Archival Report

Biological Psychiatry

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

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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

http://dx.doi.org/10.1016/j.biopsych.2015.02.037

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 ($HRSD_{17}$) score of $\leq$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 $\geq$16 on the $HRSD_{17}$ (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 $\leq$7 on the $HRSD_{17}$ (using clinician-determined scores at week 8 posttreatment), and 2) treatment response, defined as a $\geq$50% decrease from the baseline $HRSD_{17}$ (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 $HRSD_{17}$.

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