Prediction of Treatment Response in Patients with Major Depressive Disorder: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies

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Abstract

Identifying the optimal treatment for individuals with major depressive disorder (MDD) is often a long and complicated process. Functional magnetic resonance imaging (fMRI) studies have been used to help predict and explain differences in treatment response among individuals with MDD. We conducted a comprehensive meta-analysis of treatment prediction studies utilizing fMRI in patients with MDD. A multi-level kernel density analysis was applied to these primary fMRI studies, in which we analyzed brain activation patterns of depressed patients (N= 364) before receiving antidepressant treatment. The results of this analysis demonstrated that hyperactivity in six brain regions significantly predicted treatment response in patients with MDD: the right anterior cingulate, right cuneus, left fusiform gyrus, left middle frontal gyrus, right cingulate gyrus, and left superior frontal gyrus. This study provides evidence that neural activity, as measured by standard fMRI paradigms, can be used to successfully predict response to antidepressant treatment. This may be used in the future clinically to improve decision-making processes and treatment outcomes for patients.

Introduction

MDD is a mental disorder that impacts approximately 3.8% of the world's population (1) and recent projections estimate that there are 280 million people worldwide with MDD. Despite acknowledgment of MDD's vast prevalence, the etiology of depression is not well-understood, and current psychiatric diagnostic processes utilize a symptom-based approach, which does not account for the underlying neuropathology of the disorder. This lack of understanding of the underlying neuropathology as well as other factors, such as comorbidity with other disorders, often makes MDD extremely difficult to successfully treat. Many clinicians and patients with depression struggle to find an effective medication, and even successful cases often require a great deal of trial-and-error (2). Following the advent of fMRI, patterns of neural activity have been used in multiple studies to predict how patients with MDD will respond to antidepressants (3). The present meta-analysis aims to provide a quantitative synthesis of fMRI-based treatment prediction studies of patients with MDD and thereby improve our understanding of the neural predictors of treatment response to antidepressants.

Method

In this meta-analysis, we employed multi-level kernel density analysis (MKDA) to identify brain regions that exhibit patterns of activation in MDD that can be used to successfully predict treatment response to antidepressant medications. To do so, we first conducted an exhaustive primary literature search using PubMed. We then selected primary studies that included participants diagnosed with MDD who underwent an fMRI scan prior to receiving antidepressant treatment and for which the authors conducted a whole-brain analysis to predict treatment response. We then extracted the relevant brain coordinates of significant clusters reported in the primary studies and used these data to build a whole-brain indicator map in AFNI. Once the final map was constructed, 10,000 Monte Carlo simulations were performed to determine the appropriate statistical and cluster-size thresholds required to establish statistical significance and to correct for multiple comparisons.

Results

Compared to non-responders, patients with MDD who responded to antidepressant medications demonstrated hyperactivity in several brain regions, including the following regions: the right anterior cingulate ($p \leq 0.00025$), right cuneus ($p \leq 0.001$), left fusiform gyrus ($p \leq 0.001$), left middle frontal gyrus ($p \leq 0.025$), right cingulate gyrus ($p \leq 0.025$), and left superior frontal gyrus ($p \leq .025$). These clusters were found to be significant only in our aggregate analysis. No clusters demonstrated significant hypoactivity.

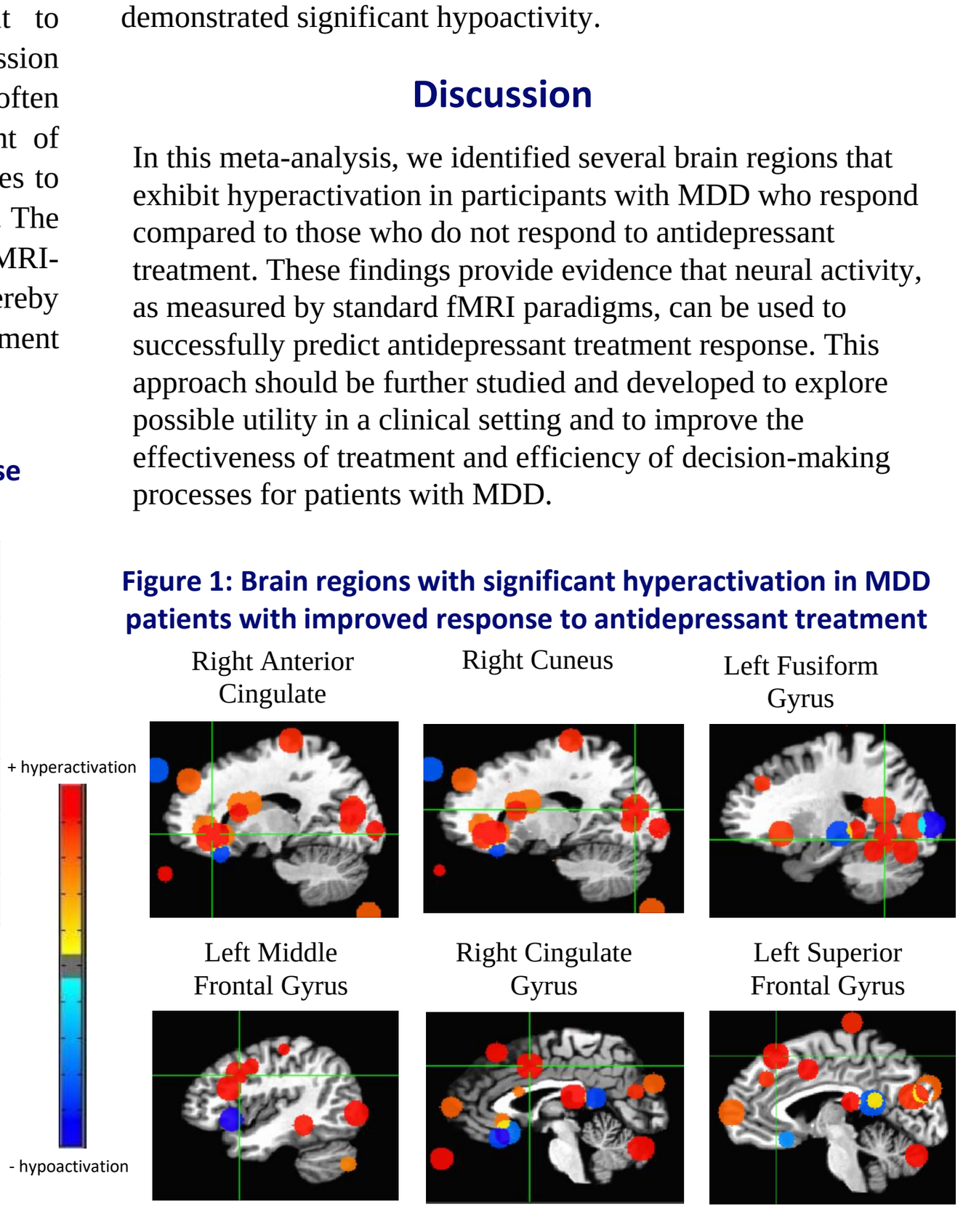
Discussion

In this meta-analysis, we identified several brain regions that exhibit hyperactivation in participants with MDD who respond compared to those who do not respond to antidepressant treatment. These findings provide evidence that neural activity, as measured by standard fMRI paradigms, can be used to successfully predict antidepressant treatment response. This approach should be further studied and developed to explore possible utility in a clinical setting and to improve the effectiveness of treatment and efficiency of decision-making processes for patients with MDD.

Table 1: Brain regions that predict difference in treatment response in adults with MDD

Brain Structure	Hemisphere	Direction of Effect	Talairach Coordinates (x, y, z)	Cluster Size	Statistical Threshold (p value)
Anterior Cingulate	Right	Hyperactive	-15, -32, -2	1,527	≤0.00025
Cuneus	Right	Hyperactive	-16, 75, 15	3,096	≤0.001
Fusiform Gyrus	Left	Hyperactive	20, 57, -8	1,524	≤0.001
Middle Frontal Gyrus	Left	Hyperactive	41, -11, 30	11,883	≤0.025
Cingulate Gyrus	Right	Hyperactive	-2, -4, 40	4,169	≤0.025
Superior Frontal Gyrus	Left	Hyperactive	4, -28, 50	4,169	≤0.25

Figure 1: Brain regions with significant hyperactivation in MDD patients with improved response to antidepressant treatment



References

1. World Health Organization. (2021). *Depression*. World Health Organization. Retrieved October 18, 2021, from https://www.who.int/news-room/fact-sheets/detail/depression.
2. Martin, L. R., Williams, S. L., Haskard, K. B., & Dimatteo, M. R. (2005). The challenge of patient adherence. *Therapeutics and clinical risk management*, *1*(3), 189–199.
3. Zhuo, C., Li, G., Lin, X., Jiang, D., Xu, Y., Tian, H., Wang, W., & Song, X. (2019). The rise and fall of MRI studies in major depressive disorder. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0680-6