

# Single gene polymorphisms as a predictor of noninvasive brain stimulation effectiveness (commentary on Pellegrini et al, 2021)

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## 1 | INTRODUCTION

The field of noninvasive brain stimulation (NIBS) including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial magnetic stimulation (TMS) has been growing exponentially since the last decade of the 20th century (Krishnan et al., 2015; Meecker et al., 2020). This is because NIBS has enabled us to move from the correlational studies performed using electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) or near-infrared spectroscopy (NIRS) to causal studies, where we can directly observe the effects of stimulation on a specific part of the brain (especially in the case of TMS; Farzan et al., 2016). By using NIBS, we can investigate neuroplasticity, cerebral connectivity, and cortical excitability (Di Lazzaro et al., 2018; Reinhart et al., 2017). On the other side, we got a powerful new tool for the treatment of different neurophysiological disorders—from 2008 the Food and Drug Administration (FDA) in the United States certified five TMS devices for treatment of drug-resistant major depressive disorder and protocols are being developed for the treatment of addiction (Yavari et al., 2016),

chronic pain (Cardenas-Rojas et al., 2020), stroke (Ovadia-Caro et al., 2019), epilepsy (Kim et al., 2020), obsessive-compulsive disorder (Grover et al., 2021) and schizophrenia (Osoegawa et al., 2018). Special emphasis in these researches is placed on neurodegenerative diseases like Parkinson's disease (Madrid & Benninger, 2021) and Alzheimer's disease (Buss et al., 2019) considering that dementia is ranked as the seventh leading cause of death in the world with no known cure or effective way to stop the progression (World Health Organization, 2019). However, despite all these potentials, the high variability in the results of NIBS studies lead some scientist to ask a very valid question "Is There a Future for Non-invasive Brain Stimulation as a Therapeutic Tool?" (Terranova et al., 2018). And their answer is "Yes" if we find a way to personalize it. A very effective way to do that would be through usage of biomarkers (like gene polymorphisms) and this is where the paper by Pellegrini et al. (2021a) attempts to give its contribution.

In their recent paper, Pellegrini et al. tried to determine if the interindividual variability to tDCS was in part genetically mediated. To address this issue, they performed the following experiment—in a group of healthy males, they used anodal bicephalic tDCS montage (the active

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electrode, 4 × 6 cm, was placed over the dominant M1 area and the return electrode, 5 × 7 cm, over the contralateral supraorbital area) to deliver 10-min 1-mA anodal stimulation with 30-s fade-in/fade-out periods. The control group received the sham stimulation with 1-mA 30-s fade in period after which the current intensity was reduced back to zero. The effects of the stimulation were then tested by using single pulse (SP) TMS to assess the changes in motor evoked potential (MEP) and by using paired-pulse (PP) TMS to assess changes in cortical excitability through short intra-cortical inhibition (SICI) and intra-cortical facilitation (ICF) indexes immediately after and 30 minutes after anodal tDCS (a-tDCS). Identical SP protocol was performed before a-tDCS in order to establish the baseline. Based on the response to the a-tDCS, the participants were then categorized in two groups—“responders” and “non-responders.” The categorization was performed in two ways—based on a predetermined threshold and SPSS’s Two-Step cluster analysis. Considering the level of similarity in the classification results, the authors decided to keep the one based on predetermined threshold in the final analysis. In total, they tested the association between 10 polymorphisms—one for brain-derived neurotrophic factor (BDNF, rs6265), four for (excitatory) glutamate N-Methyl-D-aspartate (NMDA) receptor (GRIN1 - rs6293, rs4880213; GRIN2B - rs1805247, rs7301328) and five for (inhibitory) gamma-aminobutyric acid (GABA) receptor (GABRA1 - rs6883877; GABRA2 - rs279871, rs511310; GABRA3 - rs1112122, rs4828696). The results were as follows: there were no significant differences between groups in SICI and ICF, there was no association between groups and gene polymorphisms for (excitatory) glutamate receptors and out of five analyzed polymorphisms for (inhibitory) GABA receptor genes, only two (for GABRA3) yielded significant association.

The paper by Pellegrini et al. (2021a) joins a long list of experiments performed in order to establish an association between gene polymorphisms and the effects of tDCS. While most of the previous findings relate to the BDNF and catechol-O-methyltransferase (COMT) genes, others like NMDA and GABA receptors were also explored (see Chhabra et al., 2016, for a detailed review). However, while the traditional genetic association studies usually consist of hundreds or thousands of subjects (especially when it comes to complex disorders), neuroscience genetic association studies rarely have more than 20–30 participants. Therefore, it should be commended that Pellegrini et al. managed to recruit 61 participants, which is (to their knowledge) the highest number of participants in this type of projects so far. The authors also present a thorough review of the literature and discuss other (non-genetic) reasons for different reactions to the neurostimulation (tDCS) like the stimulation sites and

the type of montage, anatomical factors such as differences in skull thickness and morphology, the time of the day in which the stimulation was applied and the phase of the menstrual cycle in the participants. Still, the experiment itself and the statistical analysis deserve some constructive criticism. The experimental design used in this study is based on a recently published manuscript in *Neuroscience Research* (Pellegrini et al., 2021c). This recent work does not include any genotyping, but it does provide the simulation of the applied tDCS montage and the resulting differences in cortical excitability. While no significant effect of the anodal tDCS on the MEP amplitude was found in Pellegrini et al. (2021c), a very significant effect was found in the present study (Pellegrini et al., 2021a). The authors do not comment on this discrepancy. Also, because the results of the cathodal stimulation part of this experiment were published in a separate paper (Pellegrini et al., 2021b), a critical discussion on the differences between the results of these two stimulations is missing. Further comparison between the results presented in these two papers raises questions as to how statistical analyses were performed. Because the two papers are identical in every aspect except the type of applied tDCS stimulation, it is hard to understand why the authors excluded three SNPs (GRIN2B rs1805247, GABRA1 rs6883877 and GABRA2 rs511310) from the cathodal study (Pellegrini et al., 2021b) due to the “disproportionate sample-sizes”, but kept them in the anodal study (Pellegrini et al., 2021a). The decision to exclude these SNPs was a correct one and should have also been applied to the BDNF SNP for the same reason. The only SNPs with positive association in this study (GABRA3 rs1112122 and rs4828696) also, significantly ( $p < 0.01$ ), depart from the Hardy–Weinberg equilibrium reducing the impact of the results. Despite these limitations, we acknowledge the authors’ contribution to the very complex field of neurostimulation and hope that our comments raise some relevant questions worth considering in the analysis and interpretation of data presented in the recent study by Pellegrini et al. (2021a).

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## PEER REVIEW

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