Using Computational Psychiatry to Rule Out the Hidden Causes of Depression

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In an ideal world, our understanding of the causes of psychiatric disorders would progress by testing mechanistic hypotheses in experimental studies, using the results of these studies to identify situations in which the hypotheses fail and then refining, or even discarding, the hypotheses in response to these failures. The reality has been somewhat less Popperian—mechanistic hypotheses in psychiatry tend to drift slowly out of fashion as attention moves to the next big thing, rather than because they have been disproved. We are rarely presented with strong negative results that challenge the currently dominant mechanistic account. Given that negative results are an essential corrective to the scientific process, why are they so rarely found in the mechanistic literature?

Some of the barriers to such work are common across scientific fields; for example, we prefer to read, and journals prefer to publish, novel positive findings, so it is more difficult to disseminate negative results. Additionally, psychiatric illness raises particular challenges that can make it difficult to design and conduct informative mechanistic studies. Causal processes in psychiatric illnesses are often complex and they are often hidden. For example, depression, and in particular anhedonia, has been suggested to develop because of an aberrant function of the dopaminergic reward–based brain system.1 However, the function of this system is complex—it does not simply report the occurrence of rewarding events, but rather the "reward prediction errors (RPEs)" that are produced when an event is more rewarding than an individual expects.2 Our expectations change over time, which means that different RPEs will be produced even with the repeated presentation of the same reward.3 The response of this system is also not directly observable (at least not in humans); rather, we need to infer its activity either from a patient’s behavior or from an indirect physiological measure, such as that collected using functional imaging. Behavior and neuroimaging measures are influenced by many factors other than RPEs, which makes it difficult to confidently attribute changes in these outcomes to the underlying RPEs. To confidently test the role of complex, hidden systems, such as the dopaminergic-based RPE system in depression, we need some way of reconciling the fact that the system adapts rapidly over time and that we can only measure it using behavior or physiology, which aggregate the influences of RPEs with many other processes.

In this issue of JAMA Psychiatry, Rutledge et al4 demonstrate how computational approaches may be helpful in overcoming these difficulties. In a series of 3 studies, including one in which 1833 participants completed an online task, the authors presented patients with moderate depression and control participants without depression with choices that led to either winning or losing points. They measured both behavioral (mood ratings) and neuroimaging (functional magnetic resonance imaging) outcomes across the studies and assessed how these outcomes were influenced by RPEs. The authors analyzed their data using generative computational models, mathematical equations that describe how RPEs are produced throughout the tasks, and how RPEs and other processes influence the behavioral and neuroimaging outcomes measured. Because these models describe how the RPEs are generated, they are able to capture the trial-by-trial variability of the RPEs during the tasks. The models also included descriptions of non-RPE processes, such as the calculation of the expected returns from a gamble, which meant that they could separate the effect of these processes from that of the RPEs on the outcomes.

These methods allowed the authors to demonstrate that the RPEs, measured using both behavioral and neuroimaging outcomes, did not vary as a function of the severity of depression an individual had experienced. These results are surprising, as previous studies have reported that, during learning, patients with depression generate different RPEs than control participants.5 The tasks used by Rutledge et al4 were specifically designed to elicit RPEs in the absence of learning, which suggests, as the authors highlight, that the underlying dopaminergic system that produces the RPEs is likely to be functioning normally and that the different responses previously described in the learning tasks probably reflect changes in the downstream effect of this system. However, the small sample sizes used in previous studies indicate that future work needs to test RPE production during and in the absence of learning within the same group of participants using a similar sample size to that used by Rutledge et al4 to be certain of this interpretation.

While computational models can be daunting to those not familiar with the mathematics on which they are based, it is often worth putting in the effort to understand them. The models provide a precise description of the hypotheses being tested in studies; thus, understanding them makes it easier to critically appraise the results. For example, in this study, the model of momentary mood described how the outcome of each trial of a gambling-type task influenced the answers of participants to the question “how happy are you at the moment?” It included terms describing how RPEs influenced this response, as well as terms that coded for the average response of the participant, the effect of choosing a certain outcome rather than a gamble, and a term that coded...
for the expected return of the gamble. This transparent description of what has been considered by the authors makes it easy to see what has not been considered; for example, one could imagine that patients with depression do not feel that they deserve to win and that this negative self-appraisal skews the happiness that they experience when winning a large number of points, but as this process was not described formally in the model, it is not tested.

More generally, the model highlighted the artificial situation created by a task in which participants are repeatedly asked how happy they feel during a game in which they win or lose points. This setup makes it likely that the ratings will be influenced by so-called demand effects (participants will believe that they are expected to report more happiness after a win), which limits the extent to which the ratings can be considered pure markers of momentary mood. Similarly, there is an array of negative, often self-referential, subjective experiences that are associated with depression, many of which may invoke RPEs, that will not be captured by such gambling tasks. While the authors have demonstrated that RPEs produced by a gambling task are intact in depression, the possibility remains that RPEs induced in other contexts may not be.

These limitations notwithstanding, the current results may prove useful in the clinical setting; the finding that the underlying RPE system is largely intact suggests that symptom improvement can be achieved by adjusting how RPEs are used in everyday life rather than by requiring a fundamental alteration in their production. Conceivably, this adjustment may constitute a useful goal for patients during psychological therapy.

In summary, by using generative models of the production and effects of RPEs, Rutledge et al. have been able to precisely delineate the function of the complex, hidden system that produces them and provide compelling evidence that this system is not universally disordered in all decision-making contexts in patients with depression. It may be that dysfunction is present among patients with more severe depression or when RPEs are induced using more ecologically relevant tasks, but future hypotheses of the role of RPEs in depression will need to explain the clear absence of dysfunction that was demonstrated in this important negative study.

ARTICLE INFORMATION


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REFERENCES


