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Commentary

Tracking the Brain: White Matter Structure Is Associated With Selective Serotonin Reuptake Inhibitor Treatment Response in Depression

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There is substantial variability in response to antidepressant drug treatments. While around 60% of patients will typically respond to first-line treatment(s), a significant proportion of individuals remain unhelped (1). Combined with the delayed clinical onset of action of antidepressants, this leaves patients, their families, and clinicians in a frustrating position while a series of different treatments are trialled, often extending over a period of weeks to months and beyond. There are currently no fully validated methods for selecting a treatment based on an individual's likelihood of treatment success or for providing an overall estimate of likely prognosis. The potential role for biomarkers or other predictors to aid attempts at more targeted prescribing—so-called precision medicine—is becoming an increasing priority for our field.

Different types of information have been considered candidates for the prediction of treatment response in depression, including the use of clinical, sociodemographic, genetic, immune, psychological, and neuroimaging measures (2). A growing body of evidence highlights that both structural and functional neuroimaging markers may have value. For example, hypoactivity of the anterior cingulate cortex is predictive of nonresponse across treatment modalities in depression, including nonresponse to selective serotonin reuptake inhibitor (SSRI) antidepressants, fast-acting agents such as ketamine, sleep deprivation, and repetitive transcranial magnetic stimulation (3). In terms of brain structure, poorer clinical response to antidepressant drug treatment has been reported as a function of reduced hippocampal volume (4). Studies using diffusion tensor imaging (DTI) measures of fractional anisotropy to explore the integrity of cortico-striatal-limbic white matter tracts have also reported associations with antidepressant drug response, but the nature and direction of these effects is unclear from the relatively small evidence base (2).

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Davis *et al.* (5) explore the potential of a more detailed characterization of white matter microstructural differences to predict response to SSRI treatment in depression, as part of the Canadian Biomarker Integration Network in Depression study. DTI data were collected from six sites before treatment and then again after 2 and 8 weeks of escitalopram treatment in 200 depressed patients and compared with 112 healthy control subjects. The depressed group was divided into responders and nonresponders on the basis of at least a 50% reduction in Montgomery–Åsberg Depression Rating Scale scores between baseline and week 8. A range of DTI metrics were explored, including fractional anisotropy and mean, axial, and radial diffusivity.

There was no effect of SSRI treatment on the DTI measures, as may have been expected with this relatively short treatment duration. However, in this patient cohort, reduced white matter integrity before treatment was associated with nonresponse. Specifically, microstructural differences in frontotemporal, cortical, and limbic white matter were significantly different between the patients who were later identified as nonresponders to escitalopram compared with the responders and/or healthy control subjects. One of the most robust differences involved the cingulum bundle (extending from the subcallosal cingulate to the hippocampus and amygdala), overlapping with evidence for an involvement of this same network using other imaging modalities (3,4). The combination of DTI measures points to reduced integrity of white matter being associated with the worst outcome.

This study is a robust test of the role of white matter integrity for SSRI response. The study benefits from a large sample size, preregistration, and a prospective longitudinal design applied across a network of sites. The use of different measures derived from the DTI data—over and above the fractional anisotropy previously explored—allowed the role and nature of white matter alterations to be more comprehensively studied. In this study, depressed patients were also compared with a group of healthy control subjects, which allowed further interpretation of the pattern of differences observed between the SSRI responders and nonresponders. In particular, responders to SSRIs appeared most like healthy control subjects, with white matter integrity being significantly lower in nonresponders. This pattern of results is consistent with other evidence that nonresponse may be associated with the presence of additional differences or brain structure abnormalities (4).

The findings of Davis *et al.* (5) have mechanistic and practical implications: they suggest that SSRI treatment effects may depend on intact white matter tracts and that changing neurochemical function will have the most benefit in a well-connected brain. This highlights a range of future research questions that are relevant for the field. For example, can we explore the factors that may contribute to these white matter abnormalities in treatment nonresponse, in order to harness these as potential predictors or to provide targets for further treatment in this group? White matter integrity is affected by a range of genetic and environmental factors, including cardiovascular function (6), which offers a way of integrating knowledge across areas of medicine for the understanding of depression and the understanding of treatment effects. Davis *et al.* (5) also revealed a potential role for the cingulate and hippocampus in depression nonresponse and, coupled with

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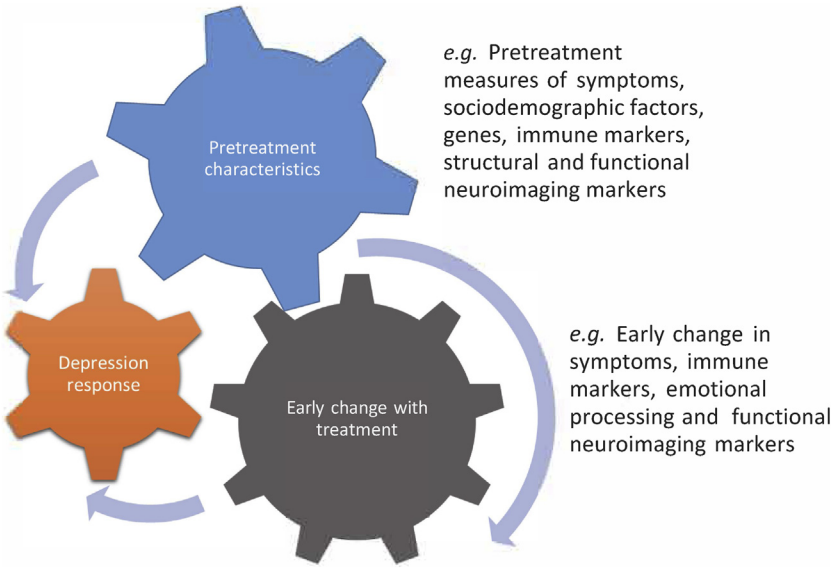

Figure 1. The prediction of treatment response in depression may require multimodal information across imaging, genetics, blood-based biomarkers, psychological, clinical, and sociodemographic factors. Both pretreatment and early change markers should be considered and may be integrated using multivariate analysis techniques.

previous work in this area (2), imply that further investigation of this network could be useful.

From a practical perspective, robust predictors of treatment response have the potential to transform the way depression is managed, modifying the way treatments are prescribed and shortening the time needed to identify the most effective treatment for each individual. However, the clinical translation of these kinds of findings is far from straightforward, and even the best-replicated neuroimaging predictors of response in depression have not yet made it into routine clinical practice. The current pattern of results does not differentiate between the response to different treatment types because only response to an SSRI was considered. This means that this approach may not be able to guide which specific antidepressant or psychological treatment may be most likely to work for an individual. A more general "poor prognosis" signal may still be useful in clinical practice but requires further investigation. Does accelerating treatment staging or applying more aggressive treatment from the start benefit this group? Do we need to target specific abnormalities using additional types of treatment to make a difference? The need for these additional large-scale studies remains a high barrier to full clinical translation. A placebo group was not included in this study, and therefore it is also unknown whether the association is a predictor of likelihood of recovery, a placebo response, or specifically a marker of response to an SSRI. Further, while the effect size observed in this study is good, it remains to be assessed whether this is sufficient to predict response at an individual level. Further studies using a priori criteria are required, measuring the specificity and sensitivity of the prediction offered by DTI measures. It is likely that the prediction will need to be extremely high to offset the use of this kind of cost-intensive and time-intensive marker.

It is possible that other factors may be correlated with these DTI measures and may be more easily assessed, and these factors should also be considered as potential confounds of the kind of association reported here. For example, it is not clear from Davis *et al.* (5) if the responders and nonresponders to escitalopram tend to have a different history of depression and previous treatment. Repeated episodes of depression are predictive of a more difficult to treat, longer-lasting episode and have also been associated with reduced white matter integrity (7). As such, the examination of a broader range of factors as potential predictors needs to be assessed within a single study to ascertain if there are any confounds or sources of overlapping information that can be harnessed.

It has been suggested that the combination of information across different measures may provide the best predictive power for understanding treatment response in depression (2). In this way, combining DTI outcome measures with other imaging techniques (such as voxel-based morphology and functional magnetic resonance imaging) as well as other factors (clinical, demographic, or blood-based) may be useful (Figure 1). Such an approach lends itself well to machine learning–driven treatment response predictors that use algorithms to detect subgroups of patients based on many patient-level characteristics, giving the opportunity to improve prediction accuracy by exploiting complex interactions between predictors.

While pretreatment predictors of response may be preferable for clinical decision making, it is also possible that early change in function may provide a more specific and accurate marker of response to a given treatment at a given dose and time in each individual. For example, baseline measures of emotional processing did not predict the response to antidepressant drug treatment, but early change in these measures after 7 days of treatment was an accurate predictor, correctly classifying later response for 77% of a sample of primary care–level depressed patients (8). Perhaps our quest for more personalized approaches for the treatment of depression needs to integrate not only across modalities and measures but also factors that affect response before and during treatment (Figure 1). Davis *et al.* (5) show the progress in the field

and the importance of using cutting-edge methodologies as they continue to be developed to understand the brain and to optimize precision medicine for mental health.

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