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Using Neuroimaging to Decipher the Mechanism of Action of Ketamine: A Pathway to Novel Therapeutics?

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A plethora of research has investigated neural changes in response to antidepressant drugs, but their mechanism of action remains only partially understood. Frustratingly, mechanistic studies of conventional antidepressants are hampered by a delay in clinical response. In addition, previous imaging studies examining antidepressant mechanisms have not themselves led to the development of novel agents. In contrast, mechanistic studies of rapid-acting antidepressant agents, such as the glutamatergic modulator ketamine, may facilitate and accelerate our understanding of these drugs, given that correlates of response and nonresponse can be examined within short periods of time, allowing investigators to assess molecular, cellular, and circuit changes in real time as patients shift from states of illness to improvement (1,2). Whether the neurobiological correlates of the response process will represent the broader mechanism of action of all antidepressant agents will be determined with time.

In this context, mechanistic studies, such as the one performed by Abdallah *et al.* (3) that appears in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, are not only needed but crucial to antidepressant drug development. Their study had two components. In the first substudy, a group of 29 healthy control subjects and 22 subjects with treatment-resistant major depressive disorder (MDD) were scanned using resting state functional magnetic resonance imaging (fMRI) at baseline and 24 hours after infusion of either ketamine or midazolam. The second substudy was a well-designed pharmacological challenge study in which a small sample of healthy control subjects received either oral placebo or lamotrigine, which inhibits glutamate release by blocking voltage-sensitive sodium channels; subjects were subsequently scanned after a placebo lead-in infusion and a second infusion of either ketamine or placebo. In both substudies, data were analyzed using global brain connectivity with global signal regression (GBCr). In this procedure, the mean

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signal from the whole brain is first removed by linear regression. A GBCr map is then created by taking the mean correlation of each gray matter voxel with all other gray matter voxels in the brain. Below, we discuss the results and implications of these substudies in turn.

In the first substudy, Abdallah *et al.* replicated their previously published finding (4) of reduced GBCr in the medial prefrontal cortex (mPFC) of subjects with MDD compared to healthy control subjects. This in itself is a valuable addition to the literature; all too often, results in the neuroimaging literature are never replicated, with new experiments and designs taking precedence over replication studies. Although the present analysis was restricted to the PFC, it would be interesting to find out whether the original findings of increased GBCr in the posterior cingulate (a default mode network core region) were also replicated. In the present study, Abdallah *et al.* (3) also found that GBCr within the mPFC increased in the 10 subjects scanned 24 hours after ketamine infusion; no significant change in GBCr was observed after the active placebo midazolam. This increase in GBCr, however, did not correlate with clinical improvements after ketamine infusion, although baseline GBCr levels were associated with subsequent changes in mood after both midazolam and ketamine infusions.

To put this finding into context, connectivity during and after ketamine infusion has been examined in the neuroimaging literature using a variety of techniques, both in depressed patients and in healthy control subjects. Joles et al. (5) used resting-state fMRI to construct connectivity matrices based on whole-brain parcellation and demonstrated a shift after ketamine infusion from cortical to subcortical connectivity using the graph theory measure of degree centrality, which reflects the number of connections each region has to all other regions. In contrast, Kraguljac *et al.* (6) found that connectivity from the hippocampus to the mPFC and posterior cingulate cortex was decreased after ketamine infusion, suggesting overall decreased connectivity in the default mode network. This latter finding is consistent with other work by Abdallah *et al.* (4) showing reduced connectivity during ketamine infusion between a posterior cingulate cortex default mode network seed and parahippocampal areas. While seed-based connectivity measures require a priori selection of a region of interest, they are immediately interpretable as functional connectivity between the seed and target region. Findings from graph theory analyses may implicate particular regions, but only in the context of that region's interactions with other nodes in the network. Nevertheless, alterations in global network structure and function in various states of psychopathology may be potentially more informative than abnormalities in specific regions. Measures such as GBCr present a thorny interpretation problem, because it can be unclear how to best interpret alterations in a PFC cluster in terms of its connectivity with the rest of the brain. This is especially true after regression of the global signal from the entire brain, given that global signal regression alters the correlation structure of the data such that the distribution of correlation values between a seed and all other voxels in the brain should be approximately zero and negative correlations are enhanced (7).

In the second substudy, Abdallah *et al.* (3) found reductions in mPFC GBCr in healthy subjects after a single 300-mg dose of oral lamotrigine plus intravenous (IV) saline compared to oral placebo plus IV saline. The authors also noted that oral lamotrigine

attenuated the GBCr increase seen after ketamine infusion compared with the oral placebo. The aforementioned study by Joules et al. (5) similarly acquired resting-state fMRI data during an IV ketamine infusion after a single 300-mg dose of oral lamotrigine. A multivariate classification technique was then used to determine if drug conditions could be distinguished via degree centrality. While the placebo and ketamine conditions were readily distinguished, the oral lamotrigine and oral placebo conditions were indistinguishable. Likewise, degree centrality maps after oral lamotrigine plus IV ketamine were indistinguishable from those after oral placebo plus IV ketamine, in contrast to the present finding by Abdallah *et al.* (3).

While our understanding of the influence of psychotropic drugs on brain function will undoubtedly benefit from additional studies such as this one, the present study is also associated with several key unknowns. For instance, it is unclear whether healthy control subjects have a similar neuronal response as MDD subjects, and what a study examining healthy control subjects can tell us about the antidepressant mechanism of action of any drug. In addition, the reported GBCr results in the second substudy were derived from fMRI images acquired during performance of a visual oddball task; the effects of this task on GBCr are unknown.

As Abdallah *et al.* state, robust measures of target engagement, as well as prognostic biomarkers, are desperately needed to further both drug development and a better understanding of psychiatric disease. In this context, a fundamental problem is that the brain is an extraordinarily complex system whose function can be measured only indirectly. It is important to note that all the studies mentioned above used fMRI, which measures alterations in hemodynamic properties occurring in response to neural activity. While fMRI has strongly demonstrated its utility as a tool for examining brain function and provides images of exquisite spatial detail, it is nevertheless fundamentally limited in its ability to measure brain function in the temporal domain. In contrast, electrophysiological measurements, such as magnetoencephalography (MEG), are emerging as a way to more directly measure neuronal function in real time rather than filtered by the response of the cardiovascular system, while still preserving some spatial localization. For example, Muthukumaraswamy et al. (8) performed MEG recordings during saline and ketamine infusions in 19 healthy subjects and found robust alterations in spectral power across a broad range of frequency bands. That study also used dynamic causal modeling, a technique that uses neural mass models incorporating N-methyl-D-aspartate, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and gamma-aminobutyric acid type A receptors to predict observed electrophysiology data. Using this technique, the authors observed significant ketamine-induced changes in both alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid- and N-methyl-D-aspartate-mediated connections from the frontal to parietal cortex, as well as changes in parietal excitability (8). Other MEG studies demonstrated that ketamine induces synaptic potentiation, but only in individuals who respond clinically (9). Along these lines, electrophysiological studies have the added benefit of enabling translational research because they allow for clearer comparisons between direct measurements of electrophysiology in animal models. Recently, Zanos et al. (10) demonstrated the potential antidepressant efficacy of the ketamine metabolite (2R,6R)-hydro-xynorketamine; these clinical findings were augmented with measurements of in vitro

excitatory postsynaptic potentials and local field potentials as well as in vivo quantitative electroencephalography. Under such a paradigm, future studies of human subjects could routinely incorporate electroencephalography or MEG recordings to ensure target engagement, with the ultimate goal of more efficiently identifying and screening potential therapeutic agents.

As noted above, mechanistic studies and pharmacologic challenge studies—such as the one by Abdallah et al. (3) and the others mentioned herein—are welcome additions to the literature. In particular, Abdallah *et al.*'s replication of previous work is a commendable contribution to the current replicability crisis across science. Additional well-designed, replicable, and highly interpretable studies that directly measure neurophysiological processes in MDD patients in response to rapid-acting treatments will undoubtedly further the goal of developing more effective treatments for mental illnesses, with concomitant improvements in public health worldwide.

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