Commentary

Biological Psychiatry: CNNI

Harnessing Neuroimaging to Enhance Our Understanding of the Effects of Ketamine in Depression

Natalia Jaworska and Jennifer L. Phillips

Worldwide, major depressive disorder (MDD) carries a large burden of disease and is associated with impaired functioning and a worsening of comorbid illness. MDD is also linked with shorter life expectancies, including increased death by suicide, which is the most tragic consequence of the disorder. Despite numerous existing pharmacological options for treating depression, many patients do not achieve remission, and significant antidepressant responses usually occur only after several weeks of treatment. There has been growing excitement, coupled with cautious optimism, regarding the discovery of the rapid-acting antidepressant properties of subanesthetic doses of intravenous ketamine. With administration of ketamine, a glutamate *N*-methyl-D-aspartate receptor antagonist, decreases in depression symptoms and suicidal ideation can emerge within hours, even in treatment-resistant patients (1,2). Importantly, Phillips *et al.* (3) and others have reported sustained antidepressant effects with repeated ketamine administration.

While evidence of ketamine's antidepressant efficacy continues to grow, and its clinical use becomes increasingly common (especially with the U.S. Food and Drug Administration's approval of intranasal esketamine [an S-enantiomer of racemic ketamine] for the treatment of refractory MDD), our understanding regarding its mechanisms of action, particularly on neural network dynamics in depressed individuals, is in its infancy. The increased integration of functional magnetic resonance imaging (fMRI) data in psychiatric research has been instrumental in expanding our knowledge about the effects of various antidepressant interventions on brain function. The same potentially holds true for ketamine. Characterizing the neural underpinnings of ketamine's antidepressant action is a critical step in eventually optimizing and predicting ketamine response (i.e., the identification of putative biomarkers of response and nonresponse).

As outlined by Reed *et al.* (4) in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, clues to the mechanisms underlying the effects of ketamine on mood symptoms may be elucidated, in part, by examining the neural correlates of emotional processing in individuals with and without MDD. After all, there has been accumulating work indicating that MDD is associated with altered brain activity during emotional information processing (5). In brief, Reed *et al.* (4) measured blood oxygen level–dependent signal changes during emotional processing in individuals enrolled in a double-blind, placebo-controlled crossover study comparing single infusions of ketamine and saline. Specifically, individuals with treatment-resistant MDD and control subjects (18–65 years of age) were scanned at baseline and again approximately 2 days after receiving infusions of ketamine and placebo (0.5 mg/kg delivered over 40 minutes, with 2 weeks separating each infusion). The number of usable scans ranged from 26 to 33 for the MDD group to 15 to 20 for the control group, depending on scanning day. During scans, participants completed implicit and explicit facial expression recognition tasks, where task-related factors included face valence (positive [neutral/happy] or sad [angry/sad]), orientation (upside down/right side up), and judgment (emotion/sex identification). Analyses focused primarily on contrasts between postketamine and postplacebo scan sessions. Reed *et al.* (4) reported hyperactivity in brain regions implicated in emotional processing in individuals with MDD relative to healthy control subjects at baseline (in the cuneus, left temporal and medial frontal gyri, and right parietal cortex), though less activity was noted in the left cingulate and right lentiform nucleus. After the ketamine versus placebo infusion, patients' activity was decreased relative to control subjects' across the precuneus, frontal, temporal, and posterior cingulate regions. In other words, in patients with treatment-resistant MDD there appeared to be a normalization of neural profiles during emotional processing after ketamine administration compared with placebo. Imaging was conducted at 2 days after infusion, a timeframe sufficiently removed from the acute side effects that are associated with ketamine administration. Overall, these findings are somewhat in line with previous work by this group wherein brain activity in depressed patients postketamine was similar to control subjects postplacebo, particularly in aspects of the medial frontal cortex, during an attentional bias dot probe task using emotional face stimuli (6). The consistency in these findings—namely, that ketamine appears to normalize aberrant patterns of neural activity in depressed individuals—is encouraging, although perhaps not surprising given that the data were derived from the same participants within a single clinical trial.

In MDD, resting-state fMRI connectivity studies have identified disturbances in networks composed of regions supporting emotional processing, attention and executive function, and in the default mode network. One group assessed resting-state fMRI profiles in patients with treatment-resistant MDD 24 hours postketamine versus postmidazolam and showed connectivity profile normalization (7). Specifically, initially decreased activity (global signal regression) in frontal regions was increased postketamine. In addition, ketamine

SEE CORRESPONDING ARTICLE ON PAGE 610

https://doi.org/10.1016/j.bpsc.2019.05.005
© 2019 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

ISSN: 2451-9022 Biological Psychiatry: Cognitive Neuroscience and Neuroimaging July 2019; 4:603–605 www.sobp.org/BPCNNI

responders showed increased connectivity in certain brain regions (the lateral prefrontal cortex, caudate, and insula) before ketamine infusion (8), speaking to the potential utility of resting-state fMRI–based biomarkers of eventual response. Similarly, previous work from Evans *et al.* (9) found that connectivity between the insula and the default mode network was normalized 2 days after ketamine infusion in depressed individuals versus healthy control subjects. These findings provide evidence that interventions with antidepressant agents, including ketamine, normalize aberrant neural network connectivity profiles at rest. However, the exact nature of what constitutes an "aberrant" neural network or activity warrants clarification; this differs from study to study. What also remains to be investigated is the relation between changes in neural activity from before ketamine to after ketamine and changes in clinical symptoms. Despite the relatively high response rates to ketamine, not all patients exhibit antidepressant effects; it will be important to determine whether brain activity changes differ in ketamine responders and nonresponders. Such investigations would reveal whether we are measuring the neural effects of ketamine itself or neural changes associated with (and perhaps underlying) the alleviation of depressive symptoms with ketamine infusions. This is an important distinction that should be further investigated.

Even though neuroimaging can provide us with insights regarding the neural effects of ketamine, certain caveats must be considered. First, the notion of a double-blind procedure when considering ketamine administration is inherently difficult. The use of saline as a placebo, as used by Reed *et al.* (4), is not optimal. Other groups, including our own, have used midazolam, a short-acting benzodiazepine, as an active control for ketamine. However, while midazolam is associated with sedative properties, it elicits few of the dissociative symptoms associated with ketamine, making it an imperfect control. The lack of an optimal placebo control for ketamine thus remains an important limitation in the field. A perhaps more relevant comment regarding the work of Reed *et al.* (4), and pertinent to the use of neuroimaging in psychiatry more generally, is the challenge of replicating fMRI data. As has been repeatedly demonstrated, replication of seemingly robust findings can be problematic, and it tempers the promise that neuroimaging has with respect to improving psychiatric illness outcomes (10). In general, some of the elements that hamper replication include small samples, methodological heterogeneity, and a lack of statistical and methodological rigor. Suggestions to improve rigor include optimizing experimental procedures, including scan duration; simplifying protocols to limit the number of factors; and using power analyses/experiment modeling (which could optimize power) before study commencement. In addition, better accounting of baseline differences between comparator groups (e.g., depressed vs. nondepressed individuals) is also an important consideration. With respect to this last point, among the fMRI research conducted to date it is unclear why ketamine's effects would manifest differently in individuals with MDD compared with healthy control subjects, and it is unclear just how much baseline differences drive these effects.

Where does the field move from here? First, replication of the effects of ketamine's neural profiles at rest and during emotional processing must be conducted in independent samples by different research groups. Second, the longer-term effects on neural features of ketamine or following repeated ketamine infusions have yet to be explored. Third, the utility of integrating imaging features in predicting response to ketamine and other rapid-acting antidepressants warrants additional attention. However, this should likely be explored in tandem with other potential predictors of response acquired using less expensive and/or more accessible approaches, including clinical measures, clinical electroencephalography, and/or genetic markers, for instance. The same is true for integrating various analytical approaches in prediction approaches, such as applying machine learning to large-scale publicly available datasets, which enables the possibility of meeting the assumptions of machine learning and multistep validation.

Finally, given the uniquely rapid nature of ketamine's antidepressant effects, ketamine offers the opportunity to probe the effects of depression itself on brain profiles. By conducting longitudinal neuroimaging and using ketamine as a tool to alleviate depressive symptoms we have the opportunity to image patients who may be depressed one day and remitted on a subsequent visit within a relatively short timescale. The short intervention period and the generally large magnitude of response to ketamine infusions makes the assessment of brain-based phenotypes highly valuable. This strategy may allow for further identification of potentially more novel and tailored antidepressant intervention approaches going forward.

Acknowledgments and Disclosures

This work was supported by the Emerging Research Innovators in Mental Health incubator program at The Royal's Institute of Mental Health Research, University of Ottawa (to NJ).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the The Royal's Institute of Mental Health Research (NJ, JLP), affiliated with the University of Ottawa; Departments of Cellular and Molecular Medicine (NJ) and Psychiatry (JLP), and the Brain and Mind Research Institute (NJ, JLP), University of Ottawa, Ottawa, Ontario, Canada.

Address correspondence to Natalia Jaworska, Ph.D., Clinical Electroencephalography Laboratory, The Royal's Institute of Mental Health Research, Room 3129, 1145 Carling Ave, Ottawa, ON K1Z 7K4, Canada; E-mail: natalia.jaworska@theroyal.ca.

Received May 10, 2019; accepted May 13, 2019.

References

1. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al.* (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864.
2. Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, Correll CU (2016): Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: A meta-analysis of efficacy, safety and time trajectories. Psychol Med 46:1459–1472.
3. Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, *et al.* (2019): Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: A randomized controlled trial. Am J Psychiatry 176:401–409.

4. Reed JL, Nugent AC, Furey ML, Szczepanik JE, Evans JW, Zarate CA Jr (2019): Effects of ketamine on brain activity during emotional processing: Differential findings in depressed versus healthy control participants. Biol Psychiatry Cogn Neurosci Neuroimaging 4:610–618.
5. Jaworska N, Yang XR, Knott V, MacQueen G (2015): A review of fMRI studies during visual emotive processing in major depressive disorder. World J Biol Psychiatry 16:448–471.
6. Reed JL, Nugent AC, Furey ML, Szczepanik JE, Evans JW, Zarate CA (2018): Ketamine normalizes brain activity during emotionally valenced attentional processing in depression. Neuroimage Clin 20:92–101.
7. Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, Krystal JH, *et al.* (2017): Prefrontal connectivity and glutamate transmission: Relevance to depression pathophysiology and ketamine treatment. Biol Psychiatry Cogn Neurosci Neuroimaging 2:566–574.
8. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, *et al.* (2017): Ketamine treatment and global brain connectivity in major depression. Neuropsychopharmacology 42:1210–1219.
9. Evans JW, Szczepanik J, Brutsché N, Park LT, Nugent AC, Zarate CA (2018): Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. Biol Psychiatry 84:582–590.
10. Dinga R, Schmaal L, Penninx BWJH, van Tol MJ, Veltman DJ, van Velzen L, *et al.* (2019): Evaluating the evidence for biotypes of depression: Mehodological replication and extension of Drysdale et al. (2017). Neuroimage Clin 22:101796.