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Neuroimaging Placebo Effects: New Tools Generate New Questions

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Placebos were historically defined as inert substances (e.g., sugar or bread pills) that cause symptom improvement but are now characterized more broadly to include contextual aspects of both active and inactive treatments that contribute to symptom improvement in therapeutic settings. These contexts may be associated with the environment, including the size and color of a pill, a doctor's demeanor, or the invasiveness and cost of a treatment. The context may also be generated by the patient's prior experience or expectations about the efficacy of a treatment. Placebo *effects* are cognitive, behavioral, or biological responses to these contextual aspects of treatment.

Although placebo effects may be a nuisance for clinical trials, they remain an important tool for clinicians and often prove beneficial for patients. Despite their efficacy, the scientific community has tended to regard placebo effects as noise rather than a potential topic of research. However, a major paradigm shift has generated renewed interest in investigating neurocognitive and neurochemical mechanisms that drive placebo effects. The timing of this renewed interest overlaps with increasing access to neuroimaging tools, allowing for investigation of these underlying mechanisms that cannot be readily assessed via self-report or observation alone.

Neuroimaging as a tool to identify mechanisms driving placebo effects

Like all mammals, humans are well equipped with endogenous mechanisms designed to maintain homeostasis in the face of a perturbation. When these systems are engaged, the body uses its own resources to promote healing and relief from distress. Placebos have the capacity to activate these endogenous mechanisms, but how do they do so?

Most studies investigating placebo effects have focused on measuring extent of symptom improvement following administration of an inert placebo. Although these studies inform our understanding of the magnitude, frequency, and pervasiveness of placebo effects, they have done relatively little to clarify the underlying mechanisms of these effects. Using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), investigators can gain insight into the neurobiological mechanisms driving placebo effects by relating this neurobiological activity to symptom improvement. By applying knowledge

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CONFLICT OF INTEREST

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gained from research in cognitive and social neuroscience, one can infer potential mechanisms that promote or inhibit these effects.

Regional activity in brain related to placebo effects

Studies relating brain function to placebo effects have been conducted across a number of outcome modalities, including affective response to emotionally evocative stimuli, social anxiety, intoxication, symptoms of irritable bowel syndrome, and analgesia. In these studies, regional brain function is indexed by change in cerebral blood flow, measured by fMRI or PET with [^{15}O]water, or change in glucose metabolism, measured by PET with [^{18}F]fluorodeoxyglucose. Studies typically involve delivering the same physically or psychologically aversive stimulus, with and without administering a placebo purported to alleviate the symptoms produced by the noxious stimulus, while the subject undergoes scanning with fMRI or PET. Change in brain activity is related to change in self-reported discomfort across the two stimuli to determine the functional correlates of placebo effects.

Change in regional brain function associated with placebo effects can be interpreted in at least two ways. Observed change may be simply an index of experiential changes associated with the experimental modality being tested. For instance, when a noxious physical stimulus is delivered with and without a placebo analgesic, those who experience placebo-induced analgesia demonstrate reduced activity in brain regions known to process pain, including the thalamus, dorsal anterior cingulate, and anterior insula. Likewise, a participant who views emotionally evocative images when treated with a placebo anxiolytic shows reduced activity in the amygdala and other brain regions associated with processing affective responses. As such, change in activity varies in the expected direction based on the specific modality being tested.

An alternative interpretation may be that change in regional brain function represents mechanisms responsible for driving experiential change, regardless of experimental modality. This activity may be associated with both self-report and behavior-based measures of placebo effects, as well as cerebral functional indexes of specific placebo effects described above. Because the mechanisms driving placebo effects probably reflect endogenous systems that restore homeostasis more generally, changes in activity should be similar across experimental modalities. In fact, activity in a number of brain regions, including inferior frontal gyrus, striatum, and rostral anterior cingulate cortex, have been positively associated with placebo effects across several outcome modalities. Activity in these brain regions is commonly linked with inhibitory control, motivation, and reward-based cognition, suggesting that placebo effects result in part from the ability to recruit these general cognitive mechanisms and direct them toward the specific outcome at hand. Additional systems that support memory of prior experience in the clinical milieu and cognitive reappraisal of noxious stimuli may also contribute to the magnitude of placebo effects. Given that cerebral response can be related to placebo effects in different ways, it is important to consider whether this activity is simply an index of experiential change, which may vary across outcome modalities, or whether it represents underlying neurocognitive mechanisms driving that change, regardless of the outcome modality.

Neurochemical response related to placebo effects

Studies that relate placebo effects to brain chemistry have also been carried out in various outcome modalities. Such studies use PET with radioligands designed to bind with D2-like dopamine receptors in the striatum ([^{11}C]raclopride) and μ -opioid receptors throughout the brain ([^{11}C]carfentanyl).

There are two primary methods for assessing the relationship between brain chemistry and placebo effects. The first method is similar to those used to study the relationship between placebo effects and cerebral functional response. For example, individuals receive the same aversive stimulus twice—with and without a placebo purported to alleviate symptoms produced by the noxious stimulus—while undergoing PET scanning with a radioligand. This method has been used to relate placebo analgesia with change in binding at μ -opioid receptors and at D2-like dopamine receptors in the brain. As with studies that relate changes in cerebral functional response to self-report or behavior-based placebo effects, these data should be interpreted carefully so that neurochemical indexes specific to pain relief are not mistaken for mechanisms driving placebo effects more generally.

The second method also involves scanning an individual twice, once before and once after administration of placebo. These studies have assessed change in binding at D2-like dopamine receptors in the striatum. Participants have been patients with Parkinson's disease who were previously treated with levodopa and received placebo levodopa before PET scanning and habitual coffee drinkers who received placebo caffeine. In each of these studies, participants showed a neurochemical response similar to the response one would expect from the active analog of the placebo. However, because each was conducted with individuals who had extensive prior exposure to the pharmacologically active form of the placebo being administered, it is difficult to determine whether neurochemical changes observed following administration of a placebo truly revealed mechanisms driving placebo effects or whether they were a conditioned response to a specific, pharmacologically active analog of the placebo.

Future directions

Although neuroimaging promises to help elucidate neurocognitive and neurochemical mechanisms that activate endogenous healing mechanisms when placebo effects occur, results must be interpreted with caution. Methodological factors in existing studies complicate the interpretation of findings and often suggest more questions than answers. For instance, are regional brain activity and neurochemical changes associated with placebo effects a consequence of experiential changes in the outcome modality of interest, or do they indicate more general mechanisms driving placebo effects, regardless of the specific modality? If individuals have extensive prior exposure to the specific pharmacologically active analog of a placebo, are the neurochemical changes associated with placebo effects a conditioned response particular to a specific placebo, or do those changes provide important information about placebo effects more generally? Further studies are needed to answer these questions.

Additionally, technological constraints have prevented more complete investigations of the relationship between placebo effects and neurochemical systems. Functional neuroimaging studies investigating the neural mechanisms of placebo effects repeatedly indicate a close relationship to activity in extrastriatal regions, including inferior frontal gyrus and rostral anterior cingulate cortex, both of which contain D2-like dopamine receptors and receive direct dopaminergic projections from the midbrain. Yet availability of radiotracers with the capacity to image D2-like dopamine receptors beyond the striatum has been limited. As such, the relationship between dopamine in each of these extrastriatal regions and placebo response remains untested. This problem is being obviated by the development of new radiopharmaceuticals, such as [^{18}F]fallypride and [^{11}C]FLB 457.

Most neuroimaging studies of placebo effects have been limited to healthy individuals receiving experimentally induced noxious stimuli. Because of this limitation, it is unclear whether findings will generalize to clinical settings. Furthermore, patient populations may

be challenging to study given the likelihood of extensive treatment histories with interventions of varying levels of efficacy. Alternatively, healthy individuals undergoing routine, yet uncomfortable procedures (e.g., colonoscopy or dental surgery) could be targeted. Such studies would remain clinically relevant but may introduce less variance due to prior clinical experience.

Placebos do not always produce positive, ameliorative placebo effects. In fact, patients who receive placebos in the context of a clinical trial frequently report negative side effects (e.g., nausea, headache) or worsening primary symptoms. These negative, or “nocebo,” effects have received relatively little empirical attention, so it is unclear whether systems driving positive, placebo effects also underlie negative, nocebo effects. Further neuroimaging studies can help clarify these mechanisms.

Although the first neuroimaging studies of placebo effects were conducted less than a decade ago, we have already learned a great deal about the neural mechanisms of placebo effects. Because many methodological and technological challenges remain to be addressed, understanding and identifying these challenges are important first steps toward resolving them in the future.