

Targeting neuronal correlates of executive function in ADHD using brain stimulation

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Improving symptomology and cognitive deficits in neurodevelopmental disorders is a crucial challenge for current medicine. One of the neurodevelopmental disorders that gained a lot of interest is attention deficit hyperactivity disorder (ADHD), which is associated with inattention and hyperactivity that impact everyday life and academic achievements and result in further difficulties in executive functions and learning (Barkley, 1997). Though prevalence is high among children, recent work has highlighted the continued impact of ADHD into adulthood (Sayal, Prasad, Daley, Ford, & Coghill, 2017). Non-invasive brain stimulation techniques have increasingly become attractive as a promising tool that have shown neuromodulatory and behavioural effects in healthy and clinical populations with very little adverse effects (Reed & Cohen Kadosh, 2018). In this issue, a study by Breitling et al. (2020) examined the impact of two types of transcranial direct current stimulation (tDCS) over the right inferior frontal gyrus on working memory processes and performance in children and adolescents with ADHD.

Interventions in ADHD using tDCS have been dominated by conventional tDCS montage, which typically leads to a widespread distribution of currents below the scalp (Breitling et al., 2020; Salehinejad, Wischniewski, Nejati, Vicario, & Nitsche, 2019). One of the novelties in Breitling et al.'s study is the use of high definition tDCS (HD-tDCS) which increases the precision of the target electrodes, and comparison of its effect to the more conventional tDCS montage and sham tDCS. While it is desirable to combine anatomical modelling for optimal stimulation via HD-tDCS to ensure alteration of the desired region, Breitling et al. reported lower sensations during HD-tDCS than during conventional tDCS and focal stimulation was not rated differently from sham stimulation. Along with lower induced current density in cortical areas that still lead to similar changes on cortical functioning, this finding indicates a great advantage for successful blinding and a lower risk for side effects in future studies, especially given the recent reports that question the effective blinding of tDCS (Turi et al., 2019).

At the neuronal level, Breitling et al. (2020) observed changes in EEG components related to executive functioning, which indicate similar neuronal processing to healthy participants after only 20 min of tDCS. Notably, these findings were observed for both tDCS protocols. Such immediate effects of short stimulation periods are believed to result from increased chances of neuron depolarization via activated ion channels and alterations in functional connectivity (Reed & Cohen Kadosh, 2018). Yet, the greatest appeal for tDCS used in clinical treatment and rehabilitation comes from longer-lasting effects that are hypothesized to originate from plastic changes such as in N-methyl-D-aspartate receptors (Nitsche et al., 2003). Therefore, it is conceivable that the observed initial processing benefit at the neural level is indicative of the prospect for greater improvement on the behavioural level with repeated sessions of tDCS, especially if combined with cognitive training (Krause & Cohen Kadosh, 2013).

Notably, many executive functions such as working memory and sustained attention have been considered rhythmic processes associated with neuronal oscillations in related networks (Helfrich et al., 2018). Thus, a tDCS-induced reduction in processing anomaly in a clinical sample might be evident in spectral analyses of EEG as well. As an example, deviations in theta and beta power between healthy and clinical samples with sustained attention difficulties and as a function of individual differences have extensively been reviewed (Arns, Conners, & Kraemer, 2013; Harty & Cohen Kadosh, 2019; Saad, Kohn, Clarke, Lagopoulos, & Hermens, 2018). As a result, other stimulation methods, such as transcranial alternating current stimulation, that target rhythmic properties of neuronal activity could be another attractive option (Reed & Cohen Kadosh, 2018). In addition, other methods, such as transcranial random noise stimulation might provide another

alternative for ameliorating atypical development (Berger, Dakwar-Kawar, Grossman, Nahum, & Cohen Kadosh, 2019; Looi et al., 2017).

As with other treatments, responsiveness to brain stimulation methods has been a persistent issue (Reed & Cohen Kadosh, 2018). Variability likely is due to a variety and combination of factors including anatomy, electrode montage, and task engagement (Krause & Cohen Kadosh, 2014; Reed & Cohen Kadosh, 2018). One of the most important challenges in the literature has been to identify reliable biomarkers for ADHD (Saad et al., 2018). These might help to adjust stimulation protocols to the individual's needs and induce maximal improvement in larger proportions of samples. In both clinical and healthy participants, resting-state EEG activity is a candidate predictor for improvements during brain stimulation (Harty & Cohen Kadosh, 2019; Saad et al., 2018). While behavioural baseline measures of executive functions have been proposed a relevant marker (Learmonth, Thut, Benwell, & Harvey, 2015), Breitling et al. (2020) did not find that baseline performance explained responsiveness to tDCS. Interestingly however, the authors found that behavioural improvement by HD-tDCS was predicted by hyperactivity in young ADHD participants, suggesting that less symptoms were favourable to profit from HD-tDCS (Breitling et al., 2020). Not only are reliable predictors of stimulation effects beneficial to avoid ineffective stimulation in non-responders, it could more importantly inform the design of personalised intervention (Schork, 2015). A replication of this finding in a larger sample, and the extension of this approach to other behavioural and biomarkers will be instrumental in order to provide an effective treatment.

In conclusion, Breitling et al. (2020) provided important new insights into potential application of non-invasive brain stimulation to guide future treatment designs for patients with ADHD. Increased stimulation precision by focal stimulation together with individually modelled electrode placement has great potential to improve stimulation effects while decreasing adverse reactions. Changes in neural processing may indicate the basis for effective plastic changes, and such effects might be manifested in a more powerful way by using repetitive stimulation sessions. In addition, such approach will allow to examine whether and which altered frequency spectra are related to modifications of impaired cognitive functions. One major issue in the intervention literature in general is the limited response in some participants, which might indicate the need for individualised treatment based on reliable predictors. Individualised and adaptive approaches that take into account stable prior factors and actively learn how to provide the most optimal stimulation could be one way to target the discussed limits in current research.

To address the limited sample size in many clinical experiments, including the sample size in Breitling et al. (2020), future studies should consider more collaborative projects to increase sample sizes and diversity. This will provide a fuller picture of the responsiveness, predictors, and effectiveness of brain stimulation to guide optimal treatment design. We recognise that part of the difficulties are due to limited opportunities by national funding bodies to allow international collaborations. We hope that such barrier will be removed to allow innovative and larger scale studies that are needed to benefit individuals, their families, and their society.

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Conflict of Interest Statement

RCK serves on the scientific advisory boards of Neuroelectronics Inc. and Tech InnoSphere Engineering Ltd.