VIEWPOINT

Addressing the Causality Gap in Human Psychiatric Neuroscience

Amit Etkin, MD, PhD
Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California; and Veterans Affairs Palo Alto Healthcare System and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Palo Alto, California.

Overview

As clinicians, we are accustomed to stories—those that our patients tell about their lives and struggles, and those that we tell about the causes of their difficulties. As scientists, especially clinical neuroscientists, we likewise tell stories about presumed neural mechanisms of illness and its treatment. Unfortunately, the truth behind these stories remains uncertain because our science remains descriptive. Simply put, our dominant tool, neuroimaging, demonstrates correlations, ultimately revealing associations but not demonstrating by itself how a circuit perturbation causes aberrant behavior and symptoms. By confusing this evidence with substantiation of causation, we risk creating "Just-So Stories"—internally consistent explanations that have no basis in fact.[1] In the spirit of this series on pragmatic psychiatry, I outline several domains where causality at the level of brain circuitry is a critical missing link ready to be addressed. At the heart of the argument is the idea that understanding causal mechanisms, which are discoverable in a variety of ways, holds great promise not only for explaining illness, but also for furthering the efficiency and effectiveness of the pragmatic search for treatments.

The past few decades has seen an explosion of brain-imaging research in healthy humans and those experiencing a range of clinical conditions. We have witnessed waves of excitement at new findings, self-critique of core methods, and a general attempt to raise expectations in clinical neuroscience. In other words, the field is now maturing. Recent high-profile, large-scale efforts like the Human Connectome Project and UK Biobank have focused on building stronger correlations and supporting the eventual goal of using neuroimaging to inform clinically relevant biomarkers. These are clearly worthwhile efforts.

Nonetheless, it is also important to realize that some of the strongest correlations may lack any causal relationships; for example, between 2000 and 2009, the consumption of cheese per capita correlated at r greater than 0.94 with the number of people who died after becoming entangled in their bedsheets.[2] As whimsical as this example is, it reminds us that the challenge of causality cannot be addressed through mathematical tools alone (ie, in absence of direct causal investigations). Indeed, neuroimaging has become overly reliant on analytical approaches and would greatly benefit from an increased focus on direct experimental manipulations of the presumed underlying constructs (in this case, human neural circuit functioning).

The Existing Evidence

What, then, are some examples of these issues, and how might we address them? Let us start with our neural circuit models for mental illnesses. The typical neuroimaging study compares patients defined by some diagnostic category in the *DSM* with healthy individuals. Arguments are then made about how particular neural alterations might account for specific symptoms associated with the illness—a type of causal argument. However, this approach confounds illness in general with a specific illness, and typically lacks causality-revealing experimental manipulations. In fact, neuroimaging meta-analyses across psychiatric disorders have found more neural similarities than differences between disorders, despite their divergent symptoms.[3,4] As a consequence, we lack a rigorous and causal grounding of clinical symptoms and behavior in specific neural circuit alterations. This grounding is crucial, because it is necessary for accurately establishing diagnoses based in pathophysiological mechanisms; explaining whether mental experience caused circuit changes or circuit changes caused mental experience; properly defining the important dimensions of brain function that determine psychopathology, including those that can be modeled in experimental animals; and providing objective and consistent bases for the conditions that are diagnosed at present via subjective self-report. In contrast, recruiting large numbers of patients for studies that focus on biomarker identification has the potential to identify useful stratifications or prognostic markers. This builds stronger and more robust correlations but does not inform causal mechanisms.

Causal neurostimulation tools such as transcranial magnetic stimulation (TMS) allow researchers to manipulate the function of targeted regions and their connected neural networks for periods that range from milliseconds to weeks. By combining these methods with concurrent functional magnetic resonance imaging or electroencephalography, we can gain further interpretational power. For example, disruptions in the causal influence of one brain region on other brain regions can be tested by using neuroimaging while stimulating a given region and visualizing downstream effects; this method would be more conclusive than simply observing connectivity patterns between brain regions when they are at rest or engaged in a task. Via this method, we have already learned that not every region that is activated during attention-demanding tasks has a similar capacity for causally deactivating the default mode network.[5] Similarly, acutely perturbing the function of a brain system in healthy individuals, or ameliorating its dysfunction in patients, can provide powerful causal information about the contribution of that brain system to behavior, in a manner that is not possible by simply testing for relationships between individual differences in brain and behavior.

Corresponding Author: Amit Etkin, MD, PhD, Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Rd, MC: 5797, Stanford, CA 94305-5797 (amitetkin@stanford.edu).

Although concurrent TMS and neuroimaging has existed for nearly 2 decades,[6] both methods have been more commonly applied to basic research than to clinical contexts. Moreover, repetitive TMS that targets a variety of brain regions has been found to be efficacious for the treatment of a number of conditions (and cleared by the US Food and Drug Administration for the treatment of depression),[7] but it generally has not been tied to studies of neural functioning and behavior. To further pragmatic goals in psychiatry, emphasis should be placed on causal human neuroscience investigations that will facilitate bringing sophisticated neurostimulation and neuroimaging tools into clinical neuroscience. Considering also that TMS devices are already widely available in clinical care, an intense focus on causal circuit mechanisms has great potential for advancing treatment (eg, by targeting different brain regions or reading out brain activity as a guide to neurostimulation) even in the near term.

But it is not only neurostimulation that can provide insights about circuit-level causality. Most psychiatric treatments appear to be in clinical equipoise,[8] but we tell stories about how treatments work, often leading to elaborations of alternative forms of a treatment that we argue exert different effects on the brain. How different, for example, are the mechanisms of action of antidepressant medications with varying receptor-targeting profiles? How much difference exists between psychotherapies that use different techniques? As valuable as these developments might be in providing patients with additional treatment options, it is nonetheless important to acknowledge that a great deal of effort has gone into treatment development without an understanding of whether the neural mechanisms they treat are indeed different. Here randomized clinical trials allows the isolation of mechanisms by which an intervention causes changes in the brain. Greater effort should be put toward answering critical questions about the neural mechanisms of treatment through the careful design of comparative treatment studies. Greater use of mechanistic comparative trials is ethical and can advance clinical outcomes by revealing the true factors affecting who responds and why.[8]

Conclusions

While many in the field might understand these points, current research practice does not reflect this. Nonetheless, some of the most crucial causality-revealing neuroscience tools are already at hand, making these challenges more readily surmountable than we might imagine. By jointly advancing causal human neuroscience and clinical psychiatric research, we can relegate "Just-So Stories" to the realm of entertainment rather than science.

ARTICLE INFORMATION

Published Online: November 22, 2017. doi:10.1001/jamapsychiatry.2017.3610

Conflict of Interest Disclosures: Dr Etkin has served as a consultant for Takeda, Otsuka, and Acadia, has received a research grant from Brain Resource Inc, and owns equity in Akili Interactive and Mindstrong Health. No other disclosures were reported.

REFERENCES

1. Kipling R. *Just-So Stories*. London, England: Macmillan; 1902.

2. Vigen T. *Spurious Correlations*. New York, NY: Hachette Books; 2015.

3. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*. 2015;72(4):305-315.

4. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am J Psychiatry*. 2017;174(7):676-685.

5. Chen AC, Oathes DJ, Chang C, et al. Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc Natl Acad Sci U S A*. 2013;110(49):19944-19949.

6. Reithler J, Peters JC, Sack AT. Multimodal transcranial magnetic stimulation: using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. *Prog Neurobiol*. 2011;94(2):149-165.

7. McClintock SM, Reti IM, Carpenter LL, et al; National Network of Depression Centers rTMS Task Group; American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry*. 2017;pii(16cs10905):16cs10905.

8. London AJ. Equipoise in research: integrating ethics and science in human research. *JAMA*. 2017;317(5):525-526.