Analysis offers new insights on the placebo effect and how to harness its therapeutic potential

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A network of brain regions activated by the placebo effect overlaps with several regions targeted by brain-stimulation therapy for depression,

according to a new analysis by a team that included several researchers from Massachusetts General Hospital (MGH), who collaborated with colleagues at Sunnybrook Health Sciences Centre at the University of Toronto. The findings of this study, published in *Molecular Psychiatry,* will aid in understanding the neurobiology of placebo effects and could influence how the results of clinical trials of brain stimulation are interpreted. This work may also offer insights on how to harness placebo effects for the treatment of a variety of conditions.

The placebo effect occurs when a patient's symptoms improve because he or she expects a therapy to help (due to a variety of factors), but not from the specific effects of the treatment itself. Recent research indicates that there is a neurological basis for the placebo effect, with imaging studies identifying a pattern of changes that happen in certain brain regions when a person experiences this phenomenon.

The use of brain-stimulation techniques for patients with depression that doesn't respond adequately to medication or psychotherapy has gained wider use in recent years. Transcranial magnetic stimulation (TMS) is a non-invasive treatment in which a clinician applies a coil to the patient's head and delivers electromagnetic pulses to the brain. The effect of TMS on brain activity has been established over the last three decades in animal and human research studies, with several TMS devices approved by the Food and Drug Administration for treating depression. What's more, there's growing research on the use of deep brain stimulation (DBS, which requires an implanted device) for hard-to-treat depression, too.

The senior author of the *Molecular Psychiatry* paper, Emiliano Santarnecchi, Ph.D., director of the Precision Neuroscience & Neuromodulation Program at the Gordon Center for Medical Imaging at MGH, saw studies of brain stimulation as a unique opportunity to learn more about the neurobiology of the placebo effect. Santarnecchi and his

co-investigators conducted a meta-analysis and review of neuroimaging studies involving healthy subjects and patients to create a "map" of brain regions activated by the placebo effect. They also analyzed studies of people treated with TMS and DBS for depression to identify brain regions targeted by the therapies. The team found that several sites in the brain that are activated by the placebo effect overlap with brain regions targeted by TMS and DBS.

Santarnecchi and his colleagues believe that this overlap has critical importance in interpreting the results of research on brain stimulation for conditions such as depression. In clinical trials, a significant portion of depression patients receiving brain stimulation improve—but so do many patients receiving placebo (sham) treatment, in which no stimulation is administered, which has led to confusion over the therapy's benefits. A possible explanation is "that there is a significant placebo effect when you do any form of brain stimulation intervention," says Santarnecchi. Unlike taking a pill, receiving TMS involves treatment in a surgery-like setting, with imaging monitors and a clinician applying a coil to the patient's head. There are loud clicks with each pulse delivered. "So the patient thinks, 'Wow, they are really activating my brain', so you get a lot of expectation," says Santarnecchi.

Elevated placebo effects associated with brain stimulation may create problems when studying the intervention, says the first author of the paper, cognitive neurologist Matthew Burke, MD, of Sunnybrook Health Sciences Centre, in Toronto. If brain stimulation and the placebo effect overlap in activating the same brain regions, then those circuits could be maximally activated by placebo effects, which could make it difficult to show any additional benefit from TMS or DBS, says Burke. If that's true, this paper may help explain why clinical trials of neurostimulation for depression and other conditions have had such variable results. Separating the placebo component of brain stimulation interventions from their direct impact on brain activity will help in designing studies

where the real potential of techniques such as TMS will be more easily quantified, thus improving the effect of treatment protocols.

The findings from this study also suggest broad applications for the placebo effect, says Santarnecchi. "We think this is an important starting point for understanding the placebo effect in general, and learning how to modulate and harness it, including using it as a potential therapeutic tool by intentionally activating brain regions of the placebo network to elicit positive effects on symptoms," he says. Santarnecchi and his colleagues are currently designing trials that they hope will "disentangle" the effects of brain stimulation from placebo effects and offer insights about how they can be leveraged in clinical settings.

More information: Matthew J. Burke et al, Placebo effects and neuromodulation for depression: a meta-analysis and evaluation of shared mechanisms, *Molecular Psychiatry* (2021). DOI: 10.1038/s41380-021-01397-3

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