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Roadblocks to driving cognitive gains through transcranial electrical stimulation

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The crucial role of cognitive dysfunction in determining functional outcomes in schizophrenia cannot be understated (Fett et al. 2011; Green 1996). Given the at-best modest benefits (Wykes et al. 2011) and time/resource intensive nature of cognitive training interventions, there is a felt clinical need to explore alternative methods, and one such promising avenue that has emerged over the last decade is non-invasive brain stimulation that includes Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) (Mehta and Keshavan 2015; Minzenberg and Carter 2012).

Despite the controversies (Polanía et al. 2018) and methodological challenges (Mehta 2016) associated with conventional non-invasive brain stimulation techniques like tDCS, there is certainly a tremendous opportunity for its translational applications in a neuroscience-guided approach. Over the years, researchers have, in a phased manner been able to demonstrate the utility of anodal tDCS over the prefrontal cortex in improving cognitive functions in healthy individuals and patients with depression (Mondino et al. 2014). There have been attempts to determine “engagement” of both general (Vercammen et al. 2011) and social (Rassovsky et al. 2015) cognitive functions using single-session tDCS, as well as, investigations into the appropriate dose of tDCS (Hoy et al. 2014).

In this edition of Schizophrenia Research, Jeon and colleagues report findings from a randomized sham controlled trial of anodal-tDCS to the left dorsolateral prefrontal cortex in 56 individuals with schizophrenia – one of the largest trials of a brain stimulation technique for this indication (Jeon et al., 2018). The study design (randomization, blinding, presence of a sham treatment arm, appropriate cognitive assessments and 3-month follow-up) and stimulation parameters (10 sessions of 2 mA, each for 30-min) were thoughtfully chosen to maximize gains, without making any compromise on methodological rigor. The authors report: (a) No immediate cognitive gains with anodal-tDCS at the end of the 10-day treatment, (b) Significantly better working memory and overall cognitive performance and significantly lesser depression scores at the end of 3-months with anodal-tDCS.

However, at baseline, the anodal-tDCS group had significantly poorer scores on precisely these three outcomes – working memory, overall cognition and depression, as compared to the sham-tDCS group. The cognitive and symptom gains with anodal-tDCS were no longer significant when the authors controlled for these baseline differences. This humbling observation could be due to a greater potential for cognitive change in the active group that had more deficits than the sham group, who were possibly hitting a ceiling effect, with limited scope for change. This chance baseline difference (despite randomization), should give the authors an opportunity to re-examine the patient clinical characteristics (e.g., outliers) and processes of subject selection for identifying systematic biases that could have contributed to baseline differences despite randomization.

There are important statistical nuances that one needs to consider when the issue of baseline differences does emerge despite randomization. It is important to note, not all baseline differences are confounders that can influence treatment outcomes. That is to say, potential confounders shouldn't be chosen based on just any statistical difference at baseline, but based on the prognostic value of the variable different at baseline (de Boer et al. 2015). These baseline variables of prognostic value ideally should be pre-specified on the basis of available evidence (Roberts and Torgerson 1999), or could be inferred based on their strength of correlation with the observed primary outcome (Kahan et al. 2014). Nevertheless, in the analyses reported by Jeon and colleagues, it was indeed important to have controlled for baseline differences, as only those variables that were rated significantly poorer at baseline showed a change in the positive direction.

Despite the understandable enthusiasm regarding the clinical utility of tDCS and other non-invasive brain stimulation techniques in cognitive enhancement for schizophrenia (Mervis et al. 2017; Smith et al.

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2015), it is extremely important to reserve the final verdict until more stable and reliable evidence is gathered. This calls for not only methodologically sound studies with optimal stimulation parameters (as in this study), but also trials with larger sample sizes that not only provide sufficient power and hence enhanced replicability (Button et al. 2013), but also a resultant reduction in the absolute size of the imbalance in baseline characteristics, especially the pre-intervention measures of outcome variables, owing to a reduction in sampling error (Roberts and Torgerson 1999). Trials with large sample sizes are also likely to yield crucial information on responders and non-responders to active stimulation; these clues can then be exclusively examined in future systematic studies to refine our clinical understanding of this intervention.

One important message for future trials on any cognitive enhancement intervention would be to have a more carefully planned patient selection approach rather than recruiting any stable schizophrenia patient. To counter the tremendous clinical heterogeneity that could influence treatment outcomes, it might be helpful to consider more careful methods of patient selection. Recruiting individuals with a minimum degree of cognitive impairment (severity) as assessed using cognitive screening tools will reduce heterogeneity – this needs-based approach also enhances the veridicality of the intervention. Stratifying the treatment and placebo arms into groups defined by baseline cognitive impairment severity and performing block randomization within each of these groups will also ensure a balance of baseline characteristics of the outcome measure.

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Contributions

UMM conceptualized the critique of the manuscript by Jeon et al. (2018), and drafted the manuscript.

Conflict of interest statement

I report no potential conflict of interest.

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