VIEWPOINT

Psychopharmacology and Explanatory Pluralism

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In recent decades, there has been increasing appreciation that understanding psychopathology requires explanations referring to mechanisms and processes residing at multiple levels of organization, such that higher-level explanations cannot be reduced to lower-level explanations.[1] This appreciation is also underway in the area of psychopharmacology, where there has historically been a tendency to explain mechanisms of actions of psychotropics predominantly in terms of receptor actions and neurotransmitter changes. Psychopharmacological research has already begun to remedy that by incorporating the potential explanatory role of higher-level mechanisms and processes and investigating how psychotropics produce a cascade of effects that links neurotransmitters to neural networks to complex behaviors. A pluralistic approach to psychopharmacology makes these developments explicit and recognizes that a restricted focus on interactions between psychotropic effects and disorder mechanisms at a molecular level ignores vital questions. This Viewpoint reaffirms pluralistic developments in psychopharmacology that embrace interactions at multiple levels via multiple pathways with top-down and bottom-up causal influences. Three key points are as follows.

First, a pluralistic framework is necessary to incorporate higher levels of explanation in clinical psychopharmacology. Take the example of antipsychotic medications. While considerable work on antipsychotic agents has focused on their dopaminergic and serotonergic effects, hypotheses have been proposed about how these medications may produce antipsychotic effects by attenuating aberrant novelty and assignment of salience to objects and associations,[2] or in computational terms, how antipsychotics may block aberrant prediction error signals, allowing for extinction learning and recovery from delusions.[3] Considering these hypotheses does not merely add connecting details to mechanisms of interactions, but generates different models of action. If dopaminergic actions are the key to understanding antipsychotic effects, this points us toward the dopaminergic hypothesis in which antipsychotics block excessive or aberrant dopaminergic signaling underlying psychosis. On the other hand, if attenuation of salience is seen as the central mechanism, this points toward a hypothesis in which psychotic states are characterized by aberrant or excessive assignment of salience, which is counteracted by a dampening effect on salience by antipsychotics. We may even talk about a class of "anti-salience" psychotropics with attenuation of salience as the shared mechanism, which may be used clinically in conditions characterized by excessive or aberrant salience. Of note, the dopaminergic hypothesis and the salience hypothesis are not necessarily mutually contradictory; they refer to phenomena at different levels of organization[2] and offer different explanatory power and suggest different research agendas, allowing for the possibility of "patchy reduction" and "piecemeal integration" between the 2 explanations.[1]

The existence of interactions at higher levels is exemplified strikingly but also more controversially in the case of psychedelics, for which it has been suggested that the phenomenological content of the psychedelic experience, and resulting alterations such as in perceptions of the self, may be vital in explaining their putative therapeutic effects.[4] Another leading hypothesis about the mechanism of therapeutic action of psychedelics suggests that psychedelics exert effects by relaxing or loosening the "the precision weighting of pathologically overweighted priors."[5] To the extent that the phenomenological content of the psychedelic experience or higher-order interactions such as relaxation of priors are essential for the therapeutic effect, any adequate explanation of the mechanism of action will have to extend beyond molecular mechanisms to involve higher levels of explanation. It is apparent that the most comprehensive scientific hypotheses about how psychotropic agents exert therapeutic effects, despite the presently speculative nature of many of these hypotheses, invoke explanatory pluralism.

Second, a pluralistic framework highlights vital aspects of clinical psychopharmacology that are likely to be overlooked by a framework more restrictive in scope. The more distal the outcomes of interest are from the immediate receptor actions of the psychotropic, the more likely it becomes that different pathways may be at play in different individuals. The sedative effects of benzodiazepines, for instance, can be understood as direct effects of γ-aminobutyric acid (GABA) receptor actions, but if we look at the association between benzodiazepines and mortality rates in older patients, a very distal outcome, there is no singular explanation to be found (eg, mortality may be associated with increased falls, respiratory depression, increased risk of pneumonia). The same logic applies to therapeutic effects. Selective serotonin reuptake inhibitors may exert beneficial effects by enhancing neuroplasticity for one person,[6] but for another, the beneficial effect may arise from a blunting effect on painful emotions.[7] Symptom rating scales in clinical trials (as operational measures of syndromic states) allow for a variety of possible pathways through which score reduction may occur. For instance, changes in Hamilton Depression Rating Scale total score can reflect changes in different combinations of symptoms (such as sleep, anxiety, or anhedonia), representing different potential pathways. Therefore, when we ask how medications work, and when by "work" we refer to changes in total scores on rating scales as outcomes, there may be no singular answer, only a set of processes by which relevant changes in outcomes may be obtained.

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Third, complex multilevel explanations involving a range of mediating processes, including the potential influence of higher-level processes, are needed to explain a variety of phenomena in psychopharmacology, such as placebo and nocebo effects, how the concurrent use of different classes of psychotropic drugs may influence (positively or negatively) psychotherapy outcomes, and the sequential effect of psychotropics on different symptoms (eg, decrease in insomnia may increase self-efficacy and so lead to improved mood). Elwadhi and Cohen,[8] for instance, have reported that social inequality may moderate antidepressant treatment outcomes even when controlling for access to treatment and quality of care. Relevant here are also molecular-social interactions, with translational research suggesting, for example, that antidepressants act on serotonergic pathways involved in social hierarchy.[9]

The National Institute of Mental Health (NIMH) has adopted an "experimental therapeutics approach" to clinical trials,[10] which requires evidence that an intervention is engaging with a hypothesized target before demonstration of clinical efficacy. Consistent with explanatory pluralism, NIMH allows for targets to be conceptualized at multiple levels, such that appropriate targets are to be determined by the conceptual framework undergirding hypotheses about potential mechanism of action. The focus of target engagement in psychopharmacology so far has been on lower-level mechanisms, such as receptor actions, synaptogenesis, and brain circuits, but a pluralistic approach raises the possibility that cognitive and phenomenological processes can also be valid psychopharmacological engagement targets and may be more explanatorily powerful. We recommend that target engagement in future clinical trials be designed to consider and evaluate hypothesized mechanisms at multiple levels of explanation.

In conclusion, we note that psychopharmacology's traditional focus on receptor action has been immensely useful for the field; establishing how different medications act on specific neurotransmitter systems in specific brain regions has laid its foundations. However, we now know that any particular neurotransmitter system may be involved in a range of disorders, that any specific medication may act on a wide range of neurobiological systems and psychological processes, and that the effect of medications and of molecular alterations may be mediated by a range of variables, such as psychological expectancy and socioeconomic status. For future progress in our understanding of psychopharmacological mechanisms as well as in translational neuroscience and drug discovery, we therefore need to further develop research frameworks that productively integrate constructs and examine pharmacological interactions at multiple levels of explanation.

ARTICLE INFORMATION

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