Neuroimaging Advances for Depression
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Editor’s Note: Depression is one of the world’s most prevalent mental health problems, with as many as 350 million sufferers worldwide and close to 20 million sufferers in the US. While neuroimaging applications for identifying various types of depression have made enormous strides in recent years, no findings have been sufficiently replicated or considered significant enough to warrant application in clinical settings. Our authors are well equipped to tell us what the future may bring.
For those who suffer from depression, core symptoms of low mood, lack of motivation, and mental clouding are miserable and frustratingly difficult to overcome. For those treating it, the complexity arising from varied combinations of these and other symptoms\textsuperscript{1} typically leads to the default application of treatment algorithms based on “average” patient outcomes.\textsuperscript{2} Patients and clinicians alike would benefit tremendously from methods using specific clinical or biological features to personalize treatment; i.e., to select the approach most likely to help. This goal is the focus of much of today’s depression research.

Depression is best thought of as a syndrome, which takes diverse forms in different people. All sufferers share the symptoms of excessive sadness or lack of pleasurable experience, but the associated characteristics can vary widely. Some have increased appetite and sleep, while others experience the opposite. Problems with concentrating or making choices may plague some, whereas others get bound up in guilty ruminations about past actions. Of greatest concern is that some patients—not necessarily those with severe symptoms and impairment—develop thoughts of taking their lives. All this variability suggests that there should be ways to classify depression into subtypes based on specific biological disturbances.

**Clinical Classifications of Depression**

The ultimate goal of classifying depression into subtypes is to enable selection of treatments that will hasten the resolution of the illness and, ideally, prevent future episodes. Psychiatrists recognize the importance of classification, and have expended tremendous time and energy on parsing patients’ clinical features, including symptoms, age of onset, frequency of recurrent episodes, and the role of preceding events.\textsuperscript{3-5} The most important diagnostic factor to emerge has been the identification of hypomanic or manic episodes when the patient is not depressed, which serves to distinguish between bipolar disorder and major depressive disorder.\textsuperscript{6}

Prominent among other clinical features used for subtyping major depressive disorder are the presence of psychotic features, peri- or post-partum onset, and seasonal variation. Many other bases for clinical categorization have been proposed over the past century, including endogenous versus reactive or neurotic depression, anxious versus non-anxious features, and melancholic (i.e., unrelentingly low mood associated with insomnia and reduced appetite) versus atypical features
(i.e., having brief periods when the mood substantially lifts associated with increased appetite and sleep)

Of these, perhaps the most clinically relevant for treatment selection are: 1) the identification of psychotic symptoms that require the addition of an antipsychotic to an antidepressant, or electroconvulsive therapy, and 2) the prominence of atypical features, which respond better to serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors than to tricyclic antidepressants. Although DSM-5 (the standard classification of mental disorders used by mental health professionals in the US) added many additional “specifiers” to more fully characterize major depressive disorder, their utility for treatment selection has not been established. Efforts to further classify depression continue, using increasingly complex models to group and weight specific symptoms and demographic features that can predict treatment outcomes. Unfortunately, these approaches to clinical subtyping have had limited value for personalizing treatment approaches due to inadequate or unsuccessful replication studies.

Similarly, biological studies of major depression have not yet met with great success in subtyping the disorder. Evaluations of neurochemistry, genetics, electroencephalography, neuroendocrinology, inflammation, and metabolomics (the study of molecules in the blood derived from cellular processes) have been investigated, with inconsistent results. High levels of inflammatory markers are of particular interest as a potential etiology of “treatment-resistant depression,” i.e., an episode that has not responded to established depression treatments. Some preliminary analyses suggest that a biological marker of inflammation can help indicate the most appropriate treatment, though further validation is still required. Many researchers believe that advances in understanding the biology of depression will require combinations of biomarkers. For example, it is possible that genetic or chemical markers derived from blood samples may help classify depression most effectively in conjunction with brain-focused methods of research.

**Neuroimaging Applications to Depression**

Neuroimaging may provide the greatest hope for identifying depression subtypes. There are many forms of neuroimaging that have relevance to mood disorders and these have become increasingly more sophisticated over time (see Figure 1).
Neuroimaging Toolkit

Initial studies examined the structure of the brain, particularly the size or volume of specific brain regions, using static images obtained via computerized tomography (CT) or magnetic resonance imaging (MRI). These studies identified the frontal cortex and hippocampus as potentially relevant brain regions in the pathophysiology of depression, hypotheses that were supported by post-mortem studies.

Subsequent research looked at regional blood flow or energy metabolism in the brain using functional MRI (fMRI) or positron emission tomography (PET). These studies capture the activity of the brain either in the “resting state” (i.e., when patients are not focusing on any particular thought...
or stimulus) or when the brain is actively responding to a task that induces an emotional or cognitive response. More recently, researchers have applied machine learning methods to fMRI data to identify brain networks and connectivity.

Other types of neuroimaging for mood disorders include diffusion tensor imaging (DTI) to assess the integrity of the white matter tracts that connect regions of the brain, magnetic resonance spectroscopy to assess differences in chemical composition across these regions, and ligand-binding studies to measure the density of receptors or monoamine-transporters. There are clearly many approaches to imaging the brain, and many interesting models of brain function and dysfunction in depression have been developed. The challenge facing researchers today is how to reliably establish and clinically apply these various conceptualizations.

Efforts to define biomarkers that can reliably distinguish between patients with depression and healthy controls have included neuroimaging. The earliest neuroimaging studies of major depression identified several differences between non-depressed and depressed individuals. Many studies using resting state or task-based PET or fMRI found depressed patients to have reduced metabolism in the dorsolateral prefrontal cortex, along with increased activity in regions considered part of the limbic system, such as the insula, amygdala and subcallosal cingulate cortex.

A recent meta-analysis of resting state functional connectivity studies identified reduced connectivity in frontoparietal control systems in depressed versus healthy control subjects, though without sufficient accuracy for a diagnostic test. Meta-analyses of structural MRI studies have shown, on average, smaller volumes of the hippocampus or its subregions in depressed patients, along with cortical thinning in several brain regions relevant to mood processing. In some studies, smaller hippocampal volume was associated with poorer outcomes to antidepressant medication treatment, though other studies have not replicated this volumetric finding or their treatment-predictive effects.

In sum, none of these approaches have achieved the level of accuracy or reproducibility that would define at an individual level the “neural signature” of major depressive disorder. The core of
the problem is the clinical and biological heterogeneity within the diagnosis, along with high rates of comorbidity with other psychiatric disorders.28

**Neuroimaging-Based Depression Subtypes**

Despite its failure to distinguish the healthy from the depressed, neuroimaging may have value in defining subtypes of depression. A crucially important application would be distinguishing between bipolar and major depressive disorder among patients presenting with a first episode of major depressive disorder, because misdiagnosis is common and the treatments for these two disorders are quite different.29 Neural markers purported to accurately classify these patients have used structural imaging,30,31 resting state functional connectivity,32 emotion-eliciting tasks,33 and white matter integrity.34 Although these methods have identified differences at the group level, their inability to clearly distinguish individuals with bipolar disorder from those with major depressive disorder may indicate that these illnesses represent points on a spectrum, rather than distinct biological entities.35

Given the difficulty in generating markers that can reliably sort major depression and bipolar depression, it may seem unlikely that neuroimaging will achieve clinically relevant subtyping within major depression alone. However, there are many interesting neuroscience theories with potential relevance here. Several neuronal circuits (i.e., interconnected brain regions that work together during specific mental functions) have been proposed that, when dysfunctional, may result in the symptoms of depression and anxiety.36 Researchers have now begun rising to the challenge of defining which neuroimaging markers have utility for treatment selection at the individual level. This leap forward will require imaging datasets subjected to an iterative process of identification, replication, and testing for clinical utility. The most fruitful path for applying neuroimaging to achieving this goal remains to be determined.

**Various Approaches**

Researchers attempting to subtype major depressive disorder with neuroimaging have taken several approaches. One has been to examine traditional clinical subtypes, such as melancholic, psychotic, or atypical features, for their neuroimaging correlates.37-40 Most such studies have found no or limited support for underlying neural signatures for these categories.41 Small studies have
suggested that melancholic depression is specifically associated with abnormal function of the default mode network (i.e., a brain network that is active when a person is not directing their attention to external events) or reduced effective connectivity between the insula and attentional networks. Overall, although they have interest, approaches that seek links between the brain and classic symptom features do not seem to offer promise for moving toward the goal of treatment selection.

A second approach has been to examine core features of depression using task-based studies, which analyze patterns of reactivity in the brain as the patient focuses on a specific cognitive or emotional stimulus. For example, anhedonia (the loss of motivation or pleasure in activities) is common in depression, although not all patients experience this symptom. Young people who demonstrate reduced neural responses to rewarding stimuli have been accurately identified as being at risk for developing depression. Other task-based assessments that presented emotionally salient words or faces to assess the reactivity of limbic (especially amygdala, and prefrontal) emotion-regulation regions have had discrepant results. A recent meta-analysis of 57 studies that employed emotion- or cognitive-processing tasks failed to find consistent differences between depressed and healthy control patients in brain activation patterns. Because few of these studies have been large enough to identify differential patterns among depressed patients, the potential for subtyping with these methods is unclear.

A third, more ambitious approach to subtyping has worked from the bottom-up, without labeling the subjects a priori but using unsupervised machine learning methods to find inherent patterns of connectivity or reactivity in neuroimaging data. The patterns identified from these analyses can then be used to cluster patients, creating potentially novel depression subtypes. Such analyses require large datasets to ensure that these patterns don’t simply characterize the participants in the study, but can be applied to depressed patients more generally.

Recently, the largest study of this kind, published in Nature Medicine, used resting state functional connectivity data in 220 patients with treatment-resistant depression to define biological subtypes ("biotypes") of major depression. This analysis identified four forms of dysfunctional connectivity between fronto-striatal and limbic networks, which demonstrated high classification accuracy and
were differentially associated with clinical symptoms of anhedonia and anxiety. They were replicated in an independent sample. The clinical utility of these biotypes remains uncertain because treatment outcome data for most patients were not available, though in a subset of the patients the biotypes were retrospectively able to identify those who were likely to respond to treatment with a form of transcranial magnetic stimulation.\textsuperscript{50} This approach of building a new categorical system from the bottom up, uninfluenced by prior conceptualizations of depression, carries the appeal of carving nature at its joints, but will likely require decades to be sufficiently validated to use in treatment selection.

In contrast to the grand scheme of characterizing \textit{de novo} the pathophysiology of depression for the purposes of subtyping, and hoping that treatments will follow those subtypes, it may be more useful to take a direct approach: i.e., to explicitly apply the treatment outcomes of patients to the neuroimaging data. Through this fourth approach, the treatment outcomes (e.g., remission, non-response) are used to identify signatures in the pre-treatment neuroimaging data that differentiate between the outcomes. These neuroimaging signatures can then be prospectively tested by seeing how well they predict outcomes in new patients receiving the treatments. Thus, this approach takes the stance that the maximal utility from brain imaging in depression will emerge from its ability to help clinicians choose between possible treatments, not from developing depression classification schemes isolated from treatment effects. Identifying neuroimaging patterns that can predict with reasonable accuracy the probability that an individual will benefit from a specific treatment would be a substantial boon to the clinical care of depressed patients.

\textbf{Looking Forward}

Several studies using resting-state or task-based fMRI have reported markers predictive of response or non-response to antidepressant medications\textsuperscript{51-53} or to psychotherapy.\textsuperscript{54-56} A limitation of these single-intervention studies is that they do not provide information about whether an alternative treatment would likely be more or less effective than the evaluated one. This makes it impossible to determine whether the neuroimaging signal in question indicates response regardless of treatment, or is specific to the intervention in the study.\textsuperscript{57}
This treatment outcome-based approach would be most valuable if it could inform the prediction of good and poor outcomes to two or more treatments believed to work via differing mechanisms (e.g., psychotherapy versus medication versus TMS).

Using this approach, we recently published the results of two randomized studies that aimed to identify neuroimaging patterns that could differentially predict outcomes to treatment with an antidepressant medication or cognitive behavior therapy (CBT). Building off clinical observations that patients who responded poorly to one of these interventions often did well with the other, we hypothesized that neuroimaging patterns that predicted remission with one treatment would also predict poor response with the other.

The first study, using fluorodeoxyglucose-PET, found that resting state metabolism of the right anterior insula could distinguish remitters from non-responders to treatment with the antidepressant escitalopram or to CBT. More recently, a subsequent study of 122 depressed patients used resting state fMRI to identify functional connectivity patterns between the subcallosal cingulate cortex and three other brain regions that could distinguish between remitters and non-responders to antidepressant medication (escitalopram or duloxetine) and to CBT. These results support the concept that patients whose depression symptoms are similarly severe can have distinctly different patterns of brain activity, and that those patterns may be used for treatment selection. With this approach, it may be possible to predict failure to all standard first line treatments for depression, avoiding months of ineffective therapies and allowing earlier application of interventions usually reserved for treatment-resistant depression, such as TMS, electroconvulsive therapy, ketamine, or medication polypharmacy.

In sum, despite the excitement around neuroimaging methods, it is important to recognize that to date all the identified subtypes have been based on retrospective analyses. The great majority of patients already benefit from one or another of existing depression treatments. But approaches that characterize brain states responsive to specific interventions offer the possibility of advancing further, past the current trial-and-error, algorithm-based application of psychotherapy, medication, and brain stimulation to a personalized psychiatry that can choose the treatment most likely to benefit the individual patient.
Bios

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