University of Szeged
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Investigating non-invasive brain stimulation to modulate executive function in major depressive disorder and healthy individuals

Ph.D. Thesis

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Original publications directly related to this thesis:

I. Holczer, A., Németh, V. L., Vékony, T., Kocsis, K., Király, A., Kincses, Zs. T., Vécsei, L., Klivényi, P., & Must, A. (2021) The Effects of Bilateral Theta-burst Stimulation on Executive Functions and Affective Symptoms in Major Depressive Disorder. *Neuroscience*, 461, 130-139. IF = 3.590

II. Kocsis, K.*, **Holczer, A.*,** Kazinczi, Cs., Boross, K, Horváth, R., Németh, V. L., Klivényi, P., Kincses, Zs. T., & Must, A. (2021) Voxel-based asymmetry of the regional gray matter over the inferior temporal gyrus correlates with depressive symptoms in medicated patients with major depressive disorder. *Psychiatry Research: Neuroimaging*, 317, p. 111378. IF = 2.493

III. Holczer, A.*, Vékony, T.*, Klivényi, P., & Must, A. (2023) Frontal two-electrode transcranial direct current stimulation protocols may not affect performance on a combined flanker Go/No-Go task. *Scientific Reports*, *13*(1) IF = 4.996

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I. INTRODUCTION

Non-invasive brain stimulation (NIBS) techniques have gained approval for therapeutic use in treatment resistant major depressive disorder (MDD), obsessive compulsive disorder, migraine, and tobacco use disorder (Cohen et al., 2022). However, there is no consensus yet regarding the effects of NIBS on the modulation of cognition due to inconclusive results and high heterogeneity of the methods. More systematic investigations evaluating the cognitive effects of widely-used protocols are needed to expand the application of NIBS to cognitive modulation and potentially, cognitive enhancement. This thesis contributes to the literature by investigating the impact of NIBS targeting the dorsolateral prefrontal cortex (DLPFC) using conventional parameters on cognition in both healthy individuals and those with MDD.

Two NIBS protocols, namely, ***repetitive transcranial magnetic stimulation*** (rTMS) and its fast-to-administer alternative, ***theta-burst stimulation*** (TBS) apply repetitive magnetic pulses to induce electric current in the cortical tissue of the target region (Cirillo et al., 2017), and have their antidepressant efficacy proven in MDD (Voigt, 2020). However, it is to be determined whether the impairment of executive functions (EFs), attention, memory, and psychomotor speed (Perini et al., 2019), a core feature of MDD affecting everyday functioning, quality of life, and emotion regulation (Kimbarow, 2019; Pizzagalli & Roberts, 2022), could be modulated by rTMS.

There are NIBS protocols specifically designed while taking the brain alterations observed in MDD into account. One such protocol is bilateral TBS (i.e., inhibitory and facilitatory TBS sequentially applied to the right and left DLPFC, respectively) intended to reduce the rightward lateralization of the prefrontal cortices in MDD. Bilateral TBS has been found comparable to unilateral intermittent (facilitatory) TBS in terms of antidepressant efficacy (Blumberger et al., 2022); however, its effects on EFs has been scarcely investigated despite the DLPFC being involved in these processes (Panikratova et al., 2020). Considering that cognitive function has been shown sensitive to some therapies such as electroconvulsive therapy, adverse cognitive effects are also to be excluded apart from the potential of benefits of the stimulation.

The imbalance of the prefrontal cortices in MDD compared to healthy individuals can be observed in functional measures e.g., cortical excitability, activation, metabolism, and alpha frequency band activity (Greco et al., 2021; Hecht, 2010). However, structural alterations, as well as asymmetric volume of the gray matter has been suggested to be present in MDD (Liu et al., 2016; Schmaal et al., 2017). These alterations might be associated with functional abnormalities (Dai et al., 2019); however, the low spatial resolution of region of interest based imaging methods and the heterogeneity of the included sample may hinder the identification of such slight alterations. Importantly, gray matter volume asymmetry of the frontal regions has been linked to depressive symptoms, whereas cognitive impairment has previously been overlooked when investigating these associations. This approach, however, may also strengthen the rationale of bilateral stimulation protocols or uncover novel targets.

Another NIBS technique widely researched for potential applications in the motor, cognitive, and affective domains is ***transcranial direct current stimulation*** (tDCS). Delivering weak electric currents to the brain via electrodes attached to the scalp, tDCS is believed to modulate the resting membrane potential of the neurons among other mechanisms (Cirillo et al., 2017). In the cognitive domain, tDCS effects depend on several factors, including stimulation parameters, and are highly variable to the point that even the conventional concept of polarity dependent tDCS effects (i.e., anodal tDCS as facilitatory and cathodal tDCS as inhibitory) have been debated (Karuza et al., 2016). One common cognitive target is interference control and response inhibition, both strongly associated with the DLPFC (Cieslik et al., 2015; Steele et al., 2013). On the other hand, the fronto-medial regions are also believed to be involved in these processes and have been targeted by tDCS (Cieslik et al., 2015; Frings et al., 2018). However, electrode montages targeting the DLPFC alone and fronto-medial montages have not been compared to each other; although, this may elicit optimal sets of parameter.

II. AIMS AND OBJECTIVES

The main goal of the thesis is to address some of the above-mentioned issues by systematically investigate if established NIBS protocols can modulate cognitive functions (and more specifically, working memory, response inhibition, and interference control) in healthy individuals and patients with MDD. Moreover, we examined gray matter asymmetry in MDD, a feature that may be linked to the symptoms observed in MDD. Our aims can be summarized as follows:

- **Study I.** investigated the effects of bilateral TBS (that has evident antidepressant efficacy) on executive function and attention in MDD.

- **Study II.** measured voxel-based cortical asymmetry and its association with depressive symptoms and executive function in MDD.
- **Study III.** examined how tDCS delivered in two electrode montages targeting the prefrontal and fronto-medial areas influence interference control and response inhibition.

III. METHODS AND MATERIALS

Study I – Bilateral TBS in MDD

Twenty-five patients with a diagnosis of unipolar MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria on stable medication were recruited. The final analysis of complete cases included twenty participants. Participants were randomized into receiving ten sessions of verum or sham neuronavigated TBS (Fig. 1) and underwent cognitive and affective assessment before and after the stimulation protocol involving the 21-item Hamilton Depression Rating Scale (HDRS), Attention Network Task (ANT), and three levels of the n-back task (Fig 2.). The change in depressive symptoms was taken from $HDRS_{pre\text{-}TBS}$ – $HDRS_{post\text{-}TBS}$ scores and analyzed using an independent sample t-test, while median reaction time and discriminability indices were entered into analyses of variance. Bayesian statistics was also conducted to supplement the frequentist analysis.

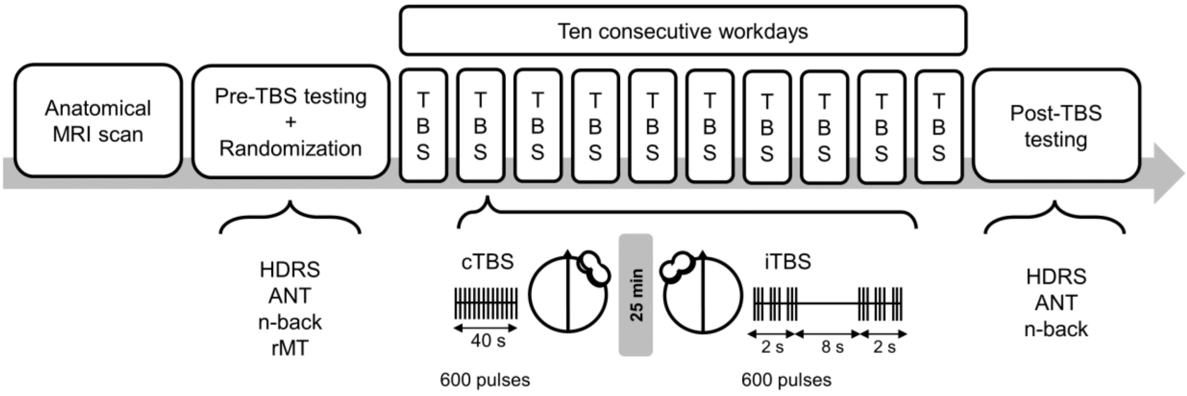

Figure 1. The experimental design of Study I. Prior to randomization into active or sham TBS groups, anatomical magnetic resonance images were acquired, and baseline measures and the resting motor threshold were taken. Participants underwent ten consecutive workdays of TBS followed by a post-TBS assessment. The protocol for the given session is presented under the curly braces. TBS sessions were identical and consisted of the inhibitory TBS of the right DLPFC and then excitatory TBS over the left DLPFC with a 25-minute-long break apart.

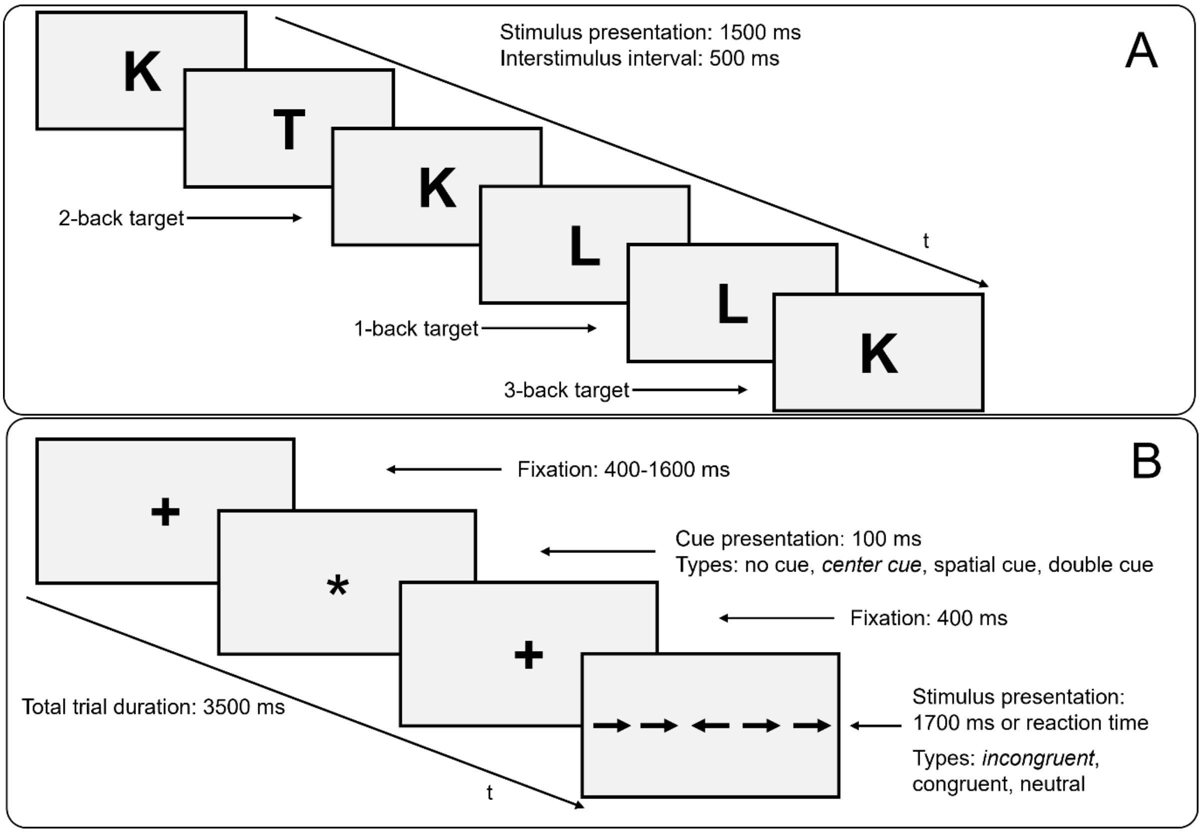

Figure 2. Design of the tasks used in Study I. **Panel A** shows the n-back task. Participants were asked to press a button if the letter presented is identical to the letter presented one, two, or three trials before (1-, 2-, and 3-back tasks, respectively). **Panel B** shows the structure of the ANT task, a cued flanker task where participants were instructed to respond to the middle arrow while ignoring the flanking stimuli.

Study II – Gray matter asymmetry in MDD

Seventeen patients diagnosed with unipolar MDD based on the DSM-IV criteria participated in the study. Three-dimensional high-resolution T1-weighted anatomical images were acquired from each participant. Depression severity and EF measures were also taken. Voxel-based gray matter asymmetry was calculated from the structural images following a detailed guideline (Kurth et al., 2015). Finally, a general linear model was performed to test bidirectional associations between the significant voxels and the cognitive and affective measures.

Study III – tDCS effects on a combined flanker Go/No-Go task

Forty healthy young adults participated in the study, from which the data of thirty-eight was included in the final analysis. Participants were randomized into receiving tDCS targeting the DLPFC in a conventional unilateral montage or the fronto-medial areas. All participants received three sessions of tDCS in a randomized order divided by at least 48 hours: anodal, cathodal, and sham tDCS (Fig. 3). During tDCS, participants were to perform a combined flanker Go-No/Go task where they were instructed to respond to the direction of the target arrow while ignoring the flanking stimuli or withhold response when ‘×’ symbols appeared around the target (Fig. 4). Median reaction time data and accuracy were analyzed using analyses of variance and Bayesian statistics.

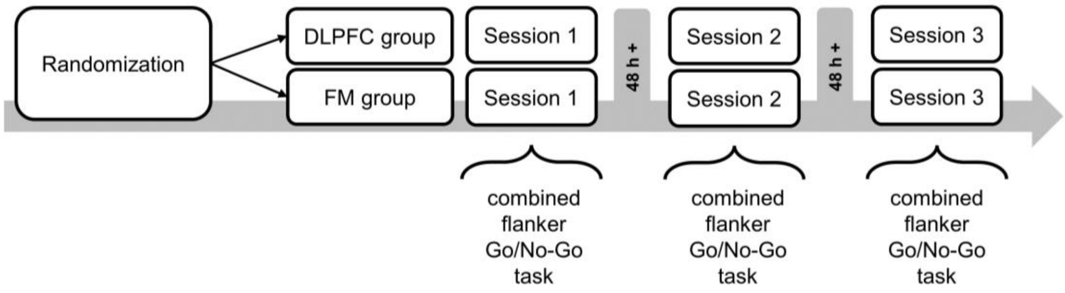

Figure 3. Experimental design of Study III. Participants were randomized into two groups based on electrode montage. Anodal, cathodal, and sham stimulation was randomly delivered throughout three sessions divided by at least 48 hours. During the stimulation, participants performed a combined flanker Go/No-Go task.

IV. RESULTS AND DISCUSSION

In **Study I**, we replicated that bilateral TBS was superior to sham TBS (Berlim et al., 2017) in reducing HDRS scores (Fig. 4) but in contrast to previous promising results (Cheng et al., 2016), did not find an effect on working memory, attention, or interference resolution. Taken that TBS using similar stimulation parameters have resulted in brain activity changes (Chung et al., 2017) and that TBS modulates theta-gamma coupling that is involved in various cognitive processes (Brooks et al., 2020), we cannot exclude the presence of subtle changes that cannot be captured on the behavioral level. In line with this, our results suggested that bilateral TBS may improve psychomotor speed; however, further support of this finding is needed. Of note, no detrimental effect of bilateral TBS on cognitive performance was found that, coupled with the antidepressant efficacy, this signifies that NIBS may be a well-tolerated technique to reduce depressive symptoms.

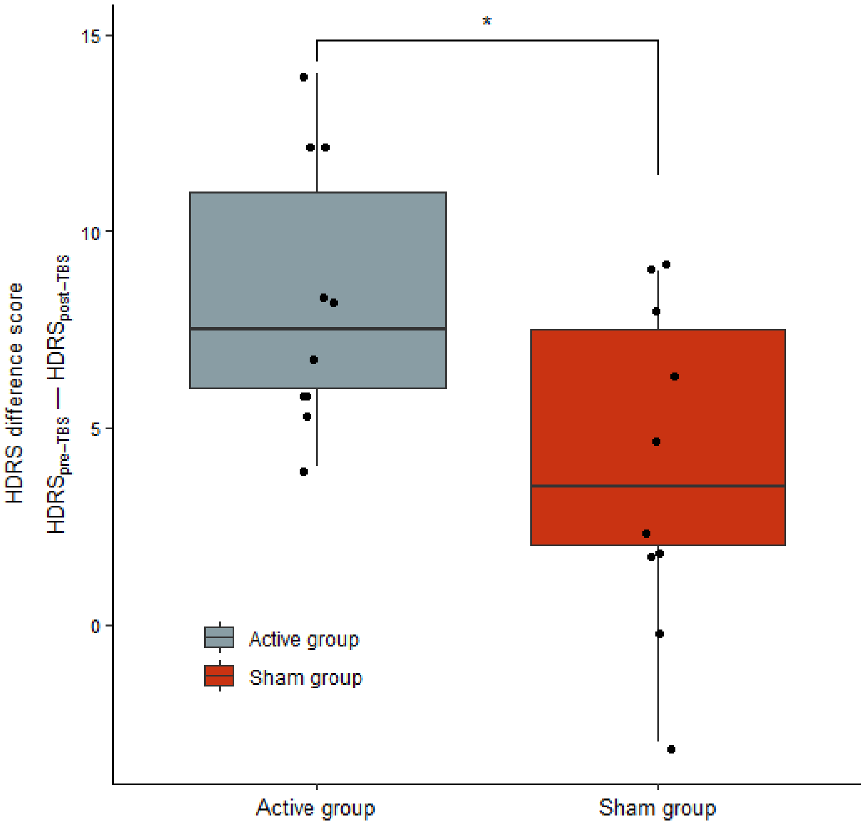

Figure 4. Box plots of the antidepressant effect of bilateral TBS. The vertical axis denotes the difference score of pre-TBS minus post-TBS HDRS scores. The active and sham groups are shown on the horizontal axis. Individual data points are also presented. Colored version of Figure 1, Panel A from Holczer et al. (2021), see Appendix I of the PhD thesis.

Using a voxel-based method in **Study II**, we found lower gray matter content in the right hemisphere, compared to the left within a cluster of voxels in the inferior temporal gyrus. This region has already been implied to be affected in MDD or at least in subgroups of patients (Peng et al., 2016; Schmaal et al., 2017). Furthermore, our results suggested that the significant voxels within the inferior temporal cortex were associated with depression severity as measured by the Hamilton Depression Rating Scale (Fig. 5). Previously, the volume, but not the asymmetry of the inferior temporal gyrus has correlated with depressive symptoms (Li et al., 2010). As part of the extended default mode network (DMN), the inferior temporal gyrus may be involved in rumination and self-referential processes realized by the network level activation of the DMN (Guo et al., 2014).

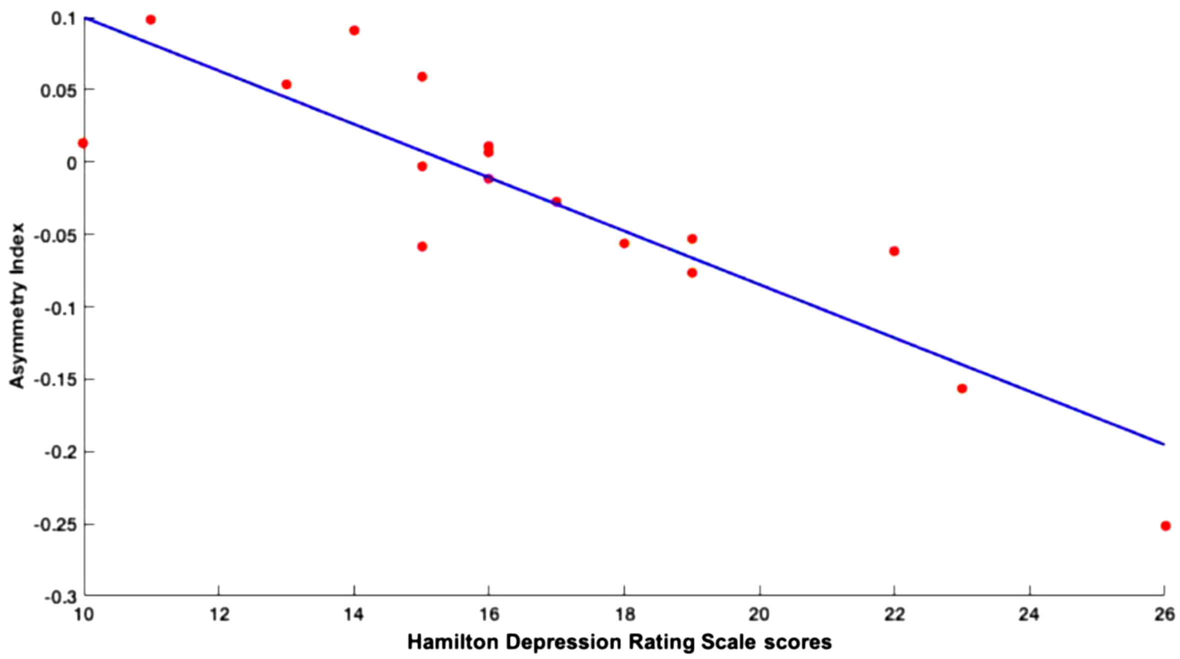

Figure 5. The correlation of the asymmetry index values of the significant clusters within the inferior temporal gyrus (MNI152 standard space coordinates: x = 18, y = 55, z = 17) and depressive symptoms. Figure from Kocsis et al. (2021), see Appendix II of the PhD thesis.

In **Study III**, we failed to replicate previous findings of tDCS improving response inhibition and interference control (e.g., Jeon & Han, 2012) and could not detect any change in performance when using a fronto-medial montage either. Neither anodal, nor cathodal stimulation resulted in altered performance compared to sham stimulation in either experimental group. These findings support the that the widely accepted concept of delivering single sessions of tDCS to healthy young adults while using cephalic return electrodes (such as in many conventional tDCS montages) may not yield reliable changes in cognitive function (Westwood & Romani, 2017).

To summarize, the findings of **Study I** and **Study III** did not support the modulation of executive functions using NIBS with the given parameters. Importantly, we did not find evidence for impaired performance following NIBS either which may support the utilization of NIBS for its antidepressant effect in patients with MDD and other neuropsychiatric disorders. Moreover, the potential of TBS to improve psychomotor speed in MDD or alter neurophysiological processes not measured in the present studies offers a promising future line of research. Further research is required to delineate whether the stimulation of networks instead of may result in more prominent effects. Targeting the right and not the left DLPFC for processes like response inhibition and interference control may also worth exploring. On that note, we encourage the systematic comparison of both left and right NIBS as in our previous study (Vékony et al., 2018). The increasing number of null results regarding the effects of NIBS on executive function are in line with our findings and call for more rigorous research and the re-consideration of common practices.

V. CONCLUSIONS

The contributions of the studies presented as part of the thesis include the following:

- We showed that ten sessions of bilateral TBS resulted in no immediate effect on working memory, interference control, and other aspects of attention while reducing depressive symptoms compared to sham stimulation.
- The inferior temporal gyrus may be involved the pathomechanism of MDD as we found gray matter volume asymmetry within the region which was also associated with depression severity. We correlated the asymmetry index of the inferior temporal gyrus with working memory performance for the first time.
- We underlined the reconsideration of common tDCS practices such as delivering a single session of 2 mA tDCS in a conventional left DLPFC montage to healthy young adults considering that we could not modulate response inhibition or interference control using this method with neither cathodal nor anodal tDCS. We were the first to compare a conventional DLPFC montage to another targeting the fronto-medial cortices.

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I dedicate this thesis to my late father, Tibor Holczer, who shaped me as a person, teaching me the value of self-improvement and perseverance. His love and unwavering belief in me have accompanied my childhood, my PhD journey and will forever guide me.

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