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Abstract: Background: Despite impairment in cognitive functioning in depression, little is currently known about its relationship to treatment outcome. Here, we examined whether pre-treatment activation of cortical circuitry during cognitive control predicts outcomes for three commonly used antidepressants.

Methods: Eighty medication-free outpatients with major depression and 34 matched healthy controls as part of the International Study to Predict Optimized Treatment in Depression (iSPOT-D) were included. During functional MRI participants completed three tasks that assessed core domains of cognitive control: response inhibition (Go/NoGo), selective attention (oddball), and selective working memory updating (1-back). Participants were randomized into one of three arms: escitalopram, sertraline (serotonin-specific reuptake inhibitors (SSRI)), or venlafaxine-extended release (serotonin and norepinephrine reuptake inhibitor (SNRI)). fMRI scans were repeated after eight weeks of treatment, and remission was assessed on the Hamilton Rating Scale for Depression.

Results: Dorsolateral prefrontal cortex (DLPFC) activation during inhibitory "No Go" responses was a general predictor of remission, with remitters having the same pre-treatment activation as control participants and non-remitters hypo-activating relative to controls. Post-treatment DLPFC activation was reduced in both remitters and controls, but not in non-remitters. By contrast, inferior parietal activation differentially predicted remission between SSRI and SNRI medications, with SSRI non-remitters showing greater pre-treatment activation than SSRI non-remitters, and the SNRI group showing the opposite pattern.

Conclusions: Intact activation in the fronto-parietal 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.

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Fronto-Parietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients with Major Depression: Outcomes from iSPOT-D

Anett Gyurak, Ph.D., [a,b,c] Brian Patenaude, Ph.D., [a, c] Mayuresh S. Korgaonkar, Ph.D., [d,e,f] Stuart M Grieve, M.D., Ph.D., [d,e,f] Leanne M. Williams, Ph.D., [a,c] Amit Etkin M.D., Ph.D. [a,c, †]

Affiliations:

a. Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA, 94305, USA.

b. Department of Psychology, Stanford University, Jordan Hall, Stanford CA 94305, USA.

c. Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC) Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304

d. The Brain Dynamics Center, Sydney Medical School, The University of Sydney and Westmead Millennium Institute, Sydney, NSW, Australia.

e. Discipline of Psychiatry, Sydney Medical School, The University of Sydney, Westmead Hospital, Sydney, NSW, Australia.

† **Correspondence and reprint requests should be addressed to:**

Amit Etkin, M.D., Ph.D.
Department of Psychiatry and Behavioral Sciences
Stanford University
Stanford, CA 94305
Telephone: (650) 725-5736
Fax: (650) 724-9900
Email: amitetkin@stanford.edu

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ABSTRACT

Background: Despite impairment in cognitive functioning in depression, little is currently known about its relationship to treatment outcome. Here, we examined whether pre-treatment activation of cortical circuitry during cognitive control predicts outcomes for three commonly used antidepressants.

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INTRODUCTION

The past two decades have brought a wealth of neuroimaging studies on depression and have provided a general understanding of brain network dysfunctions in the disorder. These studies highlight biased engagement of fronto-parietal regulatory networks, as well as alterations in the reciprocal relationship between regulatory and limbic reactivity networks (1–3). While 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 probes (4–6). Cognitive control 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 pre-potent responses (7; 8). These abilities in turn enable the individual to fine tune their behavior across a variety of domains (9–11). Deficits in depression has been documented behaviorally across working memory/continuous performance (12; 13) and response inhibition (14), for a review see (15), In line with this, neuroimaging studies also show that compared to healthy controls, depressed patients show biased activation of cognitive control circuitry across a range of probes such as working memory/continuous performance (2; 16), planning (17) and inhibition (2) .

Antidepressant medications represent the most common treatment option for major depressive disorder (MDD) (18–20), yet little is presently known about how differences in brain activity predict who will respond, and whether prediction of response differs between medications. This is particularly true with respect to the neural systems underlying cognitive control functions. To our knowledge, the only functional imaging study that has examined treatment response as a function of pre-treatment cognitive function was reported by Langenecker and colleagues (21), who studied neural activation during response inhibition in a

Go/No-Go task. They found that elevated pre-treatment activation in the right lateral and medial prefrontal cortices and in limbic regions predicted lower depression after escitalopram treatment. This prior work guides our primary hypothesis regarding the relationship of cognitive control-related activation to treatment outcome. Here we also expand on these prior findings by including multiple cognitive tasks that assess different aspects of cognitive control, and examine outcomes across multiple medication types.

Specifically, building on these prior studies, our goal was to examine whether neural activation in response to multiple probes of cognitive functions prior to treatment can 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 one of three commonly-prescribed antidepressants: escitalopram, sertraline and venlafaxine-extended release (venlafaxine-XR) (2; 22). Our aims were to determine 1) whether neural activation in medication-free pretreatment functional magnetic resonance imaging (fMRI) scans in depressed patients predicts outcome with one of three cognitive task probes (response inhibition [Go/NoGo task], selective attention [oddball task], and working memory updating [n-back continuous performance task]); 2) whether the predictive neural signal(s) interacted with medication type (SSRI: escitalopram, sertraline, or SNRI: venlafaxine-XR); 3) whether activation in treatment predictive regions differed at baseline between participants with depression, as a function of remission, and healthy control participants; and 4) whether treatment predictive regions also changed with treatment, as a function of remission.

METHOD

Participants and procedure

The methods and protocol for the study have been reported in detail elsewhere (2; 22). The current analyses focused on 80 previously non-medicated participants with major depressive disorder (MDD) and 34 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. Inclusion criteria for MDD included a primary DSM-IV-TR diagnosis of nonpsychotic major depressive disorder using the Mini-International Neuropsychiatric Interview (MINI) (23) and a score ≥16 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (24). Healthy control participants were screened for both Axis 1 and II disorders using the MINI, and they were additionally required to have an $HRSD_{17}$ score ≤7. All MDD participants were either antidepressant medication naïve or, if previously prescribed an antidepressant medication, had undergone a wash-out period of at least five 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-weeks treatment phase (Supplemental Figure 1). Imaging data was not available for one major depressive disorder participant on one of the cognitive tasks, resulting in 79 participants for the Go/NoGo task and 80 for the other two tasks.

The study received approval by the local institutional review board. After the study procedures were fully explained in accordance with the ethical guidelines of the institutional review board, participants provided written informed consent according to the National Health and Medical Research Council guidelines.

Criteria for outcomes: remission and response

We had two research outcome variables: 1) remission, defined as a score of ≤7 on the $HRSD_{17}$ (using clinician-determined scores at week 8 post-treatment), and 2) treatment response, defined as a ≥50% decrease from the baseline $HRSD_{17}$ (24) XX.

fMRI activation tasks

The details of the activation tasks and their rationale for design and inclusion have been documented previously (2). Briefly, participants viewed stimuli via a goggle and head coil setup, listened to tones via an MRI-compatible headset, and submitted keypress responses using a custom button-box. All participants completed three tasks designed to measure fundamental aspects of cognitive function (results of two emotion tasks are described elsewhere).

Response inhibition was assessed using the Go/NoGo task in which participants had to press to 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 NoGo minus Go.

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

Selective working memory updating 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 were white letters, 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 software and hardware. Due to software updates, behavioral responses during the scan were lost for 29 healthy controls and 19 major depressive disorder 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, there were no accuracy differences between healthy controls and those with major depressive disorder, nor between remitters and non-remitters (all *p*-values > .22).

Image Acquisition

MRI was performed using a 3.0 Tesla GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin). Acquisition was performed using an 8-channel head coil. Magnetic resonance images for each functional task were acquired using echo planar imaging (EPI) magnetic resonance sequence with the following parameters: TR=2500 ms, TE=27.5 ms, matrix=64 × 64, FOV=24 cm, flip angle=90°. Forty contiguous axial/oblique slices with a slice thickness of 3.5 mm were acquired to cover the whole brain in each volume. For each activation task, 120 volumes were collected with a total scan time of 5 minutes and 8 seconds. Three dummy scans were acquired at the start of every acquisition. Structural MRI 3D T1-weighted images were acquired in the sagittal plane using a 3D spoiled gradient echo (SPGR) sequence (TR=8.3 ms, TE=3.2 ms, flip angle=11°, TI=500 ms, NEX=1, ASSET=1.5, Frequency direction: S/I). A total of 180 contiguous 1 mm slices were acquired covering the whole brain with a 256 ×

256 matrix with an in-plane resolution of 1 × 1 mm, resulting in 1 mm^3 isotropic voxels. The 3D SPGR sequence was collected for use in normalization of the fMRI data to standard space.

Data preprocessing

fMRI data were preprocessed and analyzed using SPM8 software (www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks; Natick, MA). Motion correction was performed by realigning the fMRI images to the first image of each task run. A mean image for the fMRI time series was generated and was normalized to the T1-weighted structural scan using the FMRIB linear registration tool (FLIRT). The T1-weighted data was also normalized to Montreal Neurological Institute standard space using the FMRIB non-linear registration tool (25). Normalization warps from these two steps were stored for use in functional-to-standard space transformations. Global signal was estimated using a mask within the ventricles and white matter, and was removed from the motion-corrected fMRI time series. fMRI data were smoothed using an 8mm Gaussian kernel and was high-pass filtered using a cut-off period of 128 seconds.

Given that there were no accuracy differences between healthy controls and participants with major depressive disorder, or within major depressive disorder participants as a function of remission, we used a fixed, canonical timing onset model for first-level models for all participants, convolved with a canonical hemodynamic response function. Motion was modeled by including six individualized motion parameters. The following analyses were undertaken to address the four questions posed above:

<u>1) Whether pre-treatment neural activation in the cognitive tasks generally predicts outcome</u>

across medication types: We conducted a second-level random effects analysis using Fixed Factorial general linear models in SPM8 software for each task separately. Remission on the $HRSD_{17}$ (binary variable for week 8 score ≤7) and response (≥50% improvement on the $HRSD_{17}$ scale) were dependent variables in separate models. All models 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 WHO Quality of Life-BREF (28), the Social and Occupational Functioning Assessment Scale (29), the 16-item Quick Inventory of Depressive Symptomatology (30), and the $HRSD_{17}$.

Voxelwise significance was determined using a Small Volume Correction for multiple comparisons (31) in SPM at a family-wise error of $p \leq .05$ (cluster-forming threshold was $p = .001$, uncorrected) in a set of *a priori*-defined regions combined into a single spatial mask. Specifically, we used a meta-analysis of cognitive functions by Dosenbach and colleagues (32) to identify 19 regions that together represent the two primary networks that support cognitive functions broadly: the cingulo-opercular network (dorsal anterior-cingulate, and bilateral anterior prefrontal cortex, bilateral anterior insula/frontal operculum, bilateral anterior thalamus) and the fronto-parietal network (bilateral prefrontal cortex, bilateral intra-parietal sulcus, bilateral frontal cortex, bilateral dorsolateral prefrontal cortex, bilateral inferior parietal lobule, bilateral precuneus, and the midcingulate area). To create our mask, we generated 10mm radius gray-matter corrected spheres around each peak voxel coordinate as reported previously (32), and assembled them into one larger mask that encompassed all regions and networks. For regions

that passed this small volume correction, we also extracted contrast beta estimates from significant clusters for visualization purposes. Extracted values were used for separate analyses, as described below, which were not directly related to the treatment prediction finding, thus avoiding "double dipping" (33). Finally, we also undertook an exploratory voxelwise analysis of the whole brain to identify any non-hypothesized regions of activation involved in the prediction of remission, reported at a $p = .001$ uncorrected level.

2) Whether activation in the cognitive tasks differentially predicts remission between medication types: We conducted an analysis similar to the one above, except now adding regressors for medication type (SSRI versus SNRI) and interaction of remission/response outcome with medication type in the second-level Fixed Factorial SPM8 model, correcting for multiple comparisons as above. Pre-treatment severity was included as covariate in these analyses. We also tested in SAS 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 pre-treatment baseline in regions that predicted treatment outcome in Aims 1 and/or 2: We examined whether pre-treatment activation in regions identified under Aims 1 and 2 differed as a function of diagnosis, as a function of subsequent remission status, using regression on extracted beta values in SAS.

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 Aims 1 and 2 from post-treatment 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.

TABLE 1 ABOUT HERE

Pre-treatment neural activation in the 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 non-remitters by greater pre-treatment right dorsolateral prefrontal activation in the NoGo (response inhibition) minus Go contrast (Figure 1A and 1B; peak voxel x,y,z = 44,30,38; z = 3.90; p_{FWE} = .039). See Supplemental Table 1 for uncorrected results for all tasks. No regions significantly predicted the response outcome after small volume correction. Given the lack of findings for response, we focused subsequent analyses on the remission finding. See Supplemental Table 1 for uncorrected results for prediction of response on all tasks.

FIGURE 1 ABOUT HERE

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 (Figure 2A and 2B; peak voxel x,y,z = 56,-44,46; z = 4.60; p_{FWE} = .01), also only in the Go/NoGo task. This interaction was driven by greater parietal activation during inhibition in SSRI remitters compared to SSRI non-remitters, $t(74) = 4.78$, $p < .01$, d = 1.11, but less parietal activation in the same contrast for SNRI remitters compared to SNRI non-remitters, $t(74) = 2.91$, $p < .05$, d = .67. 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 ($F(1,72) < 1$, ns).

FIGURE 2 ABOUT HERE

Depressed participants differ, as a function of remission, from healthy controls at the pre-treatment baseline

Next, we compared extracted beta values for the NoGo minus Go contrast at pre-treatment data for remitters and non-remitters to that of healthy controls for the DLPFC cluster (general predictor) and inferior parietal cluster (differential predictor) identified above. While non-remitters showed DLPFC hypo-activation compared to healthy controls (Figure 3; $t(93) = 2.91$, $p < .05$, d = .60), 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 pre-treatment inferior parietal hypo-activation compared to controls, $t(44) = -2.22$, $p = .03$, while the relatively

normal parietal activation in remitters to SSRIs did not differ from healthy controls , $t(57) < 1$, ns.

Regions that predict remission also change with treatment, as a function of remission status

We used a repeated measures analysis of variance to examine the effect of treatment (baseline versus post-treatment at week 8) and remission on change in the treatment-predictive dorsolateral prefrontal cluster, including baseline severity scores as covariates. Results showed a significant interaction between remission status and pre-post treatment change in activation (Figure 3; $F(1,76) = 4.35$, $p < .05$). Planned comparisons showed that remitters had a reduction in DLPFC activation from pre- to post-treatment $t(38) = 2.87$, $p < .05$, while there was no change in non-remitters, $t(43) < 1$, $p = .61$. Parallel analyses using paired t-tests in healthy participants showed a trend level reduction of DLPFC activation from baseline to 8-week post-test, $t(33) = 1.55$, $p = .06$.

For the inferior parietal cortex, the focal three-way interaction between remission status, type of treatment and pre-post treatment change 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 were significant (Figure 4). T-test comparison of remitters to healthy participants at 8-weeks revealed the same pattern as at pre-treatment baseline such that there were no differences between participants who remitted on SSRIs and healthy controls, (Figure 4), $t(57) < 1$, but those who remitted on SNRI were different from healthy participants at trend level, (Figure 5), $t(44)$ -1.57, $p = .06$.

DISCUSSION

In this study we used functional neuroimaging to determine how pre-treatment neural activity during cognitive control tasks predicts post-treatment antidepressant outcomes in patients with major depressive disorder (MDD). We found that DLPFC activation was a general predictor of remission, while 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 pre-treatment, which attenuated post-treatment (in the same direction as controls). Patients who did not remit showed DLPFC hypo-activation at both pre and post-treatment. Remitters specifically to SSRIs showed correspondingly normal levels of inferior parietal activation, which also attenuated post-treatment, while non-remitters to SSRIs showed parietal hypo-activation. Moreover, neural activation predicting remission was seen only during response inhibition (Go/NoGo task), suggesting that inhibitory cognitive control functions in MDD, and fronto-parietal neural activation supporting this process, are diagnostic of remission outcomes in MDD. These findings thus support and expand earlier reports by Langenecker and colleagues (21).

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 hypo-activation in non-remitters 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 non-responsiveness to treatment, associated with a lack of neural cognitive resources. Indeed, after treatment, a reduction in DLPFC was seen in remitters, while non-remitters 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 post-treatment in patients, however lack of behavioral differences do not allow us to make conclusions about the amount of efficiency related changes involved. Reductions could be a sign of practice effects that are difficult to determine in the absence of behavioral differences.

Previous work has documented abnormalities in cognitive control between patients with major depressive disorder and healthy comparison groups in both response inhibition (15) and dorsolateral prefrontal activation (16). 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 (34). 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 group as compared to healthy controls (35). By contrast, in the same group of individuals that we report results from, during emotional stimuli processing *abnormal* amygdalar activity was related to *better* antidepressant response (36). Taken together, these findings collectively suggest that better antidepressant response is predicted by intact cognition, 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 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 out the medication-

versus placebo-related contributions. Future studies are also warranted to expand the array of antidepressant medication further.

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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Table 1: Demographic and clinical characteristics of remitters and non-remitters. Information for healthy controls is provided for comparison.

Characteristic	Major Depressive Disorder			Healthy Comparison	
	Remit	Non-remit	Statistics		Statistics
	Mean (SD)	Mean (SD)		Mean (SD)	
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	n/a	n/a
Gender (male/female)	20/17	20/23	F (1, 80) =.44, p=.51 χ^2=.57, p= .45	22/22	F(1,114) = .08, p = .78 χ^2 =.08, p=.77
Age at onset	19.54 (7.71)	21.33 (13.21)	t (78) = .72, p =.47	n/a	n/a
Major depressive episode duration	8.30 (6.49)	14.84 (14.19)	t (78) = 2.58, p =.01	n/a	n/a
Clinician rated severity - Hamilton Depression Rating Scales	21.78 (4.34)	20.58 (3.45)	t (78) = -1.38, p =.17	n/a	n/a

Self-rated severity - Quick Inventory of Depressive Symptomatology	14.08 (4.02)	13.48 (3.32)	t (78) = -.73, p= .46	n/a	n/a
Average dose at week 8 (mg)	Escitalopram: 9.71 (3.73) Sertraline: 57.81 (28.46) Venlafaxine-XR: 80.00 (19.36)	Escitalopram: 14.00 (9.66) Sertraline: 61.36 (25.89) Venlafaxine-XR: 109.10 (39.16)	Escitalopram: t(26) = 1.35, p = .22 Sertraline t(26) = -.33, p = .74 Venlafaxine-XR: t(25) = -2.28, p = .03	n/a	n/a

Supplemental Table 1: Uncorrected results for all tasks.

Task	*Anatomical region*	Coordinates			*t-test*	*p-value*
		x	*y*	*z*		
Go/NoGo Remission	R Mediofrontal cortex	44	32	38	4.14	< .001
	R Orbitofrontal cortex	30	64	-4	3.90	< .001
	L Orbitofrontal cortex	-14	68	-2	3.64	< .001
	Left Frontal Superior gyrus	-22	70	4	3.38	.001
	Right Inferior Parietal cortex	58	-48	44	3.28	.001
	Right Mediofrontal cortex	40	54	24	3.27	.001
Go/NoGo Response	Left postcentral gyrus	-50	-32	62	3.35	.001
Oddball Remission	Left Anterior Cingulate	-4	26	10	3.42	< .001
Oddball Response	Right precentral gyrus	52	8	46	3.49	< .001
Working memory Remission	*none*					
Working memory Response	Left Cerebellum	-38	-78	-42	3.41	.001

FIGURE LEGENDS

Supplemental Figure 1: CONSORT Diagram.

Figure 1: Prediction of remission by baseline brain activation. (A) Region in the dorsolateral prefrontal cortex in the NoGo minus Go contrast that predicts $HRSD_{17}$ remission, visualized as extracted beta values (B).

Abbreviation: $HRSD_{17}$: 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 minus Go contrast that predicts $HRSD_{17}$ remission differentially by SSRIs compared to SNRIs, visualized as extracted beta values (B).

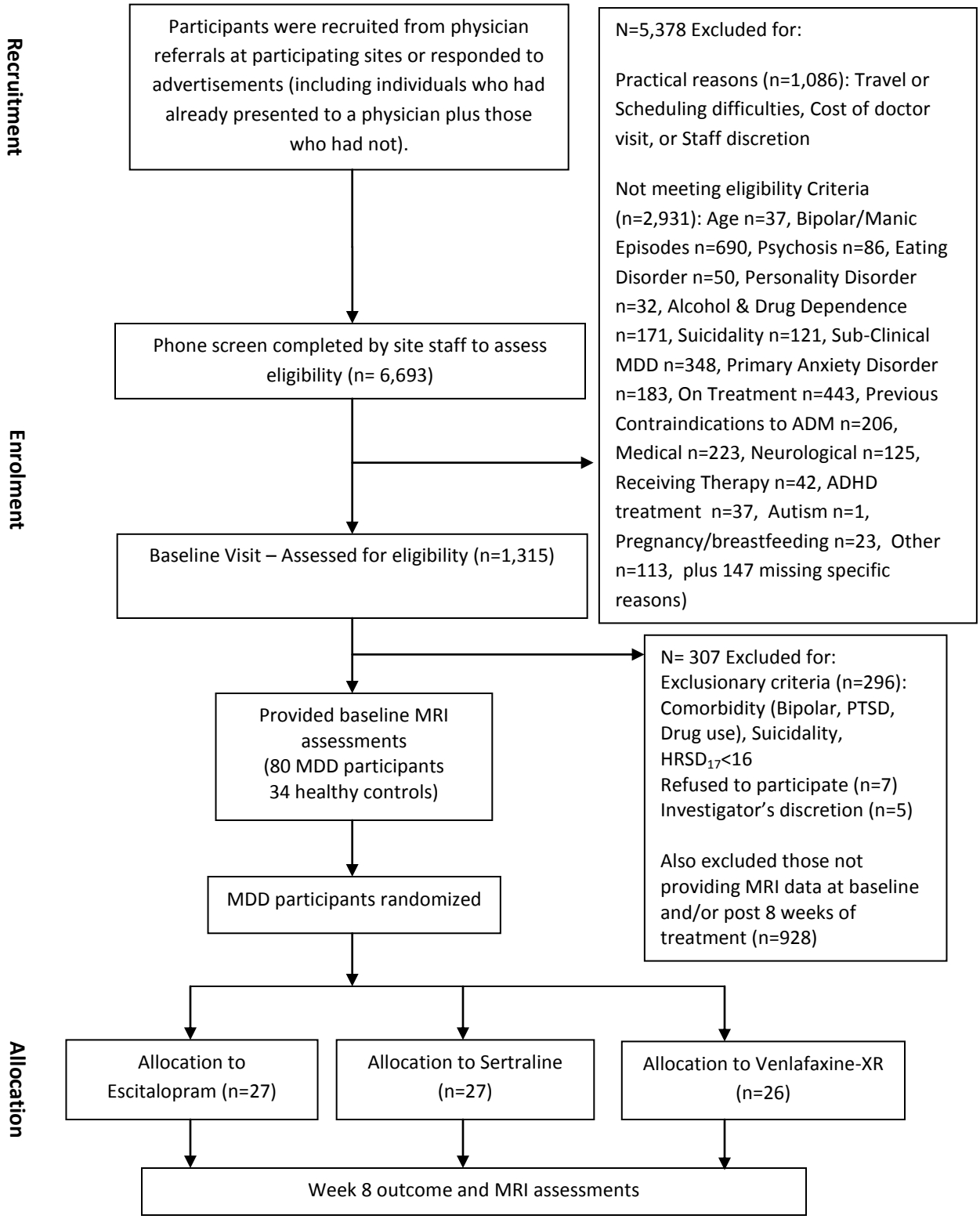
Abbreviation: $HRSD_{17}$: 17-item Hamilton Rating Scale for Depression

Figure 3: Relationship of dorsolateral prefrontal activation between participants with major depressive disorder and healthy comparison participants, both pre- and post-treatment. Patients who remit following antidepressant treatment (in grey bars) had the same level of dorsolateral prefrontal activation at baseline as healthy comparison participants (in dashed bars), which was reduced post-treatment. In contrast, participants who did not remit (in white bars) had significantly less dorsolateral prefrontal activation at baseline than healthy comparison participants, and did not change post-treatment

Figure 4: Relationship of parietal cortex activation between participants with major depressive disorder and healthy comparison participants, both pre- and post-treatment. Patients who remit

following SSRI antidepressant treatment (in dark grey bars) had the same level of parietal activation at baseline as healthy comparison participants (in dashed bars) and this was different from those remitted on SNRIs. The same pattern emerged post-treatment.

Supplemental Figure 1



Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder, ADM: antidepressant medication, $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; MDD: Major Depressive Disorder; MRI: Magnetic Resonance Imaging; PTSD, Post-Traumatic Stress Disorder

Figure 1

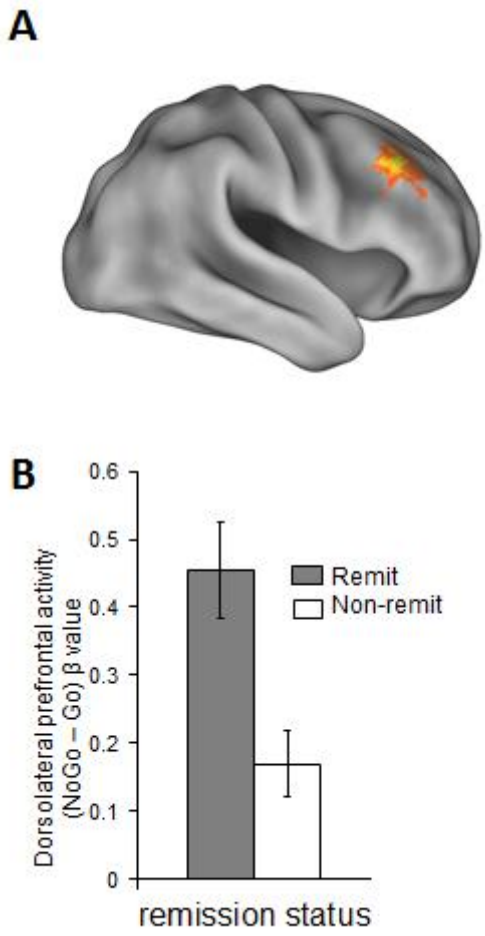

A
B
0.6
0.5
0.4
0.3
0.2
0.1
0
Dorsolateral prefrontal activity
(NoGo – Go) β value
Remit
Non-remit
remission status

Figure 2

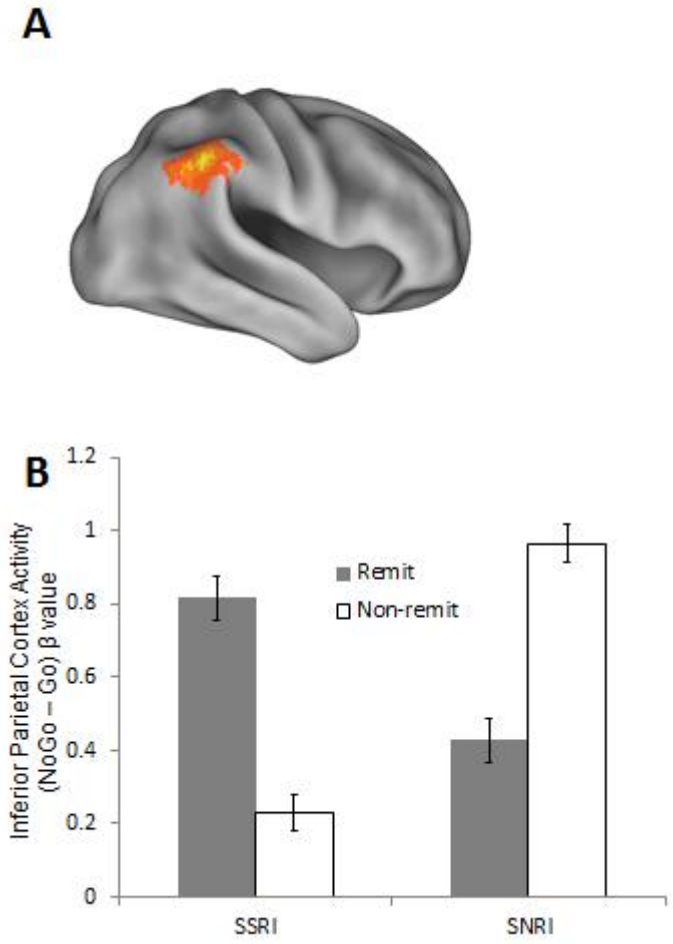

A
B
Inferior Parietal Cortex Activity
(NoGo – Go) β value
1.2
1
0.8
0.6
0.4
0.2
0
Remit
Non-remit
SSRI
SNRI

Figure 3

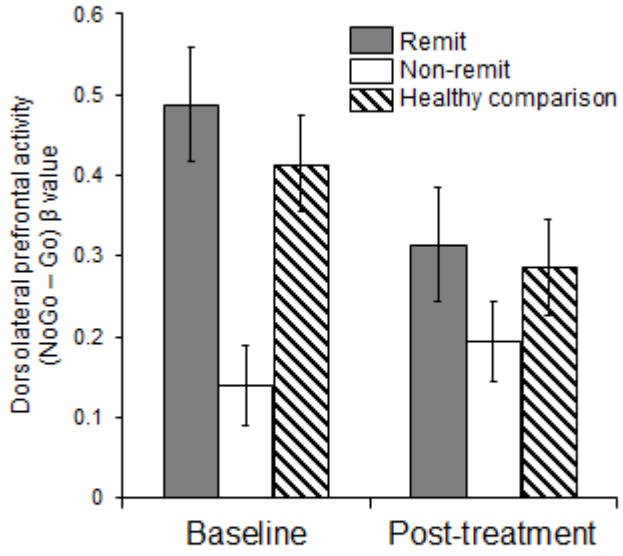
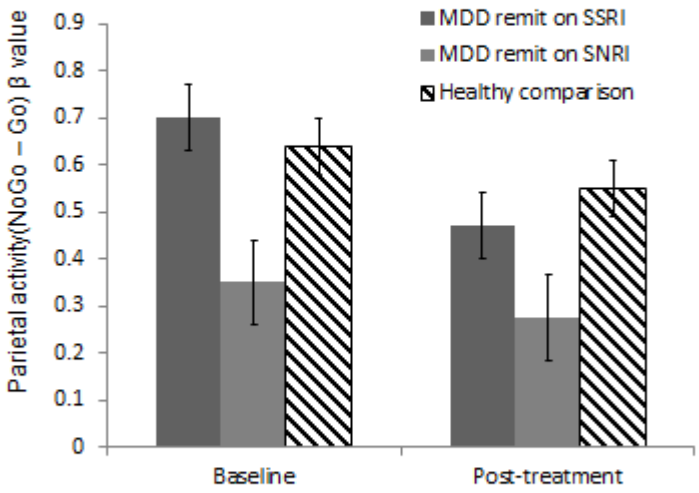

Remit
Non-remit
Healthy comparison
Dorsolateral prefrontal activity
(NoGo – Go) β value
0.6
0.5
0.4
0.3
0.2
0.1
0
Baseline
Post-treatment

Figure 4


MDD remit on SSRI
MDD remit on SNRI
Healthy comparison
Parietal activity(NoGo – Go) β value
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Baseline
Post-treatment