Medical Xpress

Closing the loop for brain imaging in depression

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Depression can have a profound impact on affected individuals and those around them. It is one of the most common mental health conditions, and its symptoms include sustained feeling of sadness, hopelessness, and guilt. In severe cases, these symptoms may be aggravated by suicidal thoughts, or even attempts. The odds of

experiencing a depressive episode are relatively high: at least one in six individuals will experience an episode in their lifetime.

Although the term depression suggests that it represents a single psychiatric condition, patients vary tremendously in their symptoms, risk factors, and response to available treatment. Risk factors include not only genetic variations and hormonal changes, but also destructive thinking patterns, or stressful and traumatising experiences. Current treatments primarily include medication and psychotherapy. Medication prescribed in depression targets different brain chemical systems, involving neurotransmitters that include serotonin and dopamine. These are involved in communication between nerve cells and, more generally, in the feeling of well-being. Psychotherapy aims to help patients develop effective coping strategies to use when they are faced with challenges and setbacks. Most depressed individuals will eventually recover – however, up to one third may not.

One branch of depression research focuses on finding biomarkers that can identify individuals that will most likely benefit from a specific therapy. The field also works on developing innovative treatments. However, both goals require a better understanding of the underlying biology. Brain imaging research, clinical psychology, and genetics have provided some fascinating answers, but have also posed new challenging questions.

We asked three experts and pioneers in depression research: How do you study clinical depression, what role does brain imaging play in your research, and what challenges lie ahead for the field?

Ian H. Gotlib (Professor of Psychology, Department of Psychology, Stanford University):

"Over the past two decades, we have learned that depression is a heterogeneous disorder, with wide variations in symptom presentation, age of onset, number and duration of episodes, and causal factors. In my lab, we take this heterogeneity seriously – we administer structured diagnostic interviews to every participant in our studies. And perhaps more important, we conduct multimodal assessments of depression – we examine brain structure, function, and connectivity; endocrine function, both under acute stress and throughout the day; cognitive functioning, including biases in attention, interpretation, and memory; and digital phenotyping of depressed children, adolescents, and adults.

The number of brain imaging studies has grown exponentially, and there is now a burgeoning literature examining brain structure, function, and connectivity in depressed individuals. Neuroimaging studies have helped to elucidate the neural circuitry involved in reward processing and the processing of emotional experiences. Because the two cardinal symptoms of depression in the Diagnostic and Statistical Manual (DSM) involve the persistent experience of negative affect and anhedonia, researchers studying depression have focused on examining their neural underpinnings. From these investigations we are learning about anomalous neural characteristics of depressed individuals that may be related to difficulties in daily functioning and that may serve as intervention targets. We know far less, however, about aspects of brain structure, function, and connectivity that place individuals at risk for developing depression, that keep high-risk persons from experiencing depression, and that influence the maintenance of and recovery from this disorder. We also know relatively little about the developmental trajectories of these anomalous neural characteristics, knowledge that is critical in understanding differences between children and adults in the presentation of depression."

Helen Mayberg (Professor of Neurology,

Neurosurgery, Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai):

"Our lab takes a circuit approach to the study of major depression: Studies integrate multimodal neuroimaging strategies and quantitative behavioral and psychophysiological metrics within experimental clinical trial protocols to define brain mechanisms that mediated anti–depressant treatments. The overarching goal is to develop imaging biomarkers and algorithms that will identify patient subgroups and optimize treatments for individual patients. This work also serves as a basis for ongoing testing and refinement of deep brain stimulation (DBS) of the subcallosal cingulate, a technique that our lab is investigating for treatment resistant depression.

Imaging has provided new perspectives on understanding the pathogenesis of depression, as well as treatment mechanisms. Studies have systematically defined a core set of consistent regional abnormalities, correlations between symptoms and abnormal function of specific brain regions, and evidence of putative depression subtypes. Multimodal imaging and advanced analytic methods have further provided strategies to build depression circuit models that directly test treatment selection biomarkers.

The challenge for the 'field' will be to define what method(s) are 'good enough' to warrant meaningful replication studies of an encouraging finding. Balancing a useful clinical biomarker that might improve treatment selection or response assessment from those addressing fundamental mechanisms of circuit dysfunction and pathophysiology require different strategies and standards."

David EJ Linden (Professor of Translational Neuroscience, Cardiff University and Maastricht

University):

"One of the main research techniques used in my group is real-time functional magnetic resonance imaging (fMRI) neurofeedback training. fMRI allows researchers to trace activation patterns that are associated with external stimuli or internal mental states in real time, and we can feed these activation changes back to patients, so they can learn to regulate them themselves. This opens up interesting potential therapeutic avenues, for example, for emotion regulation training in depression, but also other mental disorders.

Functional brain mapping with fMRI has provided crucial new insights in the neural representations of affect and its disturbances. It has become clear that there are strong links between classical emotion and motivation areas, implemented through functional anatomical links between the limbic system and the basal ganglia, for example, in the ventral striatum. This has sparked renewed interest in the role of reward mechanisms in depression. A future challenge will be to work on the standardisation of imaging protocols across sites and conduct formal studies of the potential diagnostic and predictive value of these functional imaging patterns in order to produce clinically useful biomarkers."

Researchers and clinicians agree that depression can manifest differently in each individual. Neuroimaging and multimodal studies allow investigators to examine underlying mechanisms of such variability, although identifying robust biomarkers remains challenging. This knowledge informs translational research into new brain circuit-based interventions, including clinical trials of DBS and neurofeedback treatment. Thereby, the field may "close the loop," yielding more effective and individually tailored treatments for depression.

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