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## It's all in your head: reinforcing the placebo response with tDCS

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The mechanisms of action of tDCS for behavioral modification are not yet fully understood. However, one common observation is that its behavioral effects are most pronounced and long-lasting when tDCS is paired with endogenous, training-induced brain activity (1). In humans, training produces modality-specific neural network activation and activity-dependent learning. A commonly-held notion is that tDCS encourages plasticity by exogenous priming and reinforcement of neural networks that are actively engaged in learning, although the neurophysiological mechanisms may eventually prove to be more complex (2). Given that electrical fields induced by conventional tDCS montages are likely widespread and heterogeneous, specificity of tDCS action is thought to result from concurrent activity in neural networks, i.e. through “functional targeting” rather than only anatomic localization (3).

We were thus curious about the source of functional specificity for tDCS in several recent double-blind, sham-controlled depression studies, in which concurrent training (e.g., cognitive behavioral therapy or interpersonal psychotherapy) is not given (4, 5). The beneficial effects of tDCS in depression have been attributed to its transient activation of a pathologically hypoactive left dorsolateral prefrontal cortex (DLPFC), attenuation of a hyperactive right DLPFC, and/or restoration of the interhemispheric balance between the two (4). Even if aberrant network excitability is temporarily adjusted by tDCS, given that

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paired cognitive therapy is absent and that conventional tDCS montages produce diffuse current flow, how is the specificity of these behavioral outcomes achieved?

We note that in these studies, depression scores in all sham-stimulated groups improved in the first few weeks relative to baseline. This change was even more pronounced when sham stimulation was combined with a placebo pill (5). These improvements from baseline could reflect regression toward the mean, response bias, spontaneous disease remission, or—importantly—a placebo response.

In depression, the placebo response is a psychobiological phenomenon increasingly understood to be underpinned by various learning processes, both conscious and unconscious (6). Undergoing a therapeutic ritual (e.g., receiving overt administration of a treatment in a clinical environment, experiencing a compassionate clinician-patient relationship) creates the conscious expectation of therapeutic benefit, which may guide motivation, affective responses, and learning. In non-naïve patients, prior therapeutic exposures result in conditioned learning, where an inert clinical feature (e.g., pill color, medical equipment) is associated with an eventual behavioral improvement; these conditioned associations are carried forward into new clinical contexts. In pharmacological depression studies, these processes create a significant placebo response, resulting in short-term symptomatic improvements that can match those of the drug being studied (7, 8).

Using Positron Emission Tomography imaging, Mayberg and colleagues proposed the functional neuroanatomy of the placebo response in depression (9). In this small double-blind study, depressed patients were given fluoxetine or a placebo pill, and regional brain metabolism and clinical improvement were assayed at 1 and 6 weeks after therapy. Clinical responders—regardless of having received active or placebo medication—shared metabolic activation in lateral PFC, posterior cingulate, and insula, and decreases in subgenual anterior cingulate cortex. As this pattern was not seen in non-responders, preceded the clinical effect in responders, and dissipated by the time there was a clinical effect, it was inferred that this activation pattern reflected the expectation of therapeutic benefit (9).

The potential for active placebo responses suggest an alternative explanation for effects of tDCS on depression: tDCS reinforces brain networks activated by the expectation of therapeutic benefit. In other words, tDCS fortifies the placebo response to which it may, in part, contribute (10). When given with other sources of expected benefit, such as a placebo pill in a clinical context, tDCS may reinforce additional but distinct neural substrates (6). Indeed, our modeling of the conventional cephalic tDCS montages used in depression trials suggests current flow across frontal cortices and deeper structures such as the cingulate and insula (11, 12).

An interesting question recently put forth is whether the placebo response could be exploited for clinical benefit (13). In its current practice, the safety profile of tDCS is very good. Combined with active medication, tDCS could reduce drug dosage and thus unwanted side effects. For example, in the recent SELECT trial, patients were given a daily sertraline or placebo pill, plus repeated sessions of real or sham bi-prefrontal tDCS (5). At 6 weeks, the combination of real tDCS and sertraline resulted in the most pronounced reduction in

depression, but there was no significant interaction between tDCS and active drug. This finding suggests that the additive benefit arises from independent mechanisms of action (5). One could thus envision a complementary approach in depression that optimizes response to drugs on two levels: first, using medication to modulate the limbic system or other relevant networks, and second, using tDCS to reinforce placebo network activity arising from the expectation of medication benefit and associated affective learning. In future sham-controlled depression trials, the addition of a no-stimulation arm may also help disambiguate the degree to which brain stimulation alone may contribute to the expectation of benefit (14).

Finally, the placebo response is not a single psychobiological entity, but is mediated by separate neural substrates in different diseases (6). In pain studies, where tDCS given alone has produced only minor and transient effects (15), one may thus consider the value of heightening patient expectations, such as with a placebo pill. Analgesia induced by placebo medications is associated with activity in the insula, cingulate, and thalamus (16), which are regions believed to be polarized by tDCS montages commonly used in pain trials (17). For other areas potentially involved in the placebo analgesic response, such as the midbrain periaqueductal gray and rostroventromedial medulla (18), tDCS effects may be more indirect: the current may polarize a more superficial portion of the active network, thereby altering functional connectivity to deeper, more inaccessible subcortical areas (19). We know of no studies thus far that have combined placebo or active medication with tDCS in pain.

Could placebo administration, given even explicitly in a clinical psychosocial context (20), be used to create a neural “training signal” to be reinforced by tDCS? We hypothesize that placebo-activated brain regions, particular to the pathopsychology being ameliorated, would be the physiologic substrate of tDCS neuromodulation. In clinical trials designed to enhance patient expectations through the therapeutic ritual, a behavioral prediction of this hypothesis would be an interaction of active tDCS and physiologic placebo effects. Simultaneously, it is incumbent for ongoing trials to carefully document patient expectations and blinding success.

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