VIEWPOINT

Pragmatism Instead of Mechanism
A Call for Impactful Biological Psychiatry

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Viewpoint

The opportunity for neuroscience-based approaches to impact clinical psychiatry has never been greater, yet biological measures have had almost no impact on psychiatric practice.

One would like to be able to say, "Mrs Jones, your depression test has come back and, with the current treatment, you have a 90% chance of being symptom free within the next 6 weeks." However, this statement is still science fiction. It is not for a lack of trying; brilliant minds have used technology with increasingly large study populations, yet practical results that change how we treat patients have been sorely lacking. Hopes for a neuroscience-based understanding of mental illness to bring better cures have been raised; however, there is no biological diagnostic or prognostic test in psychiatry and most interventions, behavioral or pharmacological, have been discovered serendipitously.

Why are we not further along? Making neuroscience useful for clinical psychiatry is an extremely difficult problem. Given the complexity of the human brain, both in terms of its array of topographically organized units, which are highly interconnected, the complex orchestration of molecular events that accompany even simple psychological processes, and the multilevel organization that occurs from a molecular to a circuit level, this argument is hard to dispute. However, one would expect that predictable relationships would have emerged by now between different levels of brain functioning and practical clinical problems. So why haven't they? Perhaps the focus on a misguided search for neural "mechanisms" of mental illnesses has hindered progress. Implicit in this approach is that a mechanistic understanding will provide better diagnosis or treatment. My argument is that focusing on mechanisms encourages a searchlight bias[1] (ie, a focus on explanation of complex clinical phenomena based on simple causal relations, instead of advancing clinical use). Here, I propose that—instead of succumbing to scientific nihilism that might emerge from a continued search for mechanisms—we need a pragmatic focus on prediction, which provides an alternative with clearly identifiable metrics to test strong hypotheses about clinically relevant issues in psychiatry.

As noted by Weiskopf,[2] "We are in the midst of a mania for mechanisms." The term *mechanism* is often used loosely and is rarely defined, even when it figures prominently into the conceptualization of research findings. *Mechanistic explanation* is the process of relating functions, behaviors, or activities of a system as a whole to some of its components, their properties, functions, behaviors, or activities and is tightly linked to causal relationships.[3] *Causation*, in turn, can be defined as an antecedent event, condition, or characteristic that was necessary for the occurrence of a disease or a clinical phenomenon at the moment it occurred, given that other conditions are fixed.[3]

As cited in the article by Rothman and Greenland,[3] the Hill criteria distinguish causation from association based on strength, consistency, specificity, temporality, biological gradient (ie, a dose-response curve), plausibility, coherence (ie, consistency with the natural history and biology of the disease), experimental evidence, and analogy (ie, similarities across diseases). However, Rothman and Greenland[3] argued that causal relationships insufficiently characterize the association between the system and its components and, thus, cannot be used to establish the validity of an inference. Finally, Kendler[4] emphasized "to develop an etiologically based nosology for psychiatric disorders is deeply problematic. Psychiatric disorders are a result of multiple etiological processes impacting on many different levels and often further intertwined by meditational and moderational interactions between levels." Taken together, the use of mechanisms as explanations of the whole and its parts based on causation to better understand psychiatric disorders is an ill-defined venture and has failed to solve practical problems in psychiatry.

The reverse inference problem is one example of misguided mechanistic explanations, which is often observed for neuroimaging findings,[5] For example, individuals with anxiety disorder exhibit an increased activation of the amygdala to facial stimuli, while others have found that the amygdala strongly activates to erotic pictures; therefore, anxious individuals might be hypersexual. Subsequently, particularly if investigators chase a popular candidate process, other researchers will emphasize and focus on this process as a possible explanation for their imaging findings. This combination of inverse inference and searchlight bias[1] exemplifies how the urge for mechanistic explanations overshadows considerations of practical use.

Risk-prediction models provide a complementary framework, which does not depend on formulating mechanisms but uses predictors (covariates) to estimate the absolute probability or risk that a certain outcome is present (diagnostic) or will occur within a specific period (prognostic) in an individual with a particular predictor profile.[6] These models naturally fit into a Bayesian framework, which quantifies knowledge before and after an observation in terms of conditional probabilities. Most importantly, these models provide a quantitative risk assessment for an individual patient and therefore can have an immediate impact for clinical practice (**Table**). In other words, the mental health care professional will have numbers at his or her fingertips when a patient asks, "How likely is it that I will get better?" For

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Table. Parameters of Risk-Prediction Models

Parameter	Explanation
Accuracy	The risk classification within each risk group can be compared with observed events, and true-positive rate (sensitivity) or false-positive rate (1-specificity) can be ascertained for a particular cutoff value.
Calibration	The extent to which observed and predicted event rates agree across the risk spectrum from low- to high-risk categories.
Reclassification	Quantifies the directional movement when reclassifying individuals across patients with events (cases) and patients without events (noncases) who move up or down a risk category.
Dispersion	The variance in predicted outcomes.
Discrimination	How well the model discriminates between individuals who go on to show the outcome of interest (cases) and those who do not (noncases).
Separability	The degree to which outcomes are different.
Precision	The confidence intervals of the model.
Regret	The cost associated with making the wrong prediction.
Utility	The fraction of the expected use of perfect prediction achieved at the optimal cutpoint for a risk-prediction model.

example, the MyLungRisk online calculator (https://secure2.utlnet.co.uk/mylungrisk/welcome.aspx) uses the Liverpool Lung Project risk-prediction model to calculate the chance that an individual will develop lung cancer within 5 years. Therefore, a risk-prediction framework provides an empirical approach using biological measures to aid the solution of clinical problems including the effect of interventions, high-risk behaviors, and individual differences that are useful for health care professionals and patients.

Mechanisms in neuroscience-based psychiatric research are elusive and sometimes metaphorical approaches to communicate some insight into processes we deem important for mental illness and function as placeholders for true understanding. On the other hand, predictors, once appropriately derived and replicated, can be used immediately and are practical or pragmatic. Is it possible that too much research effort and funding are currently being spent on searching for mechanisms rather than searching for predictors? Currently, there is a predominance of using neuroscience-based measures as corollaries of ongoing studies in search for mechanisms. Future studies should use prospective randomized clinical trial designs for neuroscience-based measures as an information source to predict or affect outcomes. Rigorous testing within a risk-prediction framework and subsequent distribution of these results as practical risk calculators will go a long way toward impacting psychiatric practice. Thus, I propose that we shift from a search for elusive mechanisms to implementing studies that focus on predictions to help patients now.

ARTICLE INFORMATION

Published Online: May 20, 2015. doi:10.1001/jamapsychiatry.2015.0497.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Paulus receives funding from the National Institutes of Health.

Role of the Funder/Sponsor: The National Institutes of Health had no role in the preparation, review, or approval of the manuscript, and the decision to submit the manuscript for publication.

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