Biological Psychiatry: Celebrating 50 Years

Commentary

Mapping Causal Circuitry in Human Depression

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Depression has long been a subject of study in clinical neuroscience, frequently with the use of functional or structural brain imaging approaches. Such work, carried out by many researchers across the globe, has highlighted several brain regions whose activity or connectivity are altered in patients who are depressed compared with healthy control subjects. Despite the impact of this research, these types of studies nonetheless suffer from a central shortcoming: they are only able to describe neural features associated with depression and do not necessarily illuminate causal circuit-level mechanisms leading to depression (1,2). To understand putative causal mechanisms, in particular at the level of how particular brain regions or circuits contribute to a depressive phenotype, it is necessary to manipulate brain activity in a specific manner and then observe the consequent effects on depression. One approach for doing so, which I will return to later, is through noninvasive neuromodulation with repetitive transcranial magnetic stimulation (rTMS) (1).

Another approach that has its own decades-long history is through the study of people who developed depression after suffering a stroke. In this case, a neuroanatomical overlap is sought for depression symptom–causing brain lesions that would also need to be distinct from lesions in locations that do not result in depressive symptoms. In fact, early work on poststroke depression helped lead to the development of rTMS treatment for depression (3). Lesion symptom mapping has its own challenges in that depression resulting from a stroke may relate to other functional impairments created by the stroke; there may be a greater chance of developing depression simply because of those functional impairments. However, a bigger challenge highlighted by Padmanabhan *et al.* (4) in this issue of *Biological Psychiatry* is that lesions in many disparate regions of the brain can lead to depression. Unlike earlier studies, the authors found that there is no single region where depression-causing lesions overlap. To solve this discrepancy, the authors turned to a clever technique developed by senior author Michael D. Fox's laboratory—lesion network mapping (5).

The core hypothesis underlying lesion network mapping is that neuropsychiatric syndromes or symptoms reflect dysfunction of a large-scale distributed brain network that mediates the relevant behavior or mental processing. In other words, a lesion potentially anywhere in that circuit could cause the same symptoms (i.e., effective lesions overlap at the level of which network they affect), even if the lesion locations themselves do not overlap. The main analysis underlying this method is to examine the whole-brain normative functional connectivity of brain locations that do or do not cause poststroke depression and then contrast the two sets of connectivity maps to find the brain regions whose connectivity to depression-causing lesions differs from lesions that do not lead to depression.

What Padmanabhan *et al.* (4) found using lesion network mapping is that connectivity of depression-causing lesions overlap at a single location after a correction for multiple comparisons: the left dorsolateral prefrontal cortex (L-DLPFC). This finding is striking for several reasons. First, it helps bring together the previous expectations of a role for the DLPFC [e.g., based on neuroimaging studies (6)] and the apparent nonoverlap in depression-causing stroke locations, with the answer being that lesions associated with strokes are preferentially connected to the DLPFC. Second, the specific location that this work identified overlaps with a region targeted by a U.S. Food and Drug Administration–approved protocol for rTMS treatment of depression, which repetitively stimulates the L-DLPFC at 10 Hz. The overlap between the results of lesion network mapping and another causal, but therapeutic, intervention provides strong causal support for at least one element in a human depression circuit.

The present study also raises intriguing new questions. For example, why did only the L-DLPFC come up in the analysis? While one answer may be the relatively small sample size of lesion location data for strokes that led to depression (the study included 58 patients) and the fact that negative results are always to be interpreted with caution, it is noteworthy that many other regions considered core to depression did not show up. For example, no evidence was provided for a role for limbic regions such as the amygdala and ventral striatum, as well as cortical regions such as the subgenual anterior cingulate. One possibility is that clinical poststroke depressive syndromes overlap at only some regions implicated in non-poststroke depression, likely because of different pathophysiological mechanisms or because the symptoms that we think represent "depression" are primarily a distal phenomenological description of a more fundamental set of processes we cannot, or simply are not, measuring adequately. Another curiosity is the relatively stronger left-sided versus right-sided pattern of connectivity to the DLPFC from depression-causing stroke locations, despite there not being a hemispheric preference for the lesions locations themselves. It is likewise curious that clinically effective rTMS protocols in depression include not only L-DLPFC 10-Hz stimulation but also right DLPFC 1-Hz stimulation, yet the results for the right DLPFC were not as strong as those for L-DLPFC. Moreover, the depression-associated connectivity pattern appeared overall to resemble the frontoparietal control network. Though left-sided parietal connectivity failed to survive the correction for multiple comparisons, the overall pattern raises a question about whether any region showing lesion connectivity should be equally capable of being an effective target for rTMS treatment for depression or if there is something particularly important about the prefrontal cortex. At a conceptual level, the equipotency of different connectivity targets is implicit to lesion network mapping analysis,

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https://doi.org/10.1016/j.biopsych.2019.09.009
Biological Psychiatry November 15, 2019; 86:732–733 www.sobp.org/journal
ISSN: 0006-3223

though it remains to be shown that lesion or stimulation anywhere within a particular resting-state functional magnetic resonance imaging network has the same downstream effects on behavior or symptoms.

In sum, Padmanabhan *et al.* (4) make an important new contribution to the field by providing convergent causal evidence for elements of a circuit for human depression, and also because they help sharpen a set of testable hypotheses regarding the broader clinical syndrome of depression and the insights drawn from lesion studies.

Acknowledgments and Disclosures

AE owns equity in Mindstrong Health, Akili Interactive, and Sizung for unrelated work.

Article Information

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Received Sep 17, 2019; accepted Sep 17, 2019.

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