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Brain-derived neurotrophic factor (BDNF) polymorphism may influence the efficacy of tACS to modulate neural oscillations

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Declaration of competing interest

F.F. is the lead inventor of IP filed by UNC. F.F. is the founder, CSO, and majority owner of Pulvinar Neuro LLC.

Plasticity of human motor cortex is modulated by brain-derived neurotrophic factor (BDNF). A single nucleotide polymorphism at codon 66 (Val66Met) in the gene that codes for BDNF is associated with altered learning and memory [1]. Non-invasive brain stimulation increases excitability by recruiting BDNF-dependent neural plasticity [2]. In a previous study, the presence of the Val66Met polymorphism predicted reduced efficacy for both transcranial current stimulation and repetitive transcranial magnetic stimulation (TMS) to modulate excitability in the corticospinal tract probed as the amplitude of the motor-evoked potential elicited by TMS pulses to primary motor cortex [3]. In animal models, the Val66Met polymorphism reduces the neural response to brain stimulation by decreasing NMDA-dependent long-term potentiation of synaptic transmission [4,5]. Despite this growing literature on the potential gating of corticospinal excitability changes by the Val66Met polymorphism, the role of the Val66Met polymorphism in gating the neural response to brain stimulation at the level of brain network dynamics remains unknown. Alpha oscillations are the dominant brain rhythm in the awake resting state and modulate the neural response to sensory input [6]. Given this role in shaping state-dependent neural excitability, targeting alpha oscillations with brain stimulation represents a promising strategy to modulate and enhance brain function. In particular, transcranial alternating current stimulation with stimulation waveforms in the alpha frequency (alpha-tACS) modulate alpha oscillations and were recently investigated as a treatment for major depressive disorder [7,8], schizophrenia [9], and chronic pain [10]. Yet, the question remains if the modulation of alpha oscillations by alpha-tACS is a function of Val66Met status. We analyzed EEG data from three alpha-tACS studies in our group as a function of Val66Met polymorphism.

All data were collected in double-blind, placebo-controlled studies performed at the University of North Carolina (UNC) at Chapel Hill. All study protocols were approved by the local Institutional Review Board at UNC and all study participants provided written informed consent. The data presented here spans from August 2017 to August 2019. The first study investigated the effect of tACS on alpha oscillations in healthy controls in a cross-over design (unpublished). The second study investigated the effect of tACS on alpha oscillations in patients with chronic back pain [10]. The third study investigated the effect of tACS in depression and included a set of healthy control participants that are included in the analysis here (unpublished). In all studies included in this paper, we obtained a saliva sample from the participants using the Oragene Discover OGR-500 DNA Self-Collection kits (Genotek Inc., Ottawa, ON, Canada) for subsequent genotyping. DNA was extracted and sequenced at the Val66Met locus by Genotek (Ottawa, Canada) using the TaqMan SNP Genotyping assay. EEG data were analyzed as previously described [10]. We defined an a priori area of interest centered on the central EEG electrode Cz (group of six electrodes), where we have previously found an increase in alpha oscillation with the electrode montage used in these studies (2mA peak-to-peak at bilateral frontal electrode and 4mA peak-to-peak at central posterior “return” electrode) [10]. The amplitude of the alpha oscillation was log transformed and spatially normalized by z-scoring.

In our pooled dataset, we found 58 Val/Val, 37 Val/Met, and 5 Met/Met participants. We combined the latter two groups into a single Met carrier group. In agreement with our hypothesis, we found that the increase of the amplitude of the alpha oscillation by alpha-tACS (verum versus placebo) was a function of the Val66Met polymorphism ($F(1,96) =$

4.350, p = 0.0397, η_p^2 = 0.043) by comparing the Val66Val (N = 58) with the Met carrier group (N = 42) such that the alpha amplitude increase from alpha-tACS in the Val66Val group was greater than the one in the Met carrier group.

This finding points towards a role of BDNF-dependent plasticity in the offline, or consequent, effect of tACS. Intriguingly, a previous study concluded that plasticity explains the offline effect of tACS by demonstrating no significant difference in the effect of tACS when delivered in consecutive periods that were either phase-continuous or phase-discontinuous [11]. However, no genotyping was performed. To our knowledge, we are the first to examine how the BDNF Val66Met polymorphism affects the frequency-specific response of neural oscillation to tACS.

As with any scientific investigation, our study has several limitations. First, we are unable to answer the question whether the online, or concurrent, effect of tACS depends on the Val66Met polymorphism. Such mechanistic insights of entrainment during tACS in human EEG studies would require the recording of neural activity during stimulation and successful removal of the stimulation artefact, which remains a technical challenge. Second, we pooled across studies where some used 10Hz-tACS (Studies 1 and 2) and one used tACS at the individual alpha frequency (Study 3). In addition, the position of the return electrode slightly differed as the location of the third electrode was more anterior (Cz) for Study 3 in comparison to Studies 1 and 2 (POz). However, the two in-phase frontal electrodes were located at F3 and F4 in all three studies. Finally, we have pooled data from three different studies where the primary outcome was not to test the role of BDNF. Thus, other unaccounted differences between the three studies may play a role in our results.

In summary, our results support further investigations of how the Val66Met polymorphism shapes the response of neural oscillations to tACS. Assessing this SNP may be of particular relevance in tACS treatment clinical trials with multiple stimulation sessions.

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References

[1]. Kleim JA, et al. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat Neurosci 2006;9(6):735–7. [PubMed: 16680163]

[2]. Cheeran B, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol 2008;586(23):5717–25. [PubMed: 18845611]

[3]. Antal A, et al. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimul. 2010;3(4):230–7. [PubMed: 20965453]

[4]. Fritsch B, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010;66(2): 198–204. [PubMed: 20434997]

[5]. Podda MV, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. Sci Rep 2016;6.

[6]. Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cognit Sci 2012;16(12):606–17. [PubMed: 23141428]

[7]. Alexander ML, et al. Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). Transl Psychiatry 2019;9(1):106. [PubMed: 30837453]

[8]. Riddle J, et al. A case study of weekly tACS for the treatment of major depressive disorder. Brain Stimul. 2020;13(3):576–7. [PubMed: 32289679]

[9]. Ahn S, et al. Targeting reduced neural oscillations in patients with schizophrenia by transcranial alternating current stimulation. Neuroimage 2019;186:126–36. [PubMed: 30367952]

[10]. Ahn S, et al. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. J Pain 2019;20(3):277.e1–277.e11. [PubMed: 30268803]

[11]. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. Brain Stimul. 2015;8(3):499–508. [PubMed: 25648377]