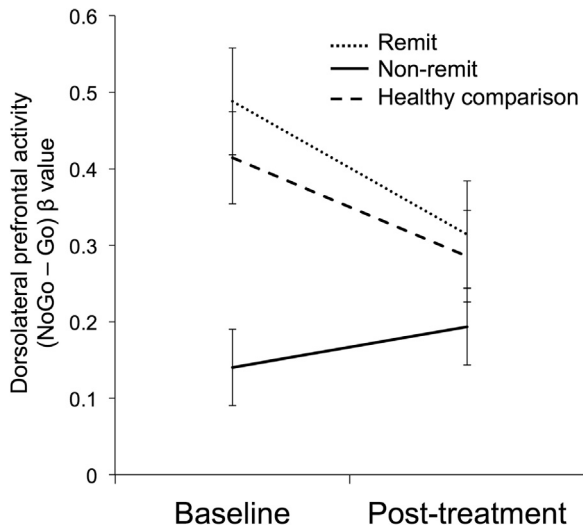


Figure 3. Relationship of dorsolateral prefrontal activation between participants with major depressive disorder and healthy comparison participants, both pre- and posttreatment. Patients who remitted following antidepressant treatment (dotted line) had the same level of dorsolateral prefrontal activation at baseline as healthy comparison participants (dashed line), which was reduced posttreatment. In contrast, participants who did not remit (solid line) had significantly less dorsolateral prefrontal activation at baseline than healthy comparison participants and did not change post-treatment. Error bars are standard errors.

DISCUSSION

In this study, we used functional neuroimaging to determine how pretreatment neural activity during cognitive function tasks predicted posttreatment antidepressant outcomes in patients with MDD. Using a Go/NoGo cognitive control task, we found that DLPFC activation was a general predictor of remission, whereas the inferior parietal activation provided additional differential prediction of remission for SSRIs in particular. MDD patients who remitted were distinguished by relatively normal levels of DLPFC activation pretreatment, which attenuated posttreatment (in the same direction as controls). Patients who did not remit showed DLPFC hypoactivation at both pre- and posttreatment. Exploratory analyses of the effects of medication found that remitters specifically to SSRIs showed correspondingly normal levels of inferior parietal activation, which also attenuated post-treatment, while nonremitters to SSRIs showed parietal hypoactivation. Thus, SSRI and SNRI responders showed opposing patterns of activation in the parietal cortex. Moreover, neural activation predicting remission was seen only during response inhibition (Go/NoGo task), suggesting that inhibitory cognitive control functions in MDD, and frontoparietal neural activation supporting this process, are diagnostic of remission outcomes in MDD. These findings thus support and expand earlier reports by Langenecker *et al.* (22).

The inclusion of healthy comparison participants enabled us to elucidate the distinction between the normative activation in eventual remitters compared to the profile of persistent hypoactivation in nonremitters especially in the DLPFC. We speculate that the greater activation in remitters

reflects a greater capacity to compensate for MDD-related impairment and to thereby mount a response to treatment. By contrast, failure to engage the DLPFC region may be a general marker of nonresponsiveness to treatment, associated with a lack of neural cognitive resources. Indeed, after treatment, a reduction in DLPFC was seen in remitters, while nonremitters showed no change after treatment. The pattern of change in healthy participants showed a reduction, similar to remitters, but these differences were only at trend level. We speculate that the reduction in recruitment of the dorsolateral prefrontal cortex represents higher efficiency of this network posttreatment in patients, but future studies incorporating adaptive designs would help to answer this possibility.

Previous work has documented abnormalities in cognitive functions between patients with major depressive disorder and healthy comparison groups in both response inhibition (4) and dorsolateral prefrontal activation (17). In an analysis of behavioral task performance data that used the full iSPOT-D sample of 1008 depressed participants, poor cognitive functioning at baseline was associated with worse outcome across multiple treatments (38). These findings support existing work between poor pretreatment cognitive functioning and poor treatment outcomes to SSRIs in adults (15), as well as in older adult populations (16). However, this pattern might be moderated by type of medication; for example, recent work found poorer baseline cognitive performance among bupropion responders versus nonresponders (15), and our own results also showed that SNRI remitters had lower parietal activation during response Go versus NoGo responses. Differential prediction for response to the three medications used in iSPOT-D has also been observed when activation is elicited by an emotion task (39).

In a subset of the current sample, we previously documented cortical thickness and voxel based morphometry reductions in the dorsolateral prefrontal cortex in this MDD

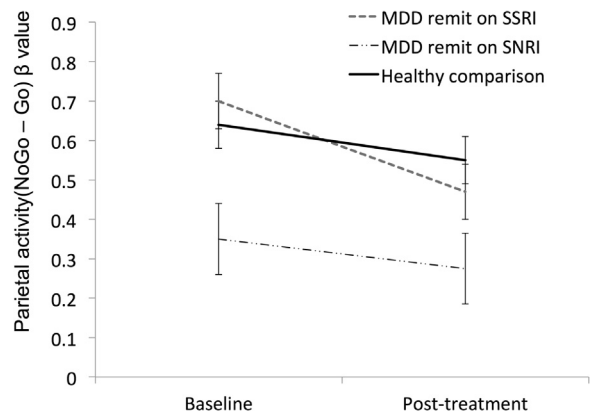


Figure 4. Relationship of parietal cortex activation between participants with major depressive disorder (MDD) and healthy comparison participants, both pre- and posttreatment. Patients who remitted following SSRI antidepressant treatment (dashed line) had the same level of parietal activation at baseline as healthy comparison participants (solid line) and this was different from those remitted on SNRIs (dash-dot line). The same pattern emerged posttreatment. Error bars are standard errors. SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, serotonin-specific reuptake inhibitors.

group as compared to healthy controls (31). By contrast, in the same group of individuals from which we reported results, during emotional stimuli processing abnormal amygdala activity was related to better antidepressant response (39). Taken together, these findings collectively suggest that better antidepressant response is predicted by intact cognition, especially on inhibition, in parallel with abnormal emotional processing. This might indicate that antidepressants target emotional processing primarily, but that the neural circuitry underlying cognition is critical as scaffolding to gate treatment response.

Our study was designed as a pragmatic trial to identify neural predictors of outcomes of treatments in real-world clinical settings, and was therefore not designed to compare active to placebo conditions, given that placebo is not a treatment choice in standard clinical practice. Future studies that address different questions about the mechanisms by which neural circuit activation contributes to antidepressant remission will have great importance in parsing the medication- versus placebo-related contributions. Future studies are also warranted to expand the array of antidepressant medication further. Here we report the results of an exploratory analysis looking at the effect of medication type and, as such, will need to be replicated and validated in larger samples with several different medications. The sensitivity and specificity of neural activation for predictive classification of treatment outcomes were in the moderate range (40). It is possible that the inclusion of other variables in the classification model would add precision to the prediction and thus increase sensitivity and specificity. For example, we achieved classification accuracy of 75%–81% in our study of emotion-elicited activation (39), and the combination of cognitive and emotion circuit data might increase the precision of predictive classification. In addition, our tasks were intentionally designed to have high level of accuracy with behavioral performance equal between groups. This approach has been recommended (33) to prevent potential effects of task difficulty and subjective responses to errors to change activation between groups with differing levels of abilities (e.g., younger vs. older, disordered vs. healthy). Future work with larger sample and more fine grained behavioral outcomes will be necessary to replicate these findings. We also note that both general treatment remission prediction and medication specific prediction emerged in the right hemisphere. Based on existing work, there is no reason to anticipate this type of lateralization in the cognitive function network in depression [although see work on right lateralization of inhibition in the stop signal task by Aron *et al.* (41) and approach motivation by Davidson *et al.* (42)], but this question requires further work. Finally, our primary outcome variable, remission status resulted in a significant age difference between groups. Additional analyses controlling for age showed that removing variance due to age did not change the pattern of results. Future work will need to consider that age might track with duration of the disorder and number of relapses, which could then result in increased cumulative neurobiological damage to brain circuits, including cognitive functions.

In the present study, the use of a large sample size relative to prior studies, and the inclusion of multiple medication arms and multiple tasks, all within a pragmatic

clinical trial design, makes important inroads towards identification of imaging predictors of antidepressant outcomes in MDD. Although replication of findings is required to support their ultimate clinical utility, the findings advance our knowledge about neuroimaging markers in supporting the tailored selection of antidepressant treatments for MDD.

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ClinicalTrials.gov: Computerized Interventions for College Students' Cognitive Functioning and Mental Well-being; <https://clinicaltrials.gov/ct2/show/NCT01694303?term=NCT01694303&rank=1>.

ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences (AG, BP, LMW, AE), and Department of Psychology (AG), Stanford University, Stanford, California; Sierra-Pacific Mental Illness Research, Education, and Clinical Center (AG, BP, LMW, AE), Veterans Affairs Palo Alto Health Care System, Palo Alto, California; The Brain Dynamics Center (MSK, SMG) and Discipline of Psychiatry (MSK, SMG), Sydney Medical School, University of Sydney and Westmead Millennium Institute, Sydney, New South Wales, Australia

Address correspondence to: Amit Etkin, M.D., Ph.D., Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California 94305; E-mail: amitetkin@stanford.edu.

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