Commentary

Biological Psychiatry: GOS

Computational Psychiatry and the Placebo Effect in Psychosis

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Placebo effects in psychiatry are robust and are growing over time. Placebo researchers differentiate between placebo responses, which are any beneficial outcomes in response to inert treatments (including natural history and regression to the mean), and placebo effects, which depend on expectations, learning, and psychological factors attributable to the psychosocial context surrounding treatment (1). While clinical trials recognize and control for placebo responses by comparing active and inert treatments, isolating placebo effects on clinical outcomes requires a no-history control group (e.g., a waiting list control group). Meta-analyses of clinical outcomes indicate that placebo effects are largest in pain and subjective outcomes (2), which are central in most psychiatric conditions. As placebo effects on subjective outcomes are challenging to differentiate from response bias, a great deal of research has focused on isolating the neurobiological mechanisms of the placebo effect to determine whether placebo effects reflect response bias or true changes in disease-relevant biological processes. Most studies of placebo mechanisms have focused on placebo analgesia (i.e., reductions in pain), as well as a few studies of depression and anxiety [for review, see (3)]. However, few have considered the role of placebo effects in psychosis.

In the current issue of *Biological Psychiatry: Global Open Science*, Hird *et al.* (4) present a call to action for researchers to consider and study the placebo effect in psychosis. They review meta-analyses of randomized controlled trials for antipsychotic medications that indicate significant placebo responses on symptoms and rating scales and suggest that placebo responses increase over time. Notably, none of the studies include a natural history control group, and thus we cannot distinguish between placebo responses and placebo effects. To determine whether these benefits reflect placebo effects per se rather than nonspecific effects, such as regression to the mean, future clinical trials of antipsychotics should include waiting list control groups or other natural history comparison groups when possible. In addition, the reviewed studies all focus on clinical trials of antipsychotic medicines in individuals with schizophrenia. Yet psychosis is a transdiagnostic symptom that can occur not only with schizophrenia but is also associated with other mental health conditions (e.g., bipolar disorder), medical conditions (e.g., malaria), and in response to substances (e.g., ketamine). Is the symptom of psychosis shared across these manifestations and equally sensitive to placebo? Or might placebo effects impact disease-specific symptoms, such as negative symptoms in schizophrenia or mood disturbances in bipolar disorder, rather than impacting psychosis per se? Are placebo effects on antipsychotics related to placebo effects on other medication classes, or is psychosis unique? There is clearly a need for better understanding of the placebo effect in these trials.

Fortunately, a great deal of mechanistic work has been done to identify the psychological and neurobiological bases of the placebo effect outside of clinical trials, and this is where the fields of computational psychiatry and placebo research can make true strides. Hird *et al.* (4) highlight the critical overlap between placebo effects and predictive coding, a computational account for how the brain updates beliefs about the world, which is one of the cornerstones of computational psychiatry (5). In both placebo effects and predictive coding, perception is biased toward expectations. Recent studies demonstrate that placebo analgesia can be explained through Bayesian inference (6), consistent with predictive coding. Likewise, predictive coding can also account for hallucinations (7) and the impact of predictions on visual perception has been linked to positive symptoms in schizophrenia (8). Thus, Hird *et al.* (4) argue that predictive coding might account for placebo effects in psychosis and encourage researchers to pursue studies that investigate the role of verbal instructions, prior learning, and uncertainty in individuals who are prone to psychosis. It will also be critical for future studies to determine whether predictive coding impacts psychosis in ways that differ from how predictive coding is implicated in placebo analgesia and placebo effects on other clinical outcomes.

Computational psychiatry can leverage these approaches to provide further insights on which specific features of perception are sensitive to placebo and moderated by psychiatric state or diagnosis. Further, aspects of the placebo effect, such as verbal instruction and associative learning, can be dissociated using mathematical models [see (9) for review], and tested computationally in relation to clinical measures (10). Several important questions remain as computational psychiatrists consider placebo effects in psychosis and other conditions. If individuals who are prone to delusion are more sensitive to beliefs and verbal instructions in general, then different perceptual outcomes (auditory hallucinations, somatosensory processes, pain, visual stimuli) may be equally sensitive to placebo or predictive processing regardless of the specific perceptual domain. Alternatively, auditory hallucinations may be particularly sensitive, which could point to basic mechanisms to be elucidated and targeted for intervention. Is heightened sensitivity to predictions a stable trait that is present across individuals who are prone to delusion, or is it a transient state that is present during psychosis but not between episodes? As the goal of computational psychiatry is to use transdiagnostic approaches and mathematical modeling to determine whether core features of clinical conditions are

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altered as a function of symptomatology or disease risk, the placebo effect is an ideal model that can capture how predictive coding directly influences clinical outcomes.

In conclusion, Hird *et al.* (4) provide a foundation from which neuroscientists, clinicians, and behavioral scientists can identify and pursue important questions that have the potential to improve mental health. Although only a few empirical studies have considered placebo effects in psychosis thus far, the area is ripe for investigation. As placebo effects inherently capture improvements in health outcomes, if we can identify the mechanisms of placebo and how placebo effects manifest in different patient groups, we can ultimately combine placebos with active treatments to improve patient outcomes. Thus, placebo effects are not a nuisance to be controlled in clinical trials, but instead an opportunity to improve mental health and wellbeing.

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