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

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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 = 4.6

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I. Bikson, M., Hanlon, C. A., Woods, A. J., Gillick, B. T., Charvet, L., Lamm, C., Madeo, G., **Holczer, A.** ... & Ay, M. R. (2020) Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. *Brain Stimulation*. IF = 9.184

II. Holczer, A., Németh, V. L., Vékony, T., Vécsei, L., Klivényi, P., & Must, A. (2020) Non-invasive Brain Stimulation in Alzheimer's Disease and Mild Cognitive Impairment—A State-of-the-Art Review on Methodological Characteristics and Stimulation Parameters. *Frontiers in Human Neuroscience,* 14. IF = 3.473

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II. Vékony, T., Németh, V.L., **Holczer, A.,** Kocsis, K., Kincses, Zs.T., Vécsei, L., & Must, A. (2018) Continuous theta-burst stimulation over the dorsolateral prefrontal cortex inhibits improvement on a working memory task. *Scientific Reports*, 8(1), 1-9. IF = 4.996

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LIST OF ABBREVIATIONS

ANCOVA	—	Analysis of covariance
ANOVA	—	Analysis of variance
ANT	—	Attention Network Task
BDNF	—	Brain derived neurotrophic factor
BF	—	Bayes Factor
BHS	—	Beck Hopelessness Scale
cTBS	—	Continuous theta-burst stimulation
DLPFC	—	Dorsolateral prefrontal cortex
DSM	—	Diagnostic and Statistical Manual of Mental Disorders
ECT	—	Electroconvulsive therapy
EEG	—	Electroencephalography
EF	—	Executive function
FDA	—	Food and Drug Administration of the United States of America
GABA	—	Gamma aminobutyric acid
HDRS	—	Hamilton Depression Rating Scale
H_0	—	Null hypothesis
H_1	—	Alternative hypothesis
iTBS	—	Intermittent theta-burst stimulation
ITG	—	Inferior temporal gyrus
MDD	—	Major depressive disorder
MRI	—	Magnetic resonance imaging
NIBS	—	Non-invasive brain stimulation
rMT	—	Resting motor threshold
RT	—	Reaction time
rTMS	—	Repetitive transcranial magnetic stimulation
SD	—	Standard deviation
tDCS	—	Transcranial direct current stimulation
TBS	—	Theta-burst stimulation
TMS	—	Transcranial magnetic stimulation

I. INTRODUCTION

Over the past decades, non-invasive brain stimulation (NIBS) has been dynamically evolving and offering a novel way to explore the functional role of specific brain regions and associated networks (Dayan et al., 2013; Lefaucheur et al., 2020). Compared to the correlational nature of conclusions drawn from neuroimaging, NIBS may contribute to finding causal evidence by temporarily enhancing or inhibiting the targeted area or node. This characteristic of NIBS also makes it a promising tool for translating brain activity changes to behavioral changes outlasting the duration of the stimulation. Following the initial reports on increased cortical excitability due to stimulation over the motor cortex (Barker et al., 1985; Merton & Morton, 1980; Nitsche & Paulus, 2001), NIBS has been used to modulate a wide range of functions in the motor, cognitive and affective domains across various samples. These efforts have led to advancements starting with the first approval of the US Food and Drug Administration (FDA) in 2008 for managing affective symptoms in treatment-resistant major depressive disorder (MDD). Further approvals have followed for therapeutic use in MDD, obsessive compulsive disorder, migraine, and tobacco use disorder (for a review, see Cohen et al., 2022) and innovative combined techniques such as closed-loop stimulation have been developed (Gebodh et al., 2023).

Despite these advances and the increasing need for tools to enhance cognition, results on the cognition-modulatory effects of NIBS are often inconclusive, have low statistical strength, or are hard to reproduce (Pesthy et al., 2021). Lately, an increasing number of null results have mingled with the initial surge of promising findings (de Graaf & Sack, 2011; Medina & Cason, 2017). Furthermore, the mechanisms through which NIBS influences brain function and behavior, along with the factors that modulate their effect (including study design and stimulation parameters as well as individual traits and characteristics), are yet to be understood. More critical approaches have even questioned the efficacy of specific NIBS methods in modulating cognition (e.g., Horvath et al., 2015).

To establish the actual role of NIBS in cognitive neuroscience and add cognitive enhancement to the currently approved antidepressant effects and other indications, it is necessary to explore NIBS effects in a systematic and thorough manner. The thesis aims to contribute to a better understanding of NIBS effects on cognition (and more specifically, on executive functions) in healthy individuals as well as in patients with MDD by systematically testing NIBS effects with widely used stimulation parameters across two studies, and by discussing the potentially relevant factors affecting the results.

NIBS as a tool of cognitive neuroscience

Despite having a far-reaching history in health sciences, NIBS in its modern form has only been introduced at the end of the 20th century. Several techniques have since been developed, but two stand out as the most frequently used and researched. ***Transcranial magnetic stimulation*** (TMS) is based on the law of electromagnetic induction. The rapidly changing magnetic fields generated by the device are able to induce electric currents in the brain. With this, TMS is believed to alter the excitability of the underlying cortical areas or even reach the threshold of directly inducing action potentials. TMS can be delivered in single or paired pulses or trains of pulses; the latter is called repetitive transcranial magnetic stimulation (rTMS). rTMS is expected to influence cortical excitability, outlasting the duration of the stimulation by (at least partly) relying on long-term potentiation and long-term depression-like plasticity (Cirillo et al., 2017). The delivery of rTMS induces activity changes in the targeted brain regions and in distant, interconnected brain areas (Eldaief et al., 2011). In a frequency-dependent manner, directional changes are expected in cortical excitability. Facilitatory effects are expected following high-frequency rTMS (5 Hz or above) and inhibitory effects following low-frequency rTMS (1 Hz).

Additionally, a patterned version of rTMS known as ***theta-burst stimulation*** (TBS) has recently gained significant attention because it is shorter in duration and is comparable to rTMS regarding its efficacy (Blumberger et al., 2018; Voigt, 2020; Zafar et al., 2008). The facilitatory pattern of TBS is called intermittent TBS (iTBS), containing trains of bursts interrupted by pauses. Inhibitory TBS, called continuous TBS (cTBS), contains trains of bursts without a pause (Huang et al., 2005).

Apart from their effect on cortical excitability, both TBS and rTMS have been linked to a variety of changes, indicating additional processes through which these techniques may act. Facilitatory rTMS has been suggested to increase cerebral blood flow under the target region in various study samples and has increased glucose metabolism in MDD (Kinney & Hanlon, 2022). rTMS has also been linked to molecular changes including brain derived neurotrophic factor (BDNF), gamma aminobutyric acid (GABA), and dopamine in MDD; however, further confirmation studies are needed as these effects seem to differ in healthy compared to patient populations (for review, see Kim et al., 2021; Kinney & Hanlon, 2022). Currently, gaps in knowledge still limit our understanding of TMS effects on neurotransmission and molecular changes (Cirillo et al., 2017; Kinney & Hanlon, 2022).

Transcranial direct current stimulation (tDCS) is one of the most frequently used transcranial electrical stimulation techniques (apart from transcranial alternating current stimulation and transcranial random noise stimulation) (Antal et al., 2021). tDCS involves the delivery of weak electric currents (usually 1-2 mA) to the brain via electrodes attached to the scalp and is believed to manifest its effects through modulation of the resting membrane potential. In a polarity-dependent manner, a facilitatory effect is expected, resulting in the depolarization of the neuronal membrane (under the electrode called the anode) and inhibitory effects by hyperpolarizing the neuronal membrane (under the other electrode or electrodes serving as a reference electrode) (for an extensive review on rTMS and tDCS mechanism of action see Cirillo et al., 2017). Stimulation over a prolonged period of time (i.e., 5 minutes or more) is believed to induce effects outlasting the duration of the stimulation through processes involved in neuroplasticity, similar to rTMS. So far, tDCS has only been used for research, with more evidence potentially supporting its future therapeutic use. Thus, it is even more pressing to deepen our knowledge of the mechanism of action and the factors affecting tDCS.

Stimulation parameters of NIBS techniques

Stimulation parameters are key parameters that can influence the neurophysiological impact of NIBS (Xu et al., 2023). Stimulation parameters for rTMS and tDCS among others include the number of sessions, stimulation intensity, and duration, the location of the target region, and the type and positioning method of the coil/electrodes. Even single-session NIBS may result in changes in performance on various cognitive tasks (e.g., Dedoncker et al., 2016), but multiple sessions are often delivered for therapeutic use (one session per day for multiple days, or multiple stimulation session per day in an accelerated manner) (Sonmez et al., 2019). Within a session, duration is defined based on the number of pulses delivered, and intensity is defined in percent with respect to the maximum stimulator output for rTMS. Intensity is usually adjusted according to the active or resting motor threshold (rMT) of the given participant; although this practice has been questioned (Kaminski et al., 2011). For tDCS, the intensity of the stimulation is determined in mA, with the duration of the stimulation defined in minutes. To position the electrodes/coil over the target area, several methods can be used, ranging from positioning based on the international 10–20 electroencephalography (EEG) system through localization based on another brain region (e.g., motor cortex) to neuronavigation using structural or functional imaging (Fitzgerald et al., 2009). Lately, the simulation of electric fields generated by NIBS has become more available, which also helps researchers determining in advance the most optimal setting for

maximizing current strength (Antonenko et al., 2019). When examining the cognitive effects of NIBS, based on the timing of cognitive assessment, online (i.e., during the stimulation) and offline (i.e., before and/or after the stimulation) testing can be distinguished. While these parameters are believed to be directly related to the efficacy of NIBS, only a few studies have conducted comparative studies on these parameters (e.g., Fertonani et al., 2014; Živanović et al., 2021).

Executive functions and their impairment in MDD

The growing interest in modulating cognition using NIBS may partly stem from neuroimaging studies describing NIBS effects on brain activity (Beynel et al., 2020; L. Chen, Wang, et al., 2023; Mendes et al., 2022; Thut & Pascual-Leone, 2010) as well as the rising attention on cognitive deficits due to aging and as an accompanying symptom in neuropsychiatric disorders. Specifically, executive functions (EFs), including working memory, inhibition, and set-shifting, have been suggested to serve as a transdiagnostic target for interventions in psychiatry and psychopathology (East-Richard et al., 2020; Romer & Pizzagalli, 2021). Accordingly, EFs have been found impaired in healthy aging as well as in various neuropsychiatric disorders such as MDD (Chen, Wang, et al., 2023; Semkovska et al., 2019), schizophrenia, addictive disorders, post-traumatic stress disorder, and stroke (for a review, see Friedman & Robbins, 2022). Playing role in adaptive and goal-oriented behavior, EFs have a critical role in initiating, planning, organizing everyday activities and flexibly adapting to the situation as needed (Kimbarow, 2019). Further emphasizing their importance, EFs are believed to support the cognitive regulation of emotion also indicated by an overlap of brain activation during these processes (Buhle et al., 2014; L. Chen, Oei, et al., 2023; Friedman & Robbins, 2022). Executive dysfunction has been linked to emotional processing difficulties in healthy participants (Faustino & Fonseca, 2023) and psychosocial functioning in individuals with depression (Albermann et al., 2023).

EFs also represent a good cognitive target for NIBS because of their strong association with the prefrontal cortex, an easy-to-reach target with a key role in integrative processes. Having rich functional and structural connectivity to cortical and subcortical structures, the dorsolateral prefrontal cortex (DLPFC) has been one of the most frequently targeted brain regions for NIBS (Lefaucheur et al., 2020). Of note, cognitive functions, especially as complex as EFs, are realized by the interplay of several nodes organized into interacting brain networks (Fan et al., 2003; Gruber & Goschke, 2004) the targeting of which may give further insight into the neural mechanisms underlying executive function. However,

a large body of evidence suggests that the DLPFC plays an essential role in realizing high-level information processing and exerting control. Activation in the DLPFC and associated brain circuits have been linked to response inhibition, working memory, emotion regulation, and other higher-order cognitive processes (Panikratova et al., 2020).

Cognitive impairment is now viewed as a core feature of MDD which may involve impaired EFs (especially working memory), attention, memory, and psychomotor speed (Perini et al., 2019). Impaired cognitive performance can be present in subclinical depression indicating an underlying pre-existing vulnerability (Malekizadeh et al., 2023), can persist even after remission from a depressive episode and can deteriorate following each further episode (L. Chen, Wang, et al., 2023; Hammar et al., 2022; Must et al., 2005; Semkovska et al., 2019). Executive dysfunction, specifically, seems to be stably present in MDD and may be related to psychological and psychosocial functioning problems (Albermann et al., 2023; Faustino & Fonseca, 2023; Pizzagalli & Roberts, 2022). The disruption of working memory, a subcomponent of EFs, has been associated with impaired decision making in MDD (Pizzagalli & Roberts, 2022). Moreover, reduced subjective quality of life was associated with lower executive function (Cotrena et al., 2016; Knight et al., 2020) further underlying the need for effective treatment options. Taken together, MDD is a widespread and debilitating disorder with global burden of disability (Vos et al., 2020) and increased functional impairment (Pan et al., 2019) that may partly stem from cognitive deficit. Cognition, and especially EF, may serve as a target for NIBS as an early intervention and at the same time is also an important target in chronic MDD.

The prefrontal cortices have been strongly linked to the pathomechanism of MDD. Abnormal structural and functional alterations of the DLPFC have been demonstrated and linked to cognitive impairment, negative processing bias, anhedonia, and decision making (Pizzagalli & Roberts, 2022). A consistently reported alteration in MDD that has affected the development of NIBS therapy protocols is the rightward lateralization of the prefrontal cortices observed primarily in functional measures of cortical excitability, activation, metabolism, and EEG measures of the alpha frequency band activity (Cotovio et al., 2022; Greco et al., 2021; Grünewald et al., 2018; Hecht, 2010). A hypoactive left DLPFC versus a hyperactive right DLPFC is in line with the approach-withdrawal models of MDD suggesting that approach behavior is inhibited, while greater right activation is in association with avoidance motivation (Henriques & Davidson, 1991; Kelley et al., 2017).

Functional alterations and structural abnormalities may both contribute to the clinical picture of MDD (Dai et al., 2019). Indeed, thicker cortical volume has been identified in the

frontal, insular and temporal regions on a sample of 2148 MDD patients compared to healthy individuals (Schmaal et al., 2017). Structural asymmetry within the white (Ran et al., 2020) and gray matter has also been suggested (Gray et al., 2020; Liu et al., 2016). A recent analysis using methods based on regions of interest, on the other hand, has concluded that gray matter volume shows no lateralization in a large sample of MDD patients (de Kovel et al., 2019; Kong et al., 2020). However, this does not exclude the possibility of structural asymmetry in specific subgroups and/or regions of interest and is still not to be rejected beyond all doubt. Voxel-based may provide higher spatial resolution eliminating the inherent bias of using pre-defined regions of interest; hence, may support the rationale of current NIBS treatment protocols or identify novel target regions (see **Study II**). Additionally, while functional asymmetry has been linked to key aspects of MDD such as suicidal behavior and cognitive symptoms (Dae-Yun et al., 2021; Park et al., 2019), and gray matter volume asymmetry of the frontal regions has correlated with depressive symptoms in a study using regions of interest-based calculations (Liu et al., 2016; Wang et al., 2023). Findings on structural asymmetry has not been investigated in relation to cognitive deficit (i.e., performance on a task measuring executive function), which again, has a high prevalence and severe impact on the quality of life of patients with MDD (Semkovska et al., 2019).

rTMS to modulate executive functions

Considering the above-described cognitive impairments in MDD and the fact that rTMS protocols have been first introduced to manage depressive symptoms in treatment-resistant MDD, exploring their impact on the cognitive function of patients with MDD is only reasonable. Nevertheless, only a small portion of studies have addressed whether rTMS can improve cognitive function in MDD. In healthy individuals, even a single session of rTMS has been found to improve performance on a range of cognitive tasks by systematic reviews and meta-analyses (Ngetich et al., 2020; Patel et al., 2020; Xu et al., 2023). Moreover, in healthy individuals, rTMS has also been suggested to alter the cognitive function-related brain activity patterns (e.g., neural efficiency, EEG power, and cortical reactivity) that are the most commonly affected in MDD (Chung, Rogasch, Hoy, & Fitzgerald, 2018; Chung, Rogasch, Hoy, Sullivan, et al., 2018; Curtin et al., 2019; Hoy et al., 2016; Xu et al., 2013).

Translating results from a healthy sample to a clinical setting, however, is often more complex. Firstly, structural and functional alterations have been reported that distinguish MDD patients from healthy controls (Pilmeyer et al., 2022; Schmaal et al., 2020). In MDD, NIBS has been suggested to exert its effect by normalizing some of these alterations implying

that some of the mechanisms of action may differ from what is observed in healthy participants. Secondly, studies involving healthy volunteers as compared to MDD patients often differ in terms of stimulation intensity and number of sessions (Rossi et al., 2021). Comparability is limited even within studies involving MDD patients due to the high variability between study design elements (e.g., inclusion criteria, stimulation parameters, coil type, target region, and outcome measures). Hence, particular attention must be given to these differences when interpreting the results. Finally, some protocols are specifically designed to target the hypothesized brain abnormalities in MDD, which limit the application on healthy participants (e.g., bilateral rTMS and TBS targeting the DLPFC).

Bilateral rTMS over the DLPFC in MDD (where cTBS and iTBS are applied sequentially to the right and left prefrontal cortices, respectively) is intended to reduce the lateralization observed in various measures, including frontal alpha asymmetry (Greco et al., 2021), cortical excitability (Cotovio et al., 2022), functional connectivity, and structural lateralization (Gray et al., 2020; Ran et al., 2020). In terms of antidepressant effects, bilateral rTMS protocols have been found comparable to unilateral stimulation and superior to sham rTMS (Berlim et al., 2013, 2017; Brunoni et al., 2017; Chen et al., 2014; Cheng et al., 2016; Eleméry et al., 2019; O'Reardon et al., 2007). Nonetheless, while a number of meta-analyses suggest that unilateral rTMS treatment is associated with a small to moderate level of cognitive enhancement affecting EFs, attention (Begemann et al., 2020; Iimori et al., 2019; Mutz & Kiebs, 2023), and psychomotor speed (Martin et al., 2017), most studies have neglected to concomitantly assess cognitive changes along with the antidepressant effects of bilateral stimulation targeting the DLPFC. This is a caveat because bilateral stimulation (even if seemingly not superior to unilateral HF-TMS over the left DLPFC in terms of antidepressant effects) (Chen et al., 2014) may exert a different effect on cognition than unilateral rTMS.

TBS has lately been favored over rTMS for research and used in combination with neuroimaging, (e.g., Chou et al., 2023; Stöhrmann et al., 2023) because of the reduced stimulation duration and stable antidepressant effect. TBS also seems to be a good option to target the enhancement of cognition as it is believed to operate with theta-gamma coupling, a cross-frequency coupling involved in several cognitive processes (Brooks et al., 2020). Bilateral TBS, in particular, was considered a potentially even more effective approach than the unilateral counterparts at the conceptualization of our study (**Study I**) (Li et al., 2014; Mutz et al., 2019).

Only a handful of studies have investigated rTMS effects on cognition, and the results are still preliminary. When aiming to modulate EFs, unilateral iTBS over the left DLPFC, rather than bilateral TBS has been suggested based on results of the Wisconsin Card Sorting Test (Cheng et al., 2016). This can suggest that EF components other than abstract reasoning and cognitive flexibility may be more reasonable to target using bilateral TBS. More stable findings on the working memory domain in healthy individuals and patients with neuropsychiatric disorders may also underpin this idea (Demirtas-Tatlidede et al., 2013; Lowe et al., 2018). Another aspect of EFs affected in MDD is inhibition, which is believed to underlie emotion regulation deficit and rumination (Monnart et al., 2016). Preliminary evidence suggests that rTMS may improve interference control on the flanker and Stroop tasks in MDD and cognitive improvement correlated with the amelioration of depressive symptoms (Corlier et al., 2020; Cristancho et al., 2020).

Strikingly, of all studies identified by a recent review exclusively focusing on bilateral TBS for depressive symptoms, only a third mentioned the cognitive symptoms of MDD, and even a smaller portion had assessed and reported cognitive changes (Li et al., 2014; Qin et al., 2023). This is also worthy of noting because other pharmacological and non-pharmacological methods, such as electroconvulsive therapy (ECT), have been associated with the (at least temporary) detriment of cognitive functions, including EFs and memory (Lechevallier-Michel et al., 2005; Ren et al., 2014) calling for a more thorough investigation of the cognitive effects of techniques like NIBS.

To sum up, exploring the cognitive effects of rTMS in MDD may sound straightforward, considering its antidepressant efficacy; however, cognitive changes have scarcely been investigated along with changes in affective symptoms. Holistic assessment is important not only because of the common co-occurring cognitive impairment in MDD but also to rule out potential adverse effects of TMS like those associated with ECT. TBS is a relatively novel form of rTMS with the potential to decrease stimulation time without giving up the efficacy to mitigate depressive symptoms (Blumberger et al., 2018). Bilateral TBS, in particular, is a technique specifically developed for MDD with promising results, especially in the working memory domain (Rostami et al., 2022; Scho et al., 2019). However, there are inconsistencies (Cheng et al., 2016), and several factors limiting the generalizability of results. One of the studies in the present thesis focused on the effects of bilateral TBS on working memory and attention (including executive attention) in a sample of medicated MDD patients using conventional neurocognitive tests.

tDCS to modulate executive functions

tDCS, regarded as a portable, easily applicable, and more economical alternative to TMS has been extensively tested to manage various cognitive symptoms in disorders including major depressive disorder (Martin et al., 2018), dementia (Vacas et al., 2019), autism spectrum disorder (García-González et al., 2021), stroke (Elsner et al., 2020), and in healthy individuals (Figeys et al., 2021; Habich et al., 2021). Cognitive functions ranging from perception (Lavezzi et al., 2022) to EFs (Huo et al., 2018; Imburgio & Orr, 2018) have been involved in the studies. However, synthesizing the results of the considerable research efforts has not yet yielded clear evidence-based utilization of tDCS. Consequently, a conventional research design in tDCS research that involves the investigation of healthy adults within a single stimulation session has been questioned (Horvath et al., 2015).

The most reliable cognitive domain-specific modulation of tDCS over the DLPFC has been linked to the working memory domain in healthy individuals (Brunoni & Vanderhasselt, 2014; Müller et al., 2022; Pergher et al., 2022). However, a recent review of meta-analyses has pointed towards anodal tDCS over the DLPFC to improve aspects of EF other than working memory in healthy individuals and neuropsychiatric patients, including response inhibition in the latter (Farhat et al., 2020). Response inhibition and interference control are essential to inhibit automatic reactions and resolve interference due to distracting or irrelevant stimuli which is key to adaptive behavior (Wöstmann et al., 2013). These processes, in part, rely on a similar neural background. Among other regions (for a review, see Ridderinkhof et al., 2021; Steele et al., 2013), the bilateral DLPFC has been linked to performance on the flanker and Stroop tasks (both assessing interference control), especially when implementing interference resolution (Luks et al., 2010; Vanderhasselt et al., 2009). The DLPFC has also been found to be active during the Go/No-Go task, with rightward lateralization (Nee et al., 2007; Steele et al., 2013). Another region reliably active during these tasks is the fronto-medial and the anterior cingulate cortex (Cieslik et al., 2015; Luks et al., 2010; Steele et al., 2013) which seems to engage with the DLPFC and play a role in conflict monitoring (Ridderinkhof et al., 2021).

Currently, there is ongoing debate about whether tDCS can modulate response inhibition and interference control in healthy participants (Frings et al., 2018). Contradicting findings have ranged from tDCS effects as expected (i.e., cathodal tDCS exerting inhibitory and anodal tDCS exerting facilitatory effect) (Bellaïche et al., 2013; Dubreuil-Vall et al., 2019; Jeon et al., 2018; Lu et al., 2021; Reinhart & Woodman, 2014; Zmigrod et al., 2016)

through no effect (Hussey et al., 2020; Lema et al., 2021; Perrotta et al., 2021) to changes in unexpected ways (e.g., cathodal tDCS facilitating performance) (Adelhöfer et al., 2021). Anodal tDCS over the DLPFC resulted in improved interference control in some cases (Dubreuil-Vall et al., 2019; Jeon & Han, 2012; Karuza et al., 2016), but not in all (Hussey et al., 2020; Lema et al., 2021). A recent review has indicated similar results for response inhibition (Friehs et al., 2021). Cathodal tDCS over the DLPFC has been reported to aggravate the interference effect (Zmigrod et al., 2016), but not in another (Karuza et al., 2016). Using a fronto-medial (FM) montage has also yielded inconclusive results despite electrophysiological changes attributed to tDCS (Adelhöfer et al., 2021; Bellaïche et al., 2013; Miler et al., 2018; Reinhart & Woodman, 2014).

Interestingly, electrode montages targeting the DLPFC alone and fronto-medial montages have not been directly compared. However, this could corroborate the idea that specific aspects of interference control (such as error monitoring associated with FM structures versus interference resolution linked to the DLPFC) may be selectively modulated. Likewise, it is possible that response inhibition or interference control are not affected in the same manner following DLPFC or FM tDCS. It has been found that stimulation of the right DLPFC, for instance, selectively affected performance on the flanker task while keeping performance on the Simon task unaffected (Zmigrod et al., 2016). It is also important to confirm or overrule the polarity-dependent mechanism of action of tDCS as it has not been reliably reported in all studies (Karuza et al., 2016). Investigation of both cathodal and anodal tDCS within a single study, preferably in a crossover design with an adequate control is needed to achieve this. Moreover, by replicating some of the previously reported results, we can also increase the robustness.

To summarize, tDCS effects are highly variable and depend on the study design, research goal, and stimulation parameters. The literature on tDCS effects has only yielded a small effect on working memory when targeting the DLPFC. Results on other domains, such as response inhibition and interference control, have been inconclusive despite the DLPFC being involved in these processes as well (Cieslik et al., 2015; Luks et al., 2010; Steele et al., 2013). Another typical target region believed to be involved in implementing response inhibition and interference control is the FM region (Cieslik et al., 2015; Luks et al., 2010; Steele et al., 2013). However, tDCS over the DLPFC and the FM regions have not been systematically compared before. Moreover, due to the variability in findings, even classical assumptions of tDCS have been challenged, such as the polarity-dependent mechanism of action of tDCS in the cognitive domain (Jacobson et al., 2012; Karuza et al., 2016). Although

some concerns have been addressed (Filmer et al., 2020), tDCS effects seem to be more sensitive to slight changes in stimulation and design parameters than TMS (Holczer et al., 2020), making it more pressing to systematically compare stimulation parameters and improving the reporting of trials. These efforts can elicit optimal constellations of parameter settings and a clinically meaningful effect for tDCS.

II. AIMS AND OBJECTIVES

The thesis presents two studies to explore the effects of two NIBS techniques, namely TBS and tDCS, on components of executive function in MDD and healthy individuals. A third study was conducted to examine cortical asymmetry, a feature of MDD that has been taken as a base for NIBS protocols (Table 1). While it seems easy to answer whether NIBS can alter cognitive function, it has been challenging to conclude from the existing literature due to the abovementioned limitations. Our goal was to investigate if established protocols of NIBS can be used to modulate cognitive functions such as working memory, response inhibition, and interference control in healthy individuals and patients with MDD.

In **Study I**, we decided to investigate the cognitive effects of TBS in MDD. Considering its established antidepressant efficacy, only a surprisingly small portion of studies have broadened the spectrum of assessment to cognitive symptoms. We asked the following questions: (1) Can we replicate reports of antidepressant efficacy of bilateral TBS?, (2) Can bilateral TBS alter attention measured by the 1-back task? (2) Can bilateral TBS alter working memory performance on the 2- and 3-back tasks?, and finally, (4) Can bilateral TBS modify performance on the Attention Network Task (measuring various aspects of attention and interference control)? In Study I, ten sessions of active or sham TBS were delivered bilaterally over the right and left DLPFC to patients diagnosed with MDD. Before and after the intervention, participants completed the 1-, 2-, and 3-back tasks along with the Attention Network Task (ANT), and the Hamilton Depression Rating Scale (HDRS) was administered. We compared the results of the active and sham groups using frequentist and Bayesian statistics. The study goes beyond previous studies as bilateral TBS has mostly been investigated for its antidepressant effects, neglecting the possibility of adverse cognitive effects as well as potential improvements in the executive function and attention domain.

This was followed by **Study II**, where we examined voxel-based cortical asymmetry in association with depressive symptom severity and EF to better understand the cerebral pathology in MDD on which some NIBS protocols are based. We were curious about (1) which group of voxels (if any) show gray matter asymmetry in MDD patients and (2) if clinical symptoms or EFs are associated with gray matter asymmetry on the voxel level. We ran voxel-wise gray matter asymmetry calculation on the data of MDD patients, including scores on the Hamilton Depression Rating Scale, the 4-item version of the Beck Hopelessness Scale (BHS), and the 1-, 2-, and 3-back tasks. The novelty of our study was the use of voxel-

based asymmetry measures instead of pre-defined regions of interest to provide a higher spatial resolution that can even outline subregions within a structure and correlate the results with both depressive and cognitive symptoms.

Finally, **Study III** aimed to systematically compare the two commonly used tDCS electrode montages, one targeting the DLPFC and the other the FM cortices across both anodal, cathodal, and sham stimulation. The main research question was whether tDCS can influence indices of response inhibition and interference control (correct response latency, interference scores, or congruency sequence effect). To answer this question, we randomized healthy participants into groups based on electrode montage; then, they randomly underwent three sessions of tDCS while performing a combined flanker Go/No-Go task. This study was the first to systematically compare conventional DLPFC montage to an FM montage. Moreover, we assessed the effects of both anodal and cathodal tDCS on the same participants, aiming to include the effect of polarity.

Table 1. The most relevant information of the studies comprising the thesis.

	Study I
The main question	How does bilateral TBS (that is expected to mitigate depressive symptoms) influence executive function in major depressive disorder?
Research question(s)	Can we replicate reports of the antidepressant efficacy of bilateral TBS? Can bilateral TBS alter attention measured by the 1-back task? Can bilateral TBS alter working memory performance on the 2 and 3-back tasks? Can bilateral TBS modify performance on the Attention Network Task?
Methods	Pre-and post-stimulation assessment of the n-back and the ANT task, and depression severity of the Hamilton Depression Rating Scale after ten daily sessions of bilateral TBS over the left and right DLPFC
Primary contributions	Holistic exploration of the antidepressant and cognitive effects of bilateral TBS
	Study II
The main question	Is there voxel-based cortical asymmetry in MDD, and is it associated with depressive symptoms or executive function that can be targeted in future MDD therapy?
Research question(s)	Is there voxel-based gray matter asymmetry in MDD? If yes, does it correlate with the severity of depression or performance on the 1-, 2-, or 3-back tasks?
Methods	Running voxel-based gray matter asymmetry calculation for high-resolution T1-weighted magnetic resonance images Correlating the results with depression severity on the Hamilton Depression Rating Scale, the Beck Hopelessness Scale, and performance on the 1-, 2- and 3-back tasks
Primary contributions	Application of a method of higher spatial resolution to explore the cortical asymmetry in MDD and correlate it with depressive symptoms and executive function
	Study III
The main question	How does tDCS delivered in two electrode montages targeting the prefrontal and fronto-medial areas affect interference control and response inhibition?
Research question(s)	Can tDCS influence reaction times, interference effect, or congruency sequence effect in a combined flanker Go/No-Go task? Can tDCS influence the congruency sequence effect in a combined flanker Go/No-Go task? Can tDCS influence accuracy in a combined flanker Go/No-Go task?
Methods	Assessment using a combined flanker Go/No-Go task during anodal, cathodal, and sham stimulation delivered in a conventional DLFPC or a fronto-medial montage
Primary contributions	Systematic comparison of anodal, cathodal, and sham tDCS effects on response inhibition and interference control in two electrode montages

III. METHODS AND MATERIALS

Study I – Bilateral TBS in MDD

Participants

Overall, 25 patients with a diagnosis of unipolar MDD were recruited in this study. We used the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria and the Structured Clinical Interview for DSM-IV Axis I disorders for the diagnosis of unipolar MDD. The exclusion criteria included having any comorbid major psychiatric disorder, a history of neurological disorders, or not meeting the TMS safety restrictions (e.g., metallic/electronic implants in close contact with TMS coil). All participants were on stable medication throughout the experiment and for at least two weeks before the first session. Participants signed an informed consent form before the start of the experiment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (University of Szeged). Data gathered from twenty participants were included in the final analysis of complete cases (M_{age} = 50.27 years, SD (standard deviation) = 13.24 years, 5 male, rMT = 60.60% of the maximum stimulator output). Three participants from the sham group withdrew participation, and another was excluded due to changes in pharmacotherapy. One participant from the active TBS group was excluded because of health concerns unrelated to the experiment.

Experimental design

Participants took part in ten sessions of TBS (see Fig. 1 for the experimental design). Before the commencement of the experiment, an anatomical magnetic resonance imaging (MRI) scan was acquired, which was used for neuronavigation. Additionally, the workday before the first and after the last stimulation sessions (pre-TBS and post-TBS), we assessed the cognitive and affective symptoms using the 21-item Hamilton Depression Rating Scale (HDRS), three levels of the n-back task, and the Attention Network Task (ANT). The order of these measurements was randomized for each subject. During this session, the resting motor threshold was also determined. Furthermore, a computer-generated randomization took place on the day of pre-TBS testing to determine whether participants received active or sham TBS. Participants were blind to the type of stimulation they received.

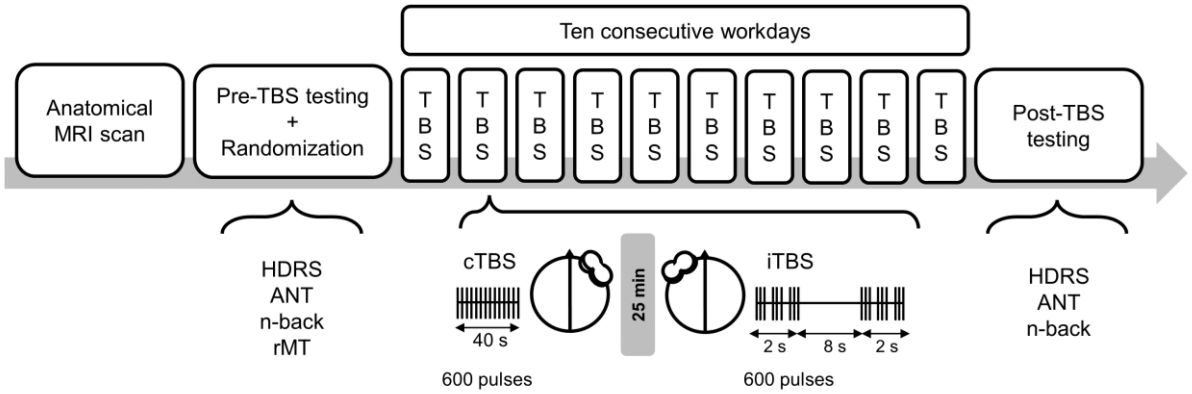

Figure 1. Experimental design of Study I. Following the acquisition of anatomical MRI images, participants were randomized into active or sham TBS groups. Participants underwent the pre-TBS testing, where various cognitive assessments were taken, and the resting motor threshold was determined. Then, ten consecutive workdays of TBS followed. After the last session, post-TBS assessment took place. The protocol for the given session is presented under the curly braces. TBS sessions were identical.

Transcranial magnetic stimulation and neuronavigation

Anatomical T1-weighted MRI scan was acquired from each participant using a 1.5T GE Signa Excite HDxt scanner (Milwaukee, WI, USA) with the following setup: 3D IR-FSPGR - TR/TE/TI: 10.3/4.1/450 ms; flip angle: 15; ASSET: 2, FOV: 25 _ 25 cm; matrix: 256 _ 256; slice thickness: 1 mm. Individual 3D brain models, based on the scans, were created to localize the target area localized at Brodmann 9/46 more precisely. Coil positioning was supported by a TMS Neuronavigator (Brain Innovation, Maastricht, the Netherlands) with an ultrasound CMS20 Measuring System (Zebris GmbH, Tübingen, Germany). On the day of the baseline testing, the resting motor threshold was determined with the visualization method (Pridmore et al., 1998).

For all participants during each session, cTBS over the right DLPFC was delivered first, and (following a 25 min long break) iTBS was applied over the left DLPFC (Fig. 1). TBS pulses were generated by a Magstim Rapid2 stimulator with a D702 70 mm figure-of-eight coil (The Magstim Company Ltd, Whitland, Wales, UK). TBS parameters we chose are frequently used and were based on Huang et al., with cTBS containing uninterrupted triplets of pulses at 50 Hz for 40 s and iTBS consisting of trains of 3 at 50 Hz for 2 ms in every 10 s for 190 s (Huang et al., 2005). The intensity was set at 30% of the maximal stimulator output for all participants. Sham TBS was identical to the active stimulation, but a plastic block elevated the coil from the scalp by 4 cm.

Outcome measures

The change of depressive symptoms was measured by the 21-item Hamilton Depression Rating Scale. Working memory was tested with three levels of the n-back task (1-, 2-, 3-back) using PsychoPy v1.82.01 (Fig. 2, Panel A). Randomly chosen capital letters taken from a set of stimuli (A, C, E, I, K, L, S, O, R, T, U) were presented successively on the screen for 1500 ms (interstimulus interval: 500 ms). Participants had to press a button (spacebar) when the letter appearing on the screen was identical to the one presented one, two, or three trials before (1-back, 2-back, 3-back tasks, respectively). Of all stimuli presented, 20% were target stimuli to which a button press was expected. Participants were presented a total of 100 trials at each level.

Attention was measured using the Attention Network Task (ANT) (Fig. 2, Panel B). ANT can be considered a cued flanker task, which consisted of a fixation cross (presented for a random duration between 400 and 1600 ms), a cue condition (100 ms), and a stimulus presentation (1700 ms or response time). Three types of cues were possible: (1) *spatial cue,* indicating the position where the target stimulus was presented (2) *center cue,* appearing in the position of the fixation cross (3) *double cue,* presented both above and below the fixation cross. If *no cue* appeared or the cue had already disappeared, the fixation cross was reintroduced for 400 ms. The stimulus presentation included a target arrow pointing to the left or right surrounded by two flanking arrows from left and right presented for 1700 ms or until a response. Participants were instructed to respond to the direction of the target arrow by pressing the corresponding arrow button on the keyboard. There were three potential scenarios: (1) in the *neutral* condition, four lines were displayed along with the target arrow (2) the *congruent* condition contained five arrows pointing to the same direction (3) the *incongruent* condition consisted of four arrows pointing to the same direction while the target arrow was pointing to the opposite way. Overall, a trial lasted for 3500 ms. If there was time left after a response, a blank screen was presented until the end of the trial. A total of 300 trials were presented, comprising three blocks of 96 trials and 24 practice trials.

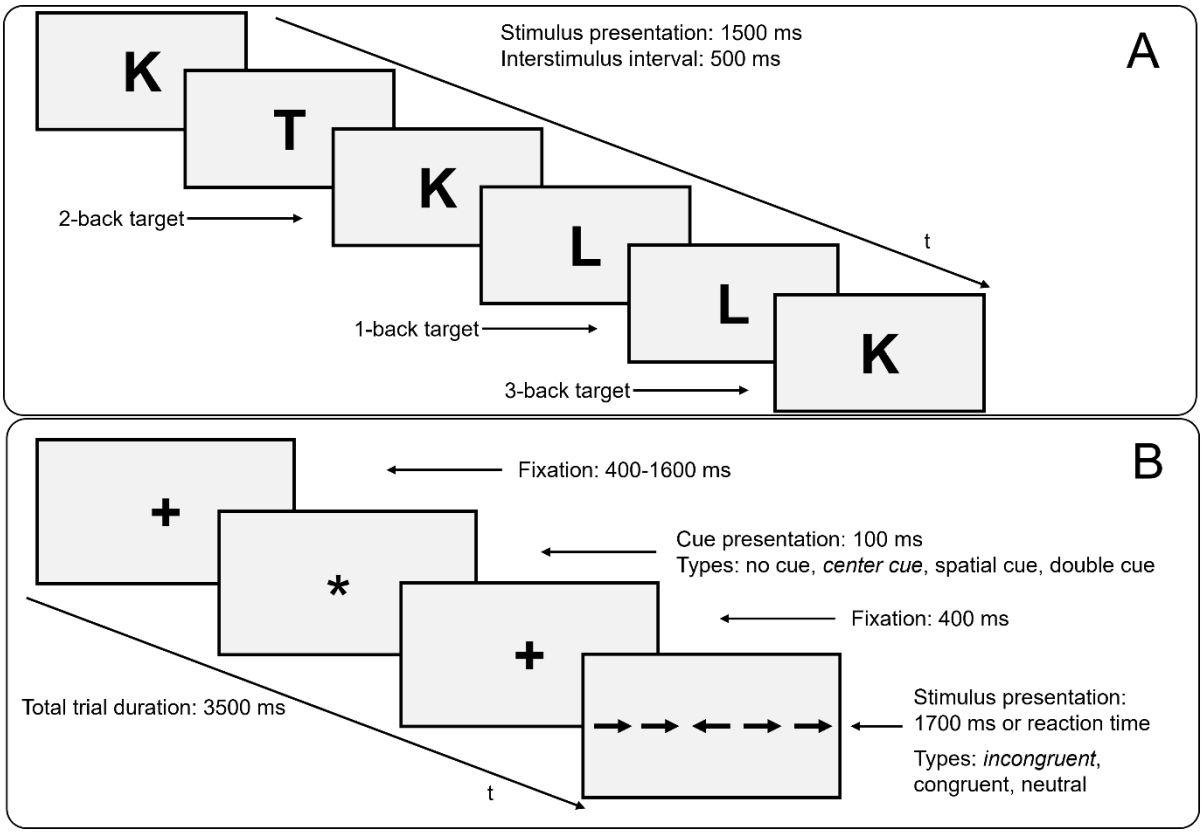

Figure 2. Design of the tasks used in Study I. **Panel A** shows the n-back task. Participants were instructed to press a button if the letter presented is identical to the letter presented one, two, or three trials earlier (1-, 2-, and 3-back tasks, respectively). **Panel B** shows the ANT task. Participants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

Statistical analysis

Statistical analysis was conducted using SPSS version 24 (IBM SPSS Statistics for Windows, 2016). Baseline and post-TBS HDRS ($HDRS_{pre\text{-}TBS}$ – $HDRS_{post\text{-}TBS}$) were subtracted from each other to create a difference score. Difference scores in the active and sham groups were compared using an independent samples t-test. For effect size, Cohen's *d* was reported. An analysis of covariance (ANCOVA) was also run with pre-TBS HDRS score used as a covariate to control for their influence on the results.

For the n-back task, accuracy and reaction time were analyzed separately. Discriminability indices (*d'* scores) were calculated from the accuracy data. *d'* score was defined as the subtraction of the hit rate (correct response to a target) and the false alarm rate (incorrect responses to non-targets) expressed in z-scores (Haatveit et al., 2010):

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}).$$

Separate 2 × 2 mixed analyses of variance (ANOVAs) were calculated for the 1-back and the mean of the 2-back and 3-back tasks. Effect sizes for all ANOVAs were estimated using partial eta squared (η_p^2), and Bonferroni correction for multiple comparisons was

calculated. Time (pre-TBS vs. post-TBS) served as a within-subject factor, and the type of Stimulation (active vs. sham) as a between-subject factor.

For the ANT, median RTs of the correct trials were used to formulate three indices also correcting to the relevant baseline RT as follows:

$$\text{alerting attention ratio} = RT_{\text{double cue}} - RT_{\text{no cue}} / RT_{\text{no cue}}$$

$$\text{orienting attention ratio} = RT_{\text{spatial cue}} - RT_{\text{center cue}} / RT_{\text{center cue}}$$

$$\text{executive attention ratio} = RT_{\text{incongruent}} - RT_{\text{congruent}} / RT_{\text{congruent}}$$

We used median RTs across all cue and stimulus conditions to calculate an estimate for psychomotor speed. For the latter, as well as for the three indices of attention, separate 2 × 2 mixed analyses of variance (ANOVAs) were calculated. Time (pre-TBS vs. post-TBS) served as a within-subject factor, and the type of Stimulation (active vs. sham) as a between-subject factor.

Bayesian ANOVAs were conducted for both the n-back and ANT using JASP (0.12.2.0 version) (JASP Team, 2020) with default priors to supplement the frequentist analysis. Our aim was to quantify the relative evidence in favor of the null (H_0) or alternative hypothesis (H_1) by calculating the Bayes Factor (BF). The BF_{10} reported is to be considered a continuous measure; however, there is a classification scheme: $BF_{10}<0.1$ indicates strong evidence for H_0, a value between 0.1 and 0.33 indicates substantial evidence for H_0, while a value between 0.33 and 1 indicates anecdotal evidence for H_0. Anecdotal evidence supports H_1 if BF_{10} is between 1 and 3, a value between 3 and 10 indicates substantial evidence for H_1, and $BF_{10}>10$ indicates strong evidence for H_1 (Wagenmakers et al., 2018). We also calculated and reported the inclusion Bayes Factor (BF_{incl}) across matched models.

Study II – Gray matter asymmetry in MDD

Participants

A total of 17 patients diagnosed with unipolar MDD were recruited in this study (M_{age} = 49.78 years, SD = 13.13 years, 3 male). The DSM-IV criteria and the Structured Clinical Interview for DSM-IV Axis I disorders were used for the diagnosis. Participants were required to be on stable medication for at least two weeks before the first session and signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (University of Szeged).

Procedure and data acquisition

Participants underwent magnetic resonance imaging (MRI) A 1.5 T GE Signa Excite HDxt MR Scanner (GE Healthcare, Chalfont St. Giles, UK) was used for data acquisition. Three-dimensional high-resolution T1-weighted anatomical images were acquired (3D spoiled gradient echo images with inversion recovery (3D FSPGR IR): echo time [TE]: 4.1 ms; repetition time [TR]: 10.276 ms; matrix: 256×256, field of view [FOV]: 25×25 cm, flip angle: 15◦, in-plane resolution: 1×1 mm, slice thickness: 1 mm).

Outcome measures

Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale. The short, 4-item version of the Beck Hopelessness Scale was also administered to explore negative expectations and hopelessness (Beck and Steer, 1988). In addition, three levels of the n-back task (1-, as well as the 2-, and 3-back) were used to assess attention and working memory, respectively. The task was identical to the one used in Study I. Briefly, capital letters were randomly presented on the screen for 1500 ms (interstimulus interval: 500 ms). Participants were asked to press a button (spacebar) when the letter appearing on the screen was identical to the one presented one, two, or three trials before (1-back, 2-back, 3-back tasks, respectively). Twenty percent of all stimuli were target stimuli to which a button press was expected. A total of 100 trials were presented at each level.

Statistical analysis

d' scores were calculated from the accuracy data of the n-back task. *d'* was defined as follows:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}).$$

i.e., the subtraction of the hit rate (correct response to a target) and the false alarm rate (incorrect responses to non-targets) expressed in z-scores (Haatveit et al., 2010).

The imaging data analysis was carried out using the VBM8 Toolbox implemented in the Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Center for Neuroimaging, London, UK) software. A symmetric gray matter skeleton containing gray matter asymmetry index values for each voxel was created using a step-by-step guideline (Kurth et al., 2015). After brain extraction, images were segmented into gray matter, white matter, and cerebrospinal fluid. Gray and white matter segments were flipped along the midline, and then, symmetric Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) template was created from the original and flipped gray and white matter

segments (Ashburner, 2007). Next, images were registered to the mean DARTEL template and averaged. Afterward, calculations were limited to the right hemisphere by creating a binarized right hemisphere mask in the symmetric template space. The asymmetry index was calculated using the following equation:

$$\text{Asymmetry index} = \left(\frac{(i1 - i2)}{(i1 + i2) * 0.5}\right) * \text{i3}$$

where i1 = warped original gray matter segment; i2 = warped flipped gray matter segment, and i3 = binarized right-hemisphere mask image. The resulting asymmetry index should be interpreted as follows: positive values indicate rightward asymmetry, while negative values refer to a more pronounced leftward asymmetry. The generated images were spatially smoothed using a smoothing kernel of 8 mm.

A general linear model was performed using the FMRIB Software Library (https://fsl.fmrib.ox.ac. uk/fsl/fslwiki/GLM). The bidirectional associations were tested using the positive and negative contrasts which were calculated for the HDRS, BHS, and the *d'* scores of the 1-, 2-, and 3-back tasks. Age and sex were entered as covariates. A non-parametric permutation test was carried out. For thresholding, a threshold-free cluster enhancement technique was used with a threshold at $p < 0.05$. A family-wise error rate (FWE) correction was used to correct for multiple comparisons. The design matrices included age, sex, HDRS, BHS, and *d'* scores for each subject. Results were visualized as an overlay on the MNI152 2 mm standard brain (see Fig. 1 of Kocsis et al., 2021, Appendix II).

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

Participants

Overall, 40 healthy young adults were recruited in this study. The exclusion criteria included having any major psychiatric or neurological disorder, the use of any drugs affecting the function of the central nervous system, or not meeting the tDCS safety restrictions. An informed consent form was signed by all participants before the start of the experiment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (University of Szeged). In the final analysis, the data of thirty-eight participants were analyzed due to two drop-outs (M_{age} = 23.82 years, SD = 3.52 years, 14 male): one subject dropped out due to unavailability following the first (anodal) session, the other withdrew participation because of headache following the first (sham) session.

Experimental design

Participants took part in three tDCS sessions (anodal, cathodal, and sham) and were randomly assigned to one of two research groups (see Fig. 3 for the experimental design). tDCS was delivered to the left DLPFC (DLPFC Group) or the fronto-medial areas (FM Group). Randomization of group allocation and the order of the sessions took place at the beginning of each participant's first session using a computer-generated randomization. Participants were unaware of the type of stimulation they received. During the stimulation, participants completed a combined flanker Go-No/Go task. At the end of each session, participants were asked to complete a questionnaire regarding potential sensations and subjective effects of tDCS they could experience.

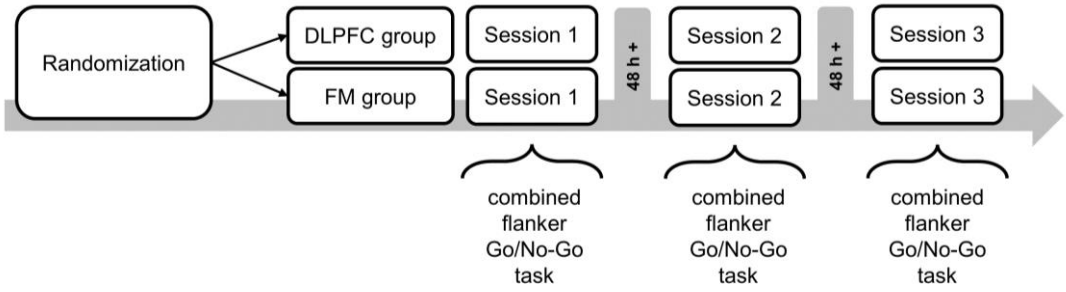

Figure 3. Experimental design of Study III. Participants were randomized into two groups based on electrode montage (DLPFC and FM group) and then underwent three sessions divided by at least 48 hours. During each session, anodal, cathodal, or sham stimulation was delivered in a random order, during which participants performed a combined flanker Go/No-Go task.

Transcranial direct current stimulation and simulation of electric fields

We performed a simulation of the current flow generated by tDCS beforehand (Fig. 4). We created three-dimensional head models with a finite element method using SimNIBS v3.2 with the 'Ernie' head model (Thielscher et al., 2015). The isotropic conductivities from the SimNIBS GUI were adopted. To localize the target area, we relied on the international 10–20 EEG localization system: for the DLPFC montage, the left DLPFC was localized as the F3 electrode position (position of the anode during anodal stimulation), and the contralateral supraorbital area as the Fp2. For the FM montage, electrodes were positioned over the AFz (position of the anode during anodal stimulation), and the Pz. The electrodes were reversed for cathodal stimulation.

Rubber electrodes covered in saline-soaked sponges of size 35 cm^2 were fixed on the head using plastic straps. tDCS was delivered using the Eldith DC Stimulator Plus (Neuro-Conn GmbH, Ilmenau, Germany). The current strength was set for 2 mA. The duration of the

stimulation was 20 minutes with 10 s of fade-in and fade-out for both groups. Sham stimulation was identical to active tDCS, except that the stimulation length was reduced to 30 s. The position of the anode and the reference electrode during sham stimulation was randomized and counterbalanced across groups.

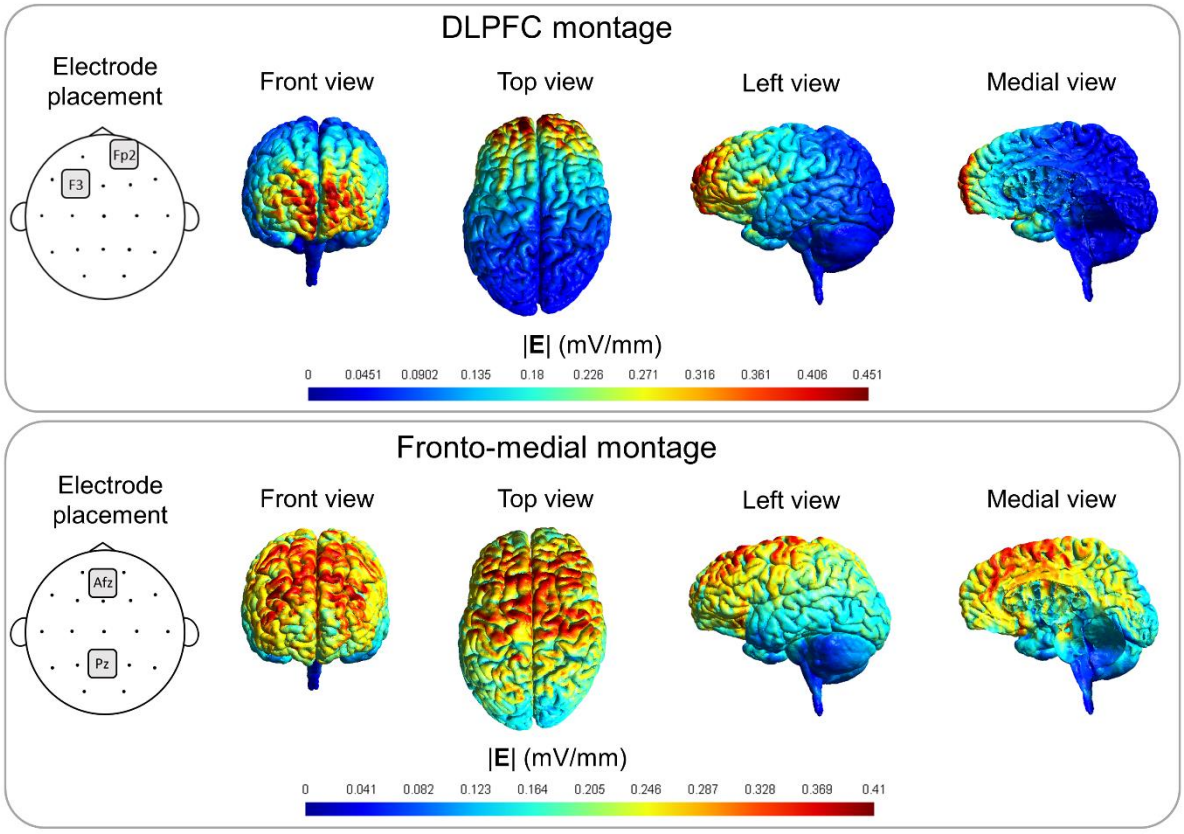

Figure 4. Simulation of normalized electric field distribution (|E|) for both montages. For anodal stimulation in the DLPFC group, the anode was placed over the F3 according to the international 10-20 EEG localization system, while the reference was positioned over the contralateral supraorbital area. For the anodal stimulation in the FM group, the anode was applied over the AFz and the reference electrode over the Pz. When applying cathodal stimulation, the position of the anode and the reference electrodes was reversed. Figure 2 of Holczer et al. (2023), see Appendix III.

Outcome measures

The combined flanker Go-No/Go task (Fig. 5) was presented using E-Prime version 2.0 (Schneider et al., 2002). The task consisted of a fixation cross presented for 500-1500 ms pseudorandomly. Then, five arrows pointing to the left or the right appeared on the screen presented for 1000 ms or until a response. Participants were instructed to respond to the direction of the middle (target) arrow by pressing the corresponding arrow button on the keyboard. Four trial types were possible, including: (1) *congruent* (surrounding stimuli trigger the same response as the target stimulus), (2) *incongruent* (surrounding stimuli trigger a different response as the target stimulus), (3) *neutral* (surrounding stimuli do not indicate

orientation), and (4) *no-go* trials (surrounding stimuli indicate response inhibition). In no-go trials, participants were instructed to withhold their response when " × " symbols surrounded the target stimulus. Six blocks of 96 trials and a 16 trial-long practice were presented for each participant. The order of the trials was randomized, with counterbalanced number of trials for each trial type. Participants could rest between blocks and continue the task at their own pace.

In addition to the cognitive task, participants filled out a self-reporting questionnaire as previously proposed by Brunoni and colleagues (2011). We specifically asked respondents regarding headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, and immediate mood changes. Participants rated their symptoms based on presence (4-point Likert scale with 1 = absent and 4 = severe) and certainty corresponding to whether sensations were related to tDCS according to the respondent (5-point scale with 1 = not related and 5 = definitely related).

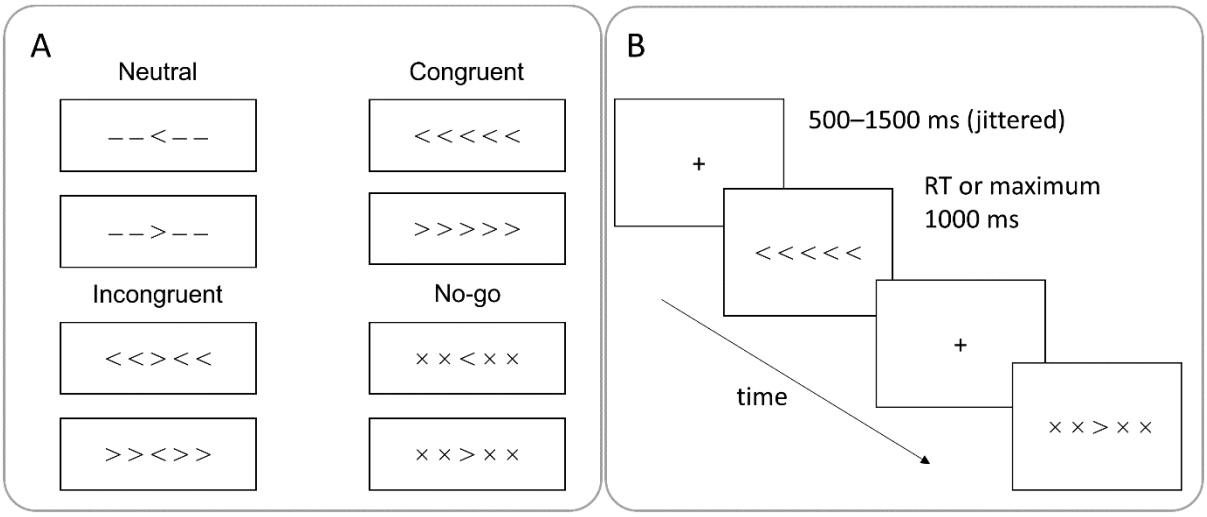

Figure 5. Design of the tasks used in Study III. Participants were instructed to press the left or right arrow button of the keyboard according to the direction of the target (middle) arrow. **Panel A** shows the possible trial types according to the characteristics of the flanking stimuli: congruent (flanking stimuli trigger the same response as the target stimulus), incongruent (flanking stimuli trigger the opposite response of the target stimulus), neutral (flanking stimuli do not indicate a direction), and no-go trials (flanking stimuli require response inhibition). **Panel B** shows the task flow of the combined flanker Go/No-Go task. Figure 1 of Holczer et al. (2023), see Appendix III.

Statistical analysis

Statistical analysis was conducted using JASP (version 0.17.2.1.). We analyzed the accuracy and reaction time collected from the combined flanker Go-No/Go task separately. A mixed model ANOVA was used to analyze the median reaction times of correct trials and accuracy. Greenhouse-Geisser correction was used if applicable for all ANOVAs. Montage (DLPFC, FM) served as a between-subject factor, while Stimulation Type (sham, anodal, cathodal) and Trial Type (neutral, congruent, incongruent) as within-subject factors. No-go

trials were not included in the RT analysis due to the lack of motor response but were used when accuracy was analyzed. From the RT data, interference effect was also calculated as follows: Interference effect = $RT_{incongruent} - RT_{congruent.}$ Then, 2 × 3 ANOVA was performed on the interference effect scores with montage (DLPFC, FM) as a between-subject factor and Stimulation Type (sham, anodal, cathodal) as a within-subject factor. The congruence sequence effect, i.e., the effect of previous trial congruency on trial n was also analyzed. For the calculation, erroneous trials, the first trials with no previous congruency, and trials preceded by neutral or Go/No-Go trials were removed. The congruency sequence effect was only defined for congruent and incongruent trials and not the Go/No-Go trials. A 2 × 3 × 2 × 2 ANOVA was conducted with Montage (DLPFC, FM) as a between-subject factor, and with Stimulation Type (sham, anodal, cathodal), Trial n Congruence (congruent, incongruent), and Trial n-1 Congruence (congruent, incongruent) as within-subject factors. Overall, four categories were possible: (1) congruent trials preceded by congruent trials (cC), (2) congruent trials preceded by incongruent trials (iC), (3) incongruent trials preceded by congruent trials (cI), and (4) incongruent trials preceded by incongruent trials (iI).

Additionally, each symptom of adverse effects was entered into a separate ANOVA where the Stimulation Type × Montage interaction was interpreted as an index of comparability between groups.

IV. RESULTS

Study I – Bilateral TBS in MDD

Can we replicate reports of the antidepressant efficacy of bilateral TBS?

The active and sham TBS group showed a difference as indicated by the independent samples t-test on the difference score of HDRS ($HDRS_{pre\text{-}TBS} - HDRS_{post\text{-}TBS}$), t, t_{18} = -2.522, p = .021, *Cohen's d* = -1.128 (Fig. 1, Panel A). A higher amelioration of HDRS scores was observed in participants receiving active TBS (mean ± SE scores: active group 8.2 ± 3.360; sham group 4.2 ± 1.172). Bayesian analysis suggested moderate evidence in favor of the H_1, BF_{10} = 3.028. The data was ~3 times more likely under the H_1 than under the H_0, signaling that bilateral TBS resulted in reduced depressive symptoms in the active group. This tendency remained intact even after controlling for baseline HDRS scores using an ANCOVA, $F_{1, 17}$ = 3.415, p = .082, η_p^2 = 0.167, BF_{incl} = 2.372. Bayesian model comparison also indicated that the best model only included the type of stimulation, but not the covariate, and still showed moderate evidence (BF_{10} = 3.028) for choosing this model over the null model (see Appendix I for more details).

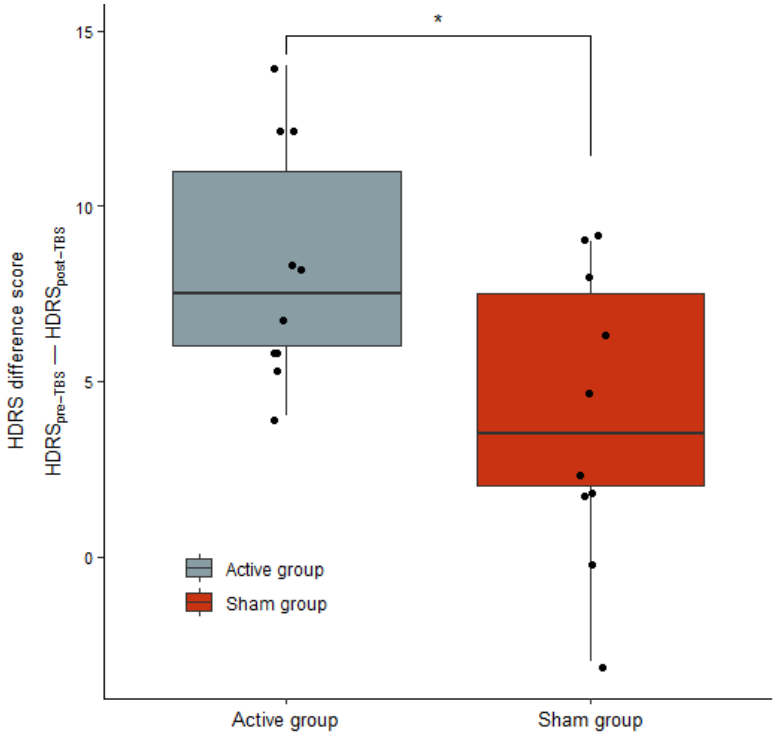

Figure 6. Box plots with individual data points depicting the changes in depressive symptoms in the active and sham groups. The vertical axis denotes the difference score of pre-TBS minus post-TBS HDRS scores. The two groups are shown on the horizontal axis. Colored version of Figure 1, Panel A from Holczer et al. (2021), see Appendix I.

Can bilateral TBS alter attention measured by the 1-back task?

For RT data, ANOVA revealed a significant Time × Stimulation interaction, $F_{1, 18}$ = 7.503, p = .013, η_p^2 = 0.294, BF_{incl} = 4.501. Pairwise comparisons revealed that in the active TBS group, RTs decreased compared to the sham group, p = .031. At the post-TBS time point the difference was significant, p = .046, while at the pre-TBS time point, the two groups did not differ in terms of RT, $p > .05$. The RTs of the active group dropped from (mean ± SE) 592.5 ± 45.3 to 524.5 ± 31.7, while the RTs of the sham group increased from 575.8 ± 45.38 to 620.7 ± 31.7 (Fig. 1, Panel B). The main effects of Time, $F_{1, 18}$ = 0.318, p = .580, η_p^2 = 0.017, BF_{incl} = 0.335, and Stimulation, $F_{1, 18}$ = 0.597, p = .450, η_p^2 = 0.032, BF_{incl} = 0.595, were not significant. Bayesian analysis yielded inconclusive evidence for the null model as it slightly outpredicted the full model (BF_{10} = 0.908, BF_{01} = 1.101) (see Panel B of Figure 1, Appendix I).

For the *d'* scores, the main effect of Time, $F_{1, 18}$ = 0.051, p = .824, η_p^2 = 0.003, BF_{incl} = 0.312, Stimulation, $F_{1, 18}$ = 1.803, p = .196, η_p^2 = 0.091, BF_{incl} = 0.806, and the Time × Stimulation interaction, $F_{1, 18}$ = 0.006, p = .939, η_p^2 < 0.001, BF_{incl} = 0.381, were not statistically significant. Bayesian analysis revealed that substantial evidence supported the null model over the full model, BF_{10} = 0.095, BF_{01} = 10.476. The data were ~10 times less likely under H_1 than under H_0.

Can bilateral TBS alter working memory performance on the n-back task?

ANOVA on the RTs of the 2-back and 3-back tasks yielded a non-significant main effect of Time, $F_{1, 18}$ = 0.520, p = .480, η_p^2 = 0.028, BF_{incl} = 0.396, and Stimulation, $F_{1, 18}$ = 1.798, p = .197, η_p^2 = 0.091, BF_{incl} = 0.710. The Time × Stimulation interaction, $F_{1, 18}$ = 1.422, p = .249, η_p^2 = 0.073, BF_{incl} = 0.630, was non-significant as well. According to the Bayesian analysis, substantial evidence supported that the null model outperformed the full model of BF_{10} = 0.180, BF_{01} = 5.556, meaning that the data were ~ 5 times less likely to be observed under H_1 than under H_0.

ANOVA on the *d'* scores showed that the main effect of Time, $F_{1, 18}$ = 2.078, p = .167, η_p^2 = 0.104, BF_{incl} = 0.712, Stimulation, $F_{1, 18}$ = 0.098, p = .758, η_p^2 = 0.005, BF_{incl} = 0.447, and the Time × Stimulation interaction, $F_{1, 18}$ = 0.321, p = .578, η_p^2 = 0.018, BF_{incl} = 0.433, were non-significant. Bayesian analysis indicated substantial evidence that the null model was the best-fitting model over the full model, BF_{10} = 0.146, BF_{01} = 6.828. Results were ~7 times less likely to be observed under H_1 compared to H_0.

Can bilateral TBS modify performance on the Attention Network Task?

Alerting attention ratio was not affected by TBS as indicated by non-significant main effects of both Time, $F_{1, 18} = 0.001$, $p = .973$, $\eta_p^2 < 0.001$, $BF_{incl} = 0.306$, and Stimulation, $F_{1, 18} = 0.233$, $p = .635$, $\eta_p^2 = 0.013$, $BF_{incl} = 0.463$, and the interaction of Time × Stimulation, $F_{1, 18} = 0.767$, $p = .393$, $\eta_p^2 = 0.041$, $BF_{incl} = 0.500$. Strong evidence supported the preference of the null model over the full model ($BF_{10} = 0.073$, $BF_{01} = 13.718$), and the data were ~14 times less likely to be observed under H_1 than under H_0.

For the orientating attention ratio, the main effect of Time, $F_{1, 18} = 0.961$, $p = .340$, $\eta_p^2 = 0.051$, $BF_{incl} = 0.495$, and Stimulation, $F_{1, 18} = 0.576$, $p = .458$, $\eta_p^2 = 0.031$, $BF_{incl} = 0.450$, as well as the Time × Stimulation interaction, $F_{1, 18} = 0.173$, $p = .682$, $\eta_p^2 = 0.010$, $BF_{incl} = 0.430$, were not significant. The full model, $BF_{10} = 0.095$, $BF_{01} = 10.545$, was outperformed by the null model, with strong evidence supporting the latter. The data was ~10 times less likely to be observed under H_1 than under H_0.

Executive attention ratio was also unaffected by TBS as a non-significant main effect of Time, $F_{1, 18} = 0.336$, $p = .570$, $\eta_p^2 = 0.018$, $BF_{incl} = 0.378$, Stimulation, $F_{1, 18} = 3.320$, $p = .085$, $\eta_p^2 = 0.156$, $BF_{incl} = 0.581$, and a non-significant interaction of Time × Stimulation, $F_{1, 18} = 0.017$, $p = .897$, $\eta_p^2 < 0.001$, $BF_{incl} = 0.373$ was found. Bayesian analysis revealed strong evidence favoring null model over the full model ($BF_{10} = 0.083$, $BF_{01} = 12.042$). The likelihood of the data being observed under H_1 was ~12 times lower than under the H_0.

Overall RTs for the ANT task were also analyzed in order to gain an estimate of psychomotor speed changes. Our analysis revealed non-significant main effects and interaction with inconclusive evidence in the Bayesian analysis (for more details see Appendix I).

Study II – Gray matter asymmetry in MDD

A significant negative correlation was found between the gray matter asymmetry index values of the inferior temporal gyrus (MNI152 standard space coordinates: x = 18, y = 55, z = 17) and the HDRS scores (Figure 9). Higher HDRS scores (indicating more severe symptoms) were associated with more negative asymmetry indices, i.e., a higher leftward asymmetry in the inferior temporal gyrus ($R = -0.879$, $p \leq 0.001$) Gray matter asymmetry was not correlated to the BHS and *d'* scores of the 1-, 2-, and 3-back tasks.

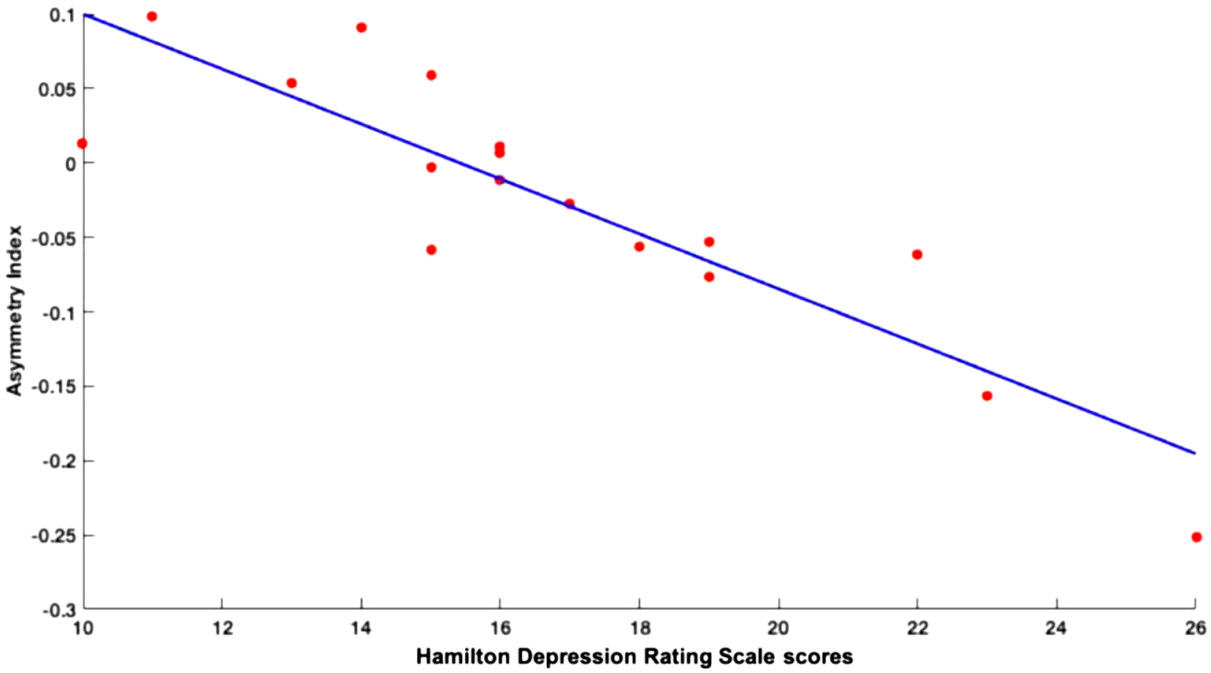

Figure 7. Correlation between the asymmetry index values of the significant clusters within the inferior temporal gyrus (MNI152 standard space coordinates: x = 18, y = 55, z = 17) and the HDRS scores. Figure from Kocsis et al. (2021), see Appendix II.

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

Can tDCS influence reaction times or interference effect in a combined flanker Go/No-Go task?

For RTs, the ANOVA revealed that the Trial Type main effect was significant, $F_{1.364, 49.111} = 212.611$, $p < .001$, $\eta_p^2 = 0.855$, $BF_{incl} > 10$, $BF_{excl} = 0.1$. Post hoc tests showed that RTs were significantly slower in the incongruent trial type as compared to the neutral ($p < .01$) and congruent trial types ($p < .01$). The Trial Type was the best factor to predict the data with the highest BF_{incl} score suggesting strong evidence to include the effect. Thus, the task was successful in evoking the flanker interference effect. The main effect of Stimulation Type and Montage were non-significant (both *p*s > .05; $BF_{incl} = 0.401$ [$BF_{excl} = 2.493$] and 0.395 **[**$BF_{excl} = 2.531$**]**, respectively). Interaction effects did not reach significance (all *p*s > .05). Bayesian statistics mostly supported these results. The best model only included the main effects of Trial Type and Stimulation type, along with the interaction of Stimulation type and Trial Type. This model outperformed the null model ($BF_{10} > 10$, $BF_{01} < 0.1$). For the interaction effect, only anecdotal evidence supported its inclusion ($BF_{incl} = 1.926$, $BF_{excl} = 0.519$). Post hoc tests complemented this as RTs did not differ significantly between different stimulation types and montages, although the FM group had higher median RTs collapsed across all trial types compared to the DLPFC group (Figure 7).

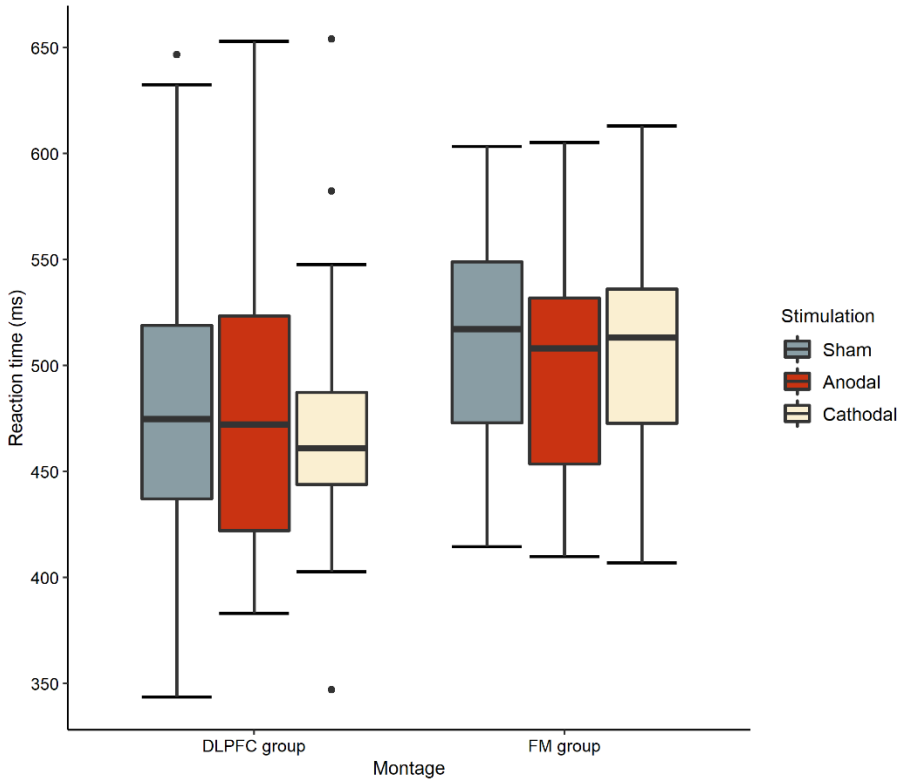

Figure 8. Box plots depicting the reaction times in the DLPFC and FM groups by stimulation types. The vertical axis denotes reaction times of correct trials. The horizontal axis denotes the two groups. Stimulation types are marked by colors. Figure 3 from Holczer et al. (2023), see Appendix III.

ANOVA for the interference scores showed that the main effect of Stimulation type, $F_{1.996,\ 71.846} = 1.882$, $p = .160$, $\eta_p^2 = 0.050$, $BF_{incl} = 0.380$, $BF_{excl} = 2.617$, and the main effect of Montage, $F_{1,\ 36} = 1.704$, $p = .704$, $\eta_p^2 = 0.004$, $BF_{incl} = 0.446$, $BF_{excl} = 2.242$, did not reach significance. BF_{incl} scores also favored the H_0. The Stimulation type × Montage interaction was also non-significant, $F_{1.996,\ 71.846} = 0.760$, $p = .471$, $\eta_p^2 = 0.021$, $BF_{incl} = 0.246$, $BF_{excl} = 4.065$. The null model was the best model in the Bayesian analysis, which also supports no effect on the interference scores (for a figure, see Appendix III).

Can tDCS influence the congruency sequence effect in a combined flanker Go/No-Go task?

ANOVA of the congruency sequence effect indicated a main effect of Trial n congruency, $F_{1,\ 36} = 11.573$, $p < .002$, $\eta_p^2 = .243$, $BF_{incl} > 10$, $BF_{excl} < 10$, as well as a main effect of Trial n-1 congruency, $F_{1,\ 36} = 175.134$, $p = .001$, $\eta_p^2 = .829$, $BF_{incl} = 9.802$, $BF_{excl} = 0.102$, both supported by substantial evidence in the Bayesian analysis. Trial n congruency is indicative to the presence of the flanker effect during trial n, i.e., the interference effect. The congruence of trial n-1 shows that previous trial congruence impacts the RTs of the current trial. More specifically, RTs were shorter if trial n was congruent compared to incongruent (*p*

< .001). RTs were also shorter when the n-1 trial was incongruent compared to congruent (p = .002). Of the interaction effects, the two-way interaction of Trial n-1 congruency × Trial n congruency was significant (Figure 8) suggested a congruency sequence effect, $F_{1, 36}$ = 44.125, p < .0001, η_p^2 = .551, BF_{incl} = 83599.050, BF_{excl} = 1.196. RTs were shorter on cC trials, and these RTs differed from cI and iI trials (ps < .001), but not from iC (p = .509). RTs on iC trials were shorter than RTs on cI or iI trials (ps < .001). RTs were longer when incongruent trials were preceded by incongruent trials (iI) as compared to congruent trials (cI) (p < .001). Another significant two-way interaction between Trial n-1 congruency × Montage, $F_{1, 36}$ = 4.188, p = 0.048, η_p^2 = 0.104, BF_{incl} = 0.466, BF_{excl} = 2.145 was found which was primarily linked to the difference of RTs between congruent and incongruent trials on Trial N-1 in the FM group (p = 0.003). The rest of the two-way interactions, three-way interactions, and the four-way interaction did not reach significance (all ps > 0.005, all BF_{incl}s < 1.375, BF_{excl}s < 0.727). Higher-order interactions were not included in the best model in the Bayesian ANOVA. The best model comprised the main effects, namely Montage, Stimulation Type, Trial n congruency, and Trial n-1 congruency and the Trial n congruence × Trial n-1 interaction. This model outperformed the null model, which supports the inclusion of these factors.

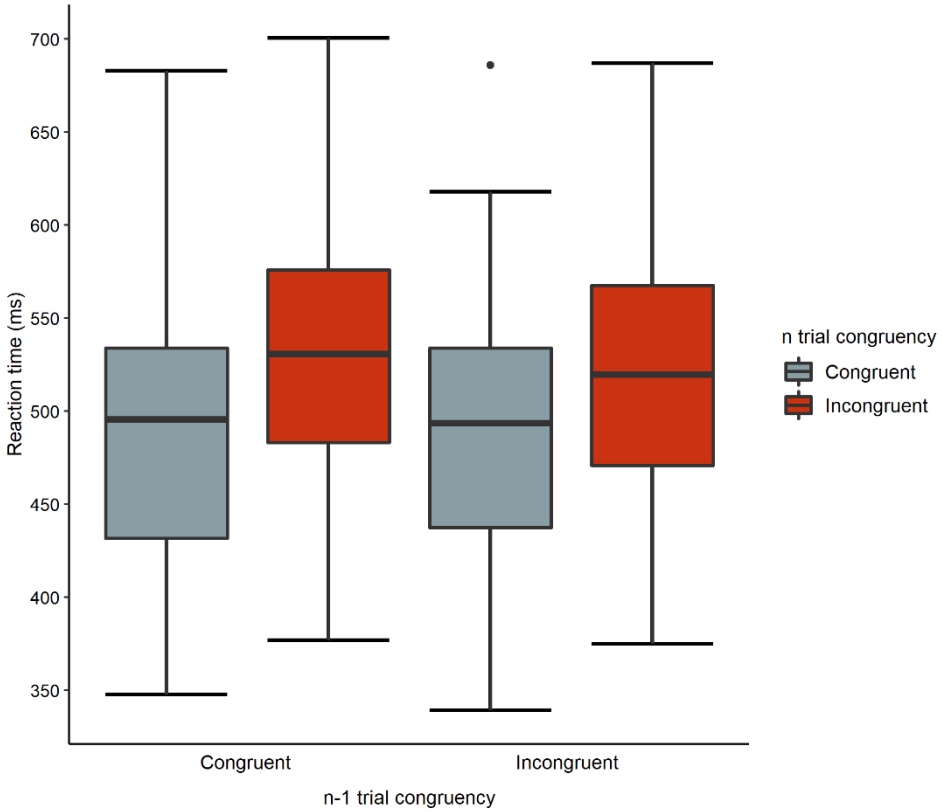

Figure 9. Box plots depicting congruency sequence effects on the combined flanker Go/No-Go task. The vertical axis denotes the reaction times of correct trials. The horizontal axis denotes the

congruency of the previous trial. The congruency of the current trial is marked by colors. Figure 5 from Holczer et al. (2023), see Appendix III.

Can tDCS influence accuracy in a combined flanker Go/No-Go task?

Regarding accuracy, a near-ceiling effect of performance on the combined flanker Go/No-Go task was observed with an overall mean accuracy of 97.97% (range = 94.73% – 99.71%). Hence, we only carried out an explanatory ANOVA, which revealed a significant main effect of Trial Type, $F_{1.166,\ 41.992} = 14.659$, $p < .01$, $\eta_p^2 = 0.289$, $BF_{incl} > 10$, $BF_{excl} < 0.1$. More errors were made in the no-go trial type as compared to the neutral, congruent, and incongruent trial type (all *p*s < .05). No difference was found between the three latter trial types (all *p*s >.05). No significant interactions were found (*p*s < .05, BF_{incl}s < 0.500, BF_{excl} < 2.000).

V. DISCUSSION

We previously outlined the challenges of NIBS with inconsistent results and low replicability due to various factors. The main goal of the studies included in the thesis was to systematically investigate whether conventional and widely accepted protocols of NIBS can be used to alter aspects of executive function, namely, working memory, response inhibition, and interference control in MDD and healthy individuals. We also investigated voxel-based cortical asymmetry in MDD and its association with cognitive and depressive symptoms that may elicit potential targets for NIBS and help understand the pathology behind the disorder on which NIBS protocols are based. Below, we will summarize the main results of each study and discuss NIBS effects on executive functions. Next, we will overview the factors that could influence the results and address methodological considerations. Finally, we will overview future directions and conclude with the contributions of the thesis.

In **Study I**, we investigated the cognitive effects of bilateral TBS in view of its antidepressant efficacy. We assessed working memory and attention (both impaired in MDD; Perini et al., 2019) using the n-back and ANT tasks, as well as depression severity using the HDRS before and after 10 daily sessions of bilateral active or sham TBS over the DLPFC in patients with MDD. We successfully replicated that active bilateral TBS was superior to sham stimulation in reducing HDRS scores (Berlim et al., 2017; Chou et al., 2023; Prasser et al., 2015; Qin et al., 2023). However, no effect on aspects of attention, interference control, and working memory was found in terms of accuracy and *d'* scores (extracted from the accuracy data of each level of the n-back task). This fits in with previous findings that have suggested limited (Chou et al., 2020; Martin et al., 2017) to no cognitive effect (Wajdik et al., 2014) of rTMS protocols, but is in contrast with some promising results (Cheng et al., 2016). Identical protocols have been reported to exert connectivity (Stöhrmann et al., 2023) and theta power changes (Chung et al., 2017), the latter of which has been linked to EFs (Cavanagh & Frank, 2014; Lisman, 2010). Thus, it still cannot be excluded that subtle changes were elicited that could not manifest in the performance. Combining TBS with neuroimaging techniques may shed light on immediate aftereffects not observable in this study.

For reaction time data, RTs in the 1-back task pointed towards a potential shortening that may be an indicator of increased psychomotor speed regardless of cognitive load. Results of the overall RTs in the ANT task may also support this, as the modulation of TBS could not be completely excluded in that case either. If future studies can reliably replicate improved RTs in MDD following rTMS, an explanation can be the reduction of frontal alpha

asymmetry (Pellicciari et al., 2017) as it has been associated with psychomotor retardation in MDD (Cantisani et al., 2015). rTMS may restore brain activity and psychomotor speed in association. Otherwise, non-specific effects may also play a part, including the facilitation of cerebral blood flow (Cho et al., 2012) or motor cortex excitability (Cao et al., 2018).

Based on our results, one may dispute the use of bilateral TBS, considering that it has similar antidepressant efficacy with no additional cognitive benefit compared to unilateral iTBS over the left DLPFC (which takes less time and delivers fewer pulses). However, adequately powered studies with neuroimaging techniques and follow-ups are needed to make further comparisons and help decide whether bilateral TBS should be discontinued. It is also possible that affective and cognitive symptoms do not completely respond identically to NIBS, and some parameters are more beneficial in terms of cognitive enhancement than the ones we chose. For instance, Rostami and colleagues have found that patients with unipolar or bipolar depression improved various cognitive functions, including EFs, when delivering 20 sessions of bilateral rTMS (Rostami et al., 2022). The higher number of pulses and stimulation sessions in that study may have resulted in more pronounced changes.

Notably, we did not find any immediate cognitive adverse effect of bilateral TBS. This is important because other therapies, such as ECT, have indeed been found to deteriorate EFs and episodic memory (Andrade et al., 2016; Ren et al., 2014). Taken together, our findings indicated that TBS may be a well-tolerated technique to reduce depressive symptoms in MDD, but with the parameters used in Study I, no changes in executive function and aspects of attention could be captured. Future research may further explore the effect of bilateral TBS on psychomotor and information processing speed.

Study II was designed to complement **Study I**. Bilateral rTMS has been specifically made to address the rightward imbalance of the DLPFC in MDD. Apart from the functional imbalance that has been widely reported and taken as a basis for the design of NIBS protocols (Greco et al., 2012), structural alterations as well as evidence for structural asymmetry have been suggested previously (Liu et al., 2016; Ran et al., 2020; Schmaal et al., 2017). Region of interest-based methods, however, may not have a sensitive enough resolution to identify such differences. Moreover, despite being prominent features of the disorder, cognitive impairment has not been investigated in relation to gray matter asymmetry previously. Thus, we measured voxel-based gray matter asymmetry on structural MRI of MDD patients to explore whether cortical asymmetry can be associated with depressive and cognitive symptoms. The resulting asymmetry indices yielded a leftward shift (i.e., lower gray matter content in the right hemisphere, compared to the left) within a cluster of voxels in the inferior temporal gyrus

(ITG), but we could not identify any further gray matter asymmetry. This aligns with the fact that large-scale region of interest-based studies have not reported gray matter asymmetry in MDD (de Kovel et al., 2019; Kong et al., 2020). On the other hand, ITG asymmetry has already been observed in some MDD subgroups (Gray et al., 2020; Peng et al., 2016; Schmaal et al., 2017), and the ITG has been found affected in other neuropsychiatric disorders as well (Gong et al., 2019; Onitsuka et al., 2004).

For the significant voxels within the ITG, we further examined whether asymmetry was linked to performance on the 1-, 2-, or 3-back tasks or depressive symptoms as measured by the HDRS or the BHS and found a correlation between ITG asymmetry and the HDRS scores. The volume, but not the asymmetry of the ITG has previously been associated with HDRS scores in MDD patients (Li et al., 2010). Moreover, the ITG is considered part of the extended default mode network (Allen & Williams, 2011), which is reported to show abnormal activity compared to healthy controls and is believed to be involved in rumination and self-referential processes in MDD (Guo et al., 2014; Hamilton et al., 2015). Our results linking gray matter asymmetry and clinical symptoms may support the contribution of ITG to these network-level processes.

Study III was designed to compare how tDCS, delivered in two electrode montages targeting the prefrontal and fronto-medial areas affects response inhibition and interference control. Participants were randomized into groups based on electrode montage and asked to perform a combined flanker Go/No-Go task during anodal, cathodal, and sham stimulation in three separate sessions. Our results did not replicate previous reports of tDCS improving response inhibition and interference control despite using the same conventional asymmetric DLPFC montage and comparable stimulation parameters (Dubreuil-Vall et al., 2019; Jeon & Han, 2012; Loftus et al., 2015), but instead fitted among the studies that have questioned left DLPFC tDCS (Friehs et al., 2021; Lema et al., 2021). tDCS delivered in a FM montage did not affect task performance (defined as correct RTs, interference effect, and congruency sequence effect) neither during anodal nor cathodal stimulation. These results align with the inconclusive and null results of the literature (Adelhöfer et al., 2021; Bellaïche et al., 2013).

Our findings contribute to the forming doubts about the reliability of single-session tDCS for modulating executive function (and cognition in a more general sense) in healthy adults (Westwood & Romani, 2017). Most of the studies referred to above used widely used stimulation parameters; at first, no clear difference contributing to the heterogeneity of the results can be outlined. Finding an optimal combination of parameters is further hindered by the lack of understanding of the mechanism of action of NIBS and scant empirical evidence

regarding stimulation parameters which we aimed to improve by our design including both tDCS polarities and directly comparing electrode montages to each other. Overall, our results may indicate that conventional two-electrode tDCS with a cephalic return electrode does not yield reliable results when used to influence EFs (for a more elaborate discussion on the effect of electrode placement, see below).

Can NIBS be used to modulate executive function?

Our results across **Study I** and **Study III** did not support that NIBS can enhance executive functions with the given parameters, although NIBS did not result in impaired performance either, not even when cathodal tDCS was administered. Previously, we did not find iTBS to enhance working memory in healthy participants (Vékony et al., 2018). While our findings in **Study I** supported the widely reported antidepressant effects of TBS, only a potential effect on psychomotor speed could be identified. We believe that this is worth further investigation; however, if our findings are replicable, the relationship of psychomotor speed increase with depressive symptom changes would still be open to debate as it may simply stem from the non-specific effect of TBS improving the affective symptoms.

Several factors add to the complexity of interpreting our results. In the studies comprising the thesis, we aimed to target the prefrontal cortex and, more specifically, the DLPFC. By doing so, we were following the mainstream of NIBS research and considered the involvement of the DLPFC in various cognitive and affective processes (Friedman & Robbins, 2022). However, there are other brain regions and network-level processes that are worth exploring, such as the fronto-medial regions, the role of which we already began to research in **Study III**, or the temporal regions that we found affected in MDD in **Study II**. It would be intriguing to examine whether stimulation over specific sites can form separate responder groups to enhance the therapeutic effect of NIBS. For rTMS protocols, similar ideas of personalization have been proposed with the aim to enhance the antidepressant effects of the intervention and consider the multifaceted nature of MDD (Zangen et al., 2023).

In **Study III**, we specifically targeted the left DLPFC and found no effect on response inhibition and interference control. It is possible that targeting the right rather than the left DLPFC may result in more pronounced effects on the given aspects of executive function. The involvement of the bilateral DLPFC in EF processes has been established (Cieslik et al., 2015); however, for some processes like response inhibition, a more pronounced rightward lateralization was suggested (Cieslik et al., 2015; Isherwood et al., 2023). Response inhibition, as measured by performance on the no-go trial type, was, indeed,

not affected by left DLPFC tDCS in Study III. On the other hand, interference resolution has been linked to an even more left-lateralized prefrontal activation (Isherwood et al., 2021) despite the lack of any changes in performance on the flanker task. There is evidence suggesting that the left and right DLPFC has somewhat different roles in implementing EFs, with the former related to information manipulation within working memory and interference resolution, while the latter is more related to verbal and spatial reasoning, adaptive decision making, and error-monitoring (Barbey et al., 2013; Harty et al., 2014; Soares et al., 2019). On this note, this may explain why we did not see any changes in the congruency sequence effect of the flanker task in Study III; however, we also did not identify any change in the interference effect despite targeting the left DLPFC. We strongly support future studies to systematically compare the effects of left and right DLPFC stimulation in order to answer some of these questions. Another possible issue is that the bilateral stimulation employed in **Study I** may cancel out activations relevant for manifesting EFs as it promotes metabolic changes that differ from what is exerted by iTBS or cTBS delivered alone (Li et al., 2018), which may explain the lack of improved EFs following bilateral TBS.

The timing of the stimulation may also be crucial. Backing this idea, Simonsmeier and colleagues have found in a meta-analysis that across various cognitive tasks, transcranial electrical stimulation improves learning and not task performance during the test phase (Simonsmeier et al., 2018). In **Study I and III**, we targeted task performance; hence, it is still possible that, allowing for a learning period and possibly more than one stimulation sessions, we might have found the modulatory effect of NIBS. Also, NIBS may not simply improve or hinder task performance but instead have a selective effect on specific subprocesses. Electrophysiological changes reported after NIBS have also supported the selective nature of the stimulation in some cases (Adelhöfer et al., 2021; Reinhart & Woodman, 2014). As previously mentioned, the possibility remains that our measures on the behavioral level are not sensitive enough to capture such changes. More sophisticated methods, such as TMS-EEG devices, concurrent TMS functional MRI, or closed-loop stimulation protocols, may shed light on the exact mechanism of action of these techniques.

Overall, our results prompt further investigation of NIBS effect, but also question some of the conventionally used and accepted techniques (for an overview of our findings, see Table 2). Furthermore, our work contributed to the existing literature by exploring NIBS effects on executive function in a systematic manner. We underscored the need for cognitive symptoms (i.e., EFs and psychomotor speed) to be measured along with depression severity changes to gain a more complete understanding of the role of rTMS in MDD therapy. Our

results provided insight into MDD pathomechanism by assessing voxel-based cortical asymmetry, which was also found to correlate with depressive symptom severity. We were the first to compare the effects of anodal, cathodal, and sham tDCS using two electrode montages targeting key EF areas where our results questioned conventionally used parameters and the efficacy of single-session tDCS in healthy adults as no changes in performance were measured in either setting.

Table 2. Main results of the studies comprising the thesis.

	Study I
The main question	How does bilateral TBS (that is expected to mitigate depressive symptoms) influence executive function in major depressive disorder?
Results	Bilateral TBS is superior to sham TBS in reducing HDRS scores but does not affect working memory, attention, or interference resolution. Bilateral TBS may improve psychomotor speed.
	Study II
The main question	Is there voxel-based cortical asymmetry in MDD, and is it associated with depressive symptoms or executive function that can be targeted in future MDD therapy?
Results	Within a cluster of voxels in the inferior temporal gyrus, gray matter content is lower on the right than on the left homologous area in our sample of MDD patients. Cortical asymmetry of the significant voxels correlates with HDRS scores.
	Study III
The main question	How does tDCS delivered in two electrode montages targeting the prefrontal and fronto-medial areas affect interference control and response inhibition?
Results	Neither anodal nor cathodal tDCS delivered in a DLPFC or a fronto-medial montage can influence RTs, interference scores, or congruency sequence effect on a combined flanker Go/No-Go task.

Methodological considerations and limitations

When designing the studies that comprise the present thesis, we made an effort to use well-established combinations of stimulation parameters in hopes of maximizing the pro-cognitive effects. However, partly due to the lack of comprehensive mechanistic understanding of NIBS (which would aid study design and help the interpretation of results), there is little information on how changing specific stimulation parameters affect the results. Certain parameters, like stimulation intensity, do not exhibit a linear trend in exerting an effect on cortical excitability or cognition (Chung, Rogasch, Hoy, Sullivan, et al., 2018;

Esmaeilpour et al., 2018; Hoy et al., 2013). Subthreshold (i.e., rTMS intensity under the rMT) and suprathreshold (i.e., rTMS intensity over the rMT) seem to elicit differential connectivity changes (Alkhasli et al., 2019). However, the overall relevance of rMT for determining the dose of DLPFC TMS seems not to be reliable (Tik et al., 2017). For this reason, Kaminski and colleagues have proposed that a fixed intensity should be chosen until more reliable effects are achieved when adapting the intensity to the individual, which we used in **Study I** (Kaminski et al., 2011). For tDCS intensity, most studies use 1 to 2 mA intensity; however, there is no clear recommendation as to which one should be preferred as the currently available results are ambiguous (Hoy et al., 2013; Papazova et al., 2020). The polarity-dependent nature of tDCS effects is a dubious concept in the cognitive domain (Jacobson et al., 2012; Karuza et al., 2016). Hence, we decided to use a complete within-subject design and compared both anodal and cathodal tDCS to a sham condition in **Study III**.

Choosing the best sham method poses as a major challenge in NIBS (see our previous review, Holczer et al., 2020). Lately, active sham conditions, i.e., the stimulation of an area not expected to be involved in the targeted behavior, are getting more recognized (Duecker & Sack, 2015) as other methods like the tilting or elevation of the rTMS coil or turning off the tDCS device can reduce scalp sensations which potentially threatens the blinding of the participants. Another limitation of our studies is that we did not assess whether the blinding of the participants was successful. Moreover, delivering active stimulation to the target area for a short duration may exaggerate the placebo effect and actually lead to electrophysical changes in the brain (Fonteneau et al., 2019). As we used a block that elevated the coil from the scalp in **Study I** and turned off the tDCS device after 30 s in **Study III**, the choice of sham method can be considered a limitation of our studies.

In **Study III**, we tested two two-electrode montages where both electrodes were placed on the head. This introduces limitations to our conclusions drawn from this study due to inhibitory effects of the reference electrode that may contribute to the observed results. Simulations conducted for both electrode montages in **Study III** suggested that the conventional left DLPFC montage also generated high electric field magnitudes in the frontopolar regions (Soleimani et al., 2022) corresponding to the location of the reference electrode. However, extracephalic montages (e.g., placing the return electrode to the shoulder or cheeks), while promising (Nitsche & Paulus, 2011), can alter the expected current flow (Bikson et al., 2010) and may not result in significant changes in terms of cognitive effects (Nozari et al., 2014). The other montage used in Study III targeted the fronto-medial areas and the simulation revealed diffuse activation in the lateral and medial surface of the frontal lobe.

A great advantage of TMS techniques is that they enable more focal stimulation. Nevertheless, simulations of electric currents induced by NIBS are helping immensely to understand and predict the outcome of the stimulation.

Two areas that are equally heterogeneous as stimulation parameters are the inclusion criteria and the assessment methods. Inclusion criteria are especially important when recruiting patient samples, like in **Study I and II**. For instance, one could wonder whether pharmacotherapy alters NIBS effects. Growing body of evidence suggests that concomitant antidepressant medication does not influence rTMS (Hebel et al., 2021; Hunter et al., 2019). On the contrary, affective and cognitive changes may be independent of each other (Corlier et al., 2020). However, specific drugs, e.g., benzodiazepines, have been suggested to reduce the beneficial effects of the stimulation (Deppe et al., 2021; Fitzgerald et al., 2020). Based on these results, we believe that the use of TBS as a concomitant therapy with ongoing stable antidepressant medication may not be a factor influencing our results in **Study I**.

In all of our studies, widely used neuropsychological tests have been chosen to measure EFs, including the ANT, n-back task, flanker task, and Go/No-Go task. However, we decided to combine two latter tasks for **Study III** in order to capture interference control and response inhibition. However, it is possible that by doing so, we changed how participants interact with the stimuli as we require the re-allocation of attention from the target stimulus to the flanking stimuli in the no-go trial type (Brydges et al., 2012). The dual-task nature of the combined flanker Go/No-Go task adds an increased cognitive load to the task, which was viewed as desirable in view of the healthy sample recruited. Nonetheless, participants had a near-ceiling level of accuracy which may prevent the manifestation of tDCS effects. We used a complete within-subject design and compared both anodal and cathodal tDCS to a sham condition specifically to capture changes in either direction, even if a ceiling effect is present. Contrary to prior expectations of tDCS acting in a polarity-dependent manner, neither anodal nor cathodal stimulation was associated with a change in accuracy. In the context of healthy individuals, it is plausible that more subtle tDCS effects get mitigated by the recruitment of compensatory mechanisms, although we also failed to improve EFs in a sample of MDD patients.

Future directions in NIBS research

Our findings (coupled with the steadily increasing number of null results being published) should be considered as a call for more rigorous research and the re-consideration of common practices. Although we did not reveal any NIBS effect on executive functions, the

field goes under constant refinement and international endeavors have been taking place to propose guidance for researchers interested in the field. One such effort in which I had the honor to partake with forty international colleagues involved the collaborative development of guidelines for facilitating the continuation of operations and NIBS research during the pandemic and any future outbreaks (Bikson et al., 2020).

New techniques have been developed to overcome some of the limitations described above. Novel techniques like deep TMS, accelerated TMS, and high-definition tDCS allow for targeting subcortical structures (Zangen et al., 2023), increasing the efficacy of the stimulation (Fitzgerald et al., 2018), and delivering more focal electric stimulation (Turski et al., 2017), respectively. More and more studies are incorporating functional MRI, EEG, or magnetoencephalography signal recording during or after stimulation to capture changes in even a single session of NIBS more comprehensively. We too started explorig EEG measures following tDCS and transcranial alternating current stimulation (Holczer et al., 2020).

Novel NIBS techniques targeting brain regions previously not feasible to reach are now available. For instance, the left anterior insula has been proposed to show activation during both response inhibition and interference control (Hung et al., 2018). Furthermore, we argued for the role of inferior temporal gyrus asymmetry in the pathomechanism of MDD based on our findings in **Study II**. Additionally, cognitive neuroscience is steered towards the framework of functional brain networks instead of focusing on finding specific regions that are responsible for implementing a certain behavior. Facilitating or inhibiting multiple nodes of the central executive network may result in more robust changes in performance. Functional-connectivity-guided NIBS has already been found superior to sham stimulation (although it has not been compared to the efficacy of other active NIBS techniques to the best of our knowledge) (Cole et al., 2022). In a pilot study with ongoing data collection, we are collecting resting state EEG signals from patients with aphasia with or without non-verbal executive function deficit. The data collected could be used to identify and target altered connectivity patterns using NIBS.

Finally, in **Study I**, we found that bilateral TBS may have an effect on psychomotor speed in MDD. We have outlined potential reasons behind this finding; however, future studies should measure frontal alpha asymmetry and/or cerebral blood flow as an outcome measure and correlate of RT data. Previously, subthreshold high-frequency rTMS over the DLPFC has been suggested to elicit improved psychomotor speed (Baeken et al., 2010; Thomas-Ollivier et al., 2015), which would also make an interesting comparison to bilateral stimulation.

VI. CONCLUSIONS

The studies presented as part of the thesis were designed with the aim of contributing to the field of NIBS by systematically examining common protocols. We contributed to the literature by showing that in MDD, 10 sessions of bilateral TBS elicited no immediate cognitive adverse effects (but also no improvements) on working memory, interference control, and other aspects of attention while providing further evidence for its antidepressant efficacy. We highlighted the role of the temporal cortex in the pathomechanism of MDD due to our findings of gray matter volume asymmetry of the ITG using voxel-based cortical asymmetry calculations and demonstrated its association with depressive symptoms. We also correlated the significant cluster of voxels with not only depressive symptoms but also working memory performance for the first time. Furthermore, we showed that a common tDCS paradigm, i.e., a single session of 2 mA tDCS delivered in a conventional left DLPFC montage to healthy adults, did not modulate response inhibition or interference control. Moreover, we were the first to compare this conventional montage to one targeting the fronto-medial cortices; although, it did not result in the modulation of executive functions. Our results have important methodological implications and promote further comparisons where systematic assessments are made for both cognitive and affective symptoms in MDD, as well as for the re-consideration of using two-electrode protocols with a reference electrode on the head. Our research group genuinely believes that the thesis added to the literature regarding the effects of NIBS techniques on executive functions and took a step towards refining NIBS research and adding to the current knowledge.

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I.

NEUROSCIENCE
RESEARCH ARTICLE
A. Holczer et al. / Neuroscience 461 (2021) 130–139

The Effects of Bilateral Theta-burst Stimulation on Executive Functions and Affective Symptoms in Major Depressive Disorder

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Abstract—Major depressive disorder (MDD) is characterized by severe affective as well as cognitive symptoms. Moreover, cognitive impairment in MDD can persist after the remission of affective symptoms. Theta-burst stimulation (TBS) is a promising tool to manage the affective symptoms of major depressive disorder (MDD); however, its cognition-enhancing effects are sparsely investigated. Here, we aimed to examine whether the administration of bilateral TBS has pro-cognitive effects in MDD. Ten daily sessions of neuronavigated active or sham TBS were delivered bilaterally over the dorsolateral prefrontal cortex to patients with MDD. The n-back task and the attention network task were administered to assess working memory and attention, respectively. Affective symptoms were measured using the 21-item Hamilton Depression Rating Scale. We observed moderate evidence that the depressive symptoms of patients receiving active TBS improved compared to participants in the sham stimulation. No effects of TBS on attention and working memory were detected, supported by a moderate-to-strong level of evidence. The effects of TBS on psychomotor processing speed should be further investigated. Bilateral TBS has a substantial antidepressive effect with no immediate adverse effects on executive functions.

Key words: major depressive disorder, theta-burst stimulation, working memory, attention, transcranial magnetic stimulation.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is now considered a therapeutic measure to reduce the affective symptoms of major depressive disorder (MDD) (see Lefaucheur et al., 2020 for review). Over the dorsolateral prefrontal cortex (DLPFC), both the left-hemispheric, facilitatory rTMS (5 Hz or above, high-frequency, HF-rTMS) (O'Reardon et al., 2007) and the right-hemispheric, inhibitory stimulation (1 Hz, low- frequency, LF-rTMS) are beneficial compared to sham stimulation (Fitzgerald et al., 2003, 2009; Isenberg et al., 2005; Stern et al., 2007). A patterned version of rTMS, namely theta-burst stimulation (TBS), significantly reduces the duration and cost of the stimulation and seemingly exerts comparable effects to rTMS (Blumberger et al., 2012; Mendlowitz et al., 2019; Nyffeler et al., 2007; Zafar et al., 2008). The inhibitory pattern of TBS is continuous TBS (cTBS), which applies an uninterrupted train of bursts, and the facilitatory is intermittent TBS (iTBS), which is fragmented by pauses among the trains of bursts (Huang et al., 2005). TBS over the DLPFC mitigates the clinical symptoms of MDD with an effect estimation similar to rTMS (Li et al., 2014; Plewnia et al., 2014; Schwippel et al., 2019; Williams et al., 2018). In addition to unilateral stimulation, sequentially applied left facilitatory and right inhibitory (bilateral stimulation) by either rTMS or TBS appears to be similarly effective (Berlim et al., 2013a, 2013b; Chen et al., 2014; Cheng et al., 2016; O'Reardon et al., 2007). Bilateral protocols are based on the observations of interhemispheric imbalance in MDD (Grimm et al., 2008; Hecht, 2010), the resolution of which is suggested to improve affective

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Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; ANT, Attention Network Task; BF, Bayes Factor; cTBS, continuous theta-burst stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; iTBS, intermittent theta-burst stimulation; MDD, major depressive disorder; rMT, resting motor threshold; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation.

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symptoms. However, most studies have focused exclusively on affective changes and did not consider other characteristic symptoms of MDD, such as cognitive impairment. Here, we aimed at exploring the effectiveness of bilateral TBS on both the affective and cognitive symptoms of MDD.

Cognitive symptoms, especially deficits of executive functions including attention (Kaiser et al., 2015) and working memory (Gärtner et al., 2018) as well as psychomotor retardation (Gorwood et al., 2014), are often present in MDD, further exacerbating the burden of disease. Moreover, the impairment of all these cognitive domains may persist even after the remission of the affective symptoms (Nebes et al., 2003; Rock et al., 2014). The effectiveness of pharmacotherapy appears to be limited to some cognitive subdomains (Pan et al., 2017), while the more promising results of rTMS are still preliminary and inconclusive (Demirtas-Tatlidede et al., 2013; Iimori et al., 2019; Martin et al., 2017) with reporting of no pro-cognitive effect (Wajdik et al., 2014). Concerning TBS, studies carried out on healthy participants revealed that it might modulate cognition at behavioral (Lowe et al., 2018; Vékony et al., 2018; Viejo-Sobera et al., 2017), electrophysiological (Chung et al., 2017), and neurochemical level (Suppa et al., 2016). Working memory and attention can be enhanced even after one session of TBS (He et al., 2013; Lowe et al., 2018; Xu et al., 2013). However, differences are present across cognitive domains, e.g., performance on tasks inquiring complex executive functions appears not to be affected (Lowe et al., 2018). Also, as the rationale of bilateral protocols derives from the clinical characteristics of MDD patients, the investigation of bilateral TBS in a preclinical setting is limited. To date, only a few studies have assessed whether TBS can mitigate cognitive impairment in MDD (Cheng et al., 2016; Scho et al., 2019) and only an even smaller proportion of these investigated bilateral TBS (Cheng et al., 2016). The present randomized, sham-controlled study aimed to examine the effects of 10 daily bilateral TBS sessions on the clinical symptoms and executive function in MDD. We assessed working memory and attention using standardized neurocognitive tests: the n-back and the Attention Network Task (ANT). Overall reaction times (RTs) for both tasks were also investigated to gather information on psychomotor processing speed. Since TBS effects on the working memory domain seem to be the most reliable based on results of healthy participants (Lowe et al., 2018) and patients with neuropsychiatric disorders (Demirtas-Tatlidede et al., 2013), enhanced performance on the n-back task was expected. As TBS is suggested to enhance attention (He et al., 2013), we also expected improvements on the ANT. To detect potential changes in clinical symptoms, the Hamilton Depression Rating Scale (HDRS) was administered. Classical statistical analysis was supplemented by Bayesian statistics to quantify the strength of the evidence.

EXPERIMENTAL PROCEDURES

Participants

Patients diagnosed with unipolar MDD by experienced physicians were recruited from the Department of Psychiatry of the Albert Szent-Györgyi Health Centre, University of Szeged. The diagnosis was established based on DSM-IV criteria using the Structured Clinical Interview for DSM-IV Axis I disorders. Patients with any confounding conditions such as comorbid major psychiatric disorders (e.g., substance abuse, psychosis) and individuals with a history of neurological disorders (e.g., stroke, epilepsy, head injury) were excluded. Those who did not meet the safety restrictions of TBS (e.g., having metallic implants in the cephalic region or any implanted electronic devices) were excluded. Based on a meta-analysis, pharmacotherapy might support the development of more stable antidepressive effects (Kedzior et al., 2012). Therefore, TBS was applied as add-on therapy. Stable pharmacological status was required from at least two weeks before the commencement of the study and maintained throughout the TBS therapy. All participants signed informed consent. The experimental protocol was approved by the local Ethics Committee of the University of Szeged in accordance with the Declaration of Helsinki.

Overall, 25 participants have been recruited and randomly assigned to receive either active or sham stimulation. Three participants assigned to the sham group withdrew participation before the completion of all TBS sessions. Two additional participants were excluded: one participant from the active TBS group was excluded due to health concerns unrelated to TBS, and one from the sham group who requested changes in medication after reporting adverse effects. These drop-outs were deemed to be at random. Analysis of complete cases was carried out involving 20 participants (Table 1).

Table 1. Demographic and clinical characteristics of the total sample completing treatment and the subgroups (mean ± SD)

	Total sample	Subgroups		
		Active group	Sham group	*p*
Sex (M/F)	5/15	1/9	4/6	0.303
Age (yr)	50.27 ± 13.24	51.86 ± 14.55	48.68 ± 12.35	0.605
Handedness (R/L)	19/1	9/1	10/0	0.352
Resting motor threshold (%)	60.6 ± 10.85	63.6 ± 10.59	57.6 ± 4.32	0.226
HDRS at baseline	17.2 ± 5.4	19.5 ± 5.7	15.0 ± 4.3	0.062
Benzodiazepine during treatment (number of patients)	3	1	2	1.000
Antidepressant during treatment (number of patients)	6	2	4	0.628
Antidepressant and benzodiazepine combined (number of patients)	11	7	4	0.370

Between group analyses were carried out using independent t-tests for continuous variables and Fisher's exact tests for categorical variables.

Experimental design

Participants were assigned to active or sham group using computer-generated allocation on the day of baseline testing, i.e., one workday before the commencement of the 10-session stimulation protocol. Participants were not aware of their group assignment. Baseline testing involved: (1) the measurement of the resting motor threshold (which was assessed to ensure the that resting motor threshold was comparable between the two groups) and (2) the administration of the HDRS, as well as (3) the neurocognitive tests (the n-back and the ANT). Subsequently, participants underwent 10 sessions of bilateral TBS delivered on consecutive workdays. The HDRS and the neurocognitive tests were then administered a second time, one day after the last TBS session.

Theta-burst stimulation protocol

Ten sessions of either active or sham stimulation were delivered on consecutive workdays. This therapy length is a frequent choice in treating MDD (e.g., Cheng et al., 2016; Chistyakov et al., 2015). A Magstim Rapid^2 stimulator with a D70^2 70 mm figure-of-eight coil (The Magstim Company Ltd, Whitland, Wales, UK) was used to generate TBS pulses. Before the start of TBS sessions, an anatomical T1-weighted MRI scan was performed using a 1.5T GE Signa Excite HDxt scanner (Milwaukee, WI, USA) with the following setup: 3D IR-FSPGR - TR/TE/TI: 10.3/4.1/450 ms; flip angle: 15; ASSET: 2, FOV: 25 × 25 cm; matrix: 256 × 256; slice thickness: 1 mm. The MRI recordings were used to generate a 3D brain model based on each participants' gyral morphology to localize the target area. The target area was localized at Brodmann 9/46, involving the anterior third of the middle frontal gyrus. This region is anatomically connected to the subgenual anterior cingulate cortex (sgACC), a region heavily involved in the pathophysiology of MDD (Drevets et al., 2008; Wu et al., 2016). Moreover, previous findings have indicated an anticorrelation between the functional connectivity of the Brodmann 9 and 46 regions and the sgACC, the targeted modulation of which is associated with higher TMS treatment efficacy (Fox et al., 2012). Precise coil positioning was supported by a TMS Neuronavigator (Brain Innovation, Maastricht, the Netherlands) with ultrasound CMS20 Measuring System (Zebris GmbH, Tübingen, Germany). This TMS localization method is suggested to require a smaller number of participants while resulting in behavioral changes (Sack et al., 2008).

Each session involved cTBS over the right DLPFC first, and then iTBS over the left DLPFC with a 25-minute pause between the stimulation of the two sites. The applied parameters were based on Huang et al. (2005). cTBS contained 600 uninterrupted pulses given for 40 s (with a pattern of 3 pulses at 50 Hz in every 200 ms). The number of pulses was identical during iTBS, but the pattern consisted of 3 pulses in a train of 2 s given at 50 Hz, repeated every 10 s for 40 trains. The stimulation intensity was set at 30% of the maximal stimulator output for all participants. The stimulation intensity was kept constant, as suggested by Kaminski et al. (2011) because motor and visual cortex excitability appears to be independent, which indicates that cortical excitability of other brain areas may not be related either (Boroojerdi et al., 2002). The chosen intensity of 30% was comparable with the average intensity of other TBS studies involving healthy participants (Lowe et al., 2018). Similar intensities also resulted in behavioral changes in MDD patients (Li et al., 2014). In addition, recent preliminary results also supported the beneficial effects of subthreshold TBS on depressive symptoms in a substantial proportion of MDD patients (Halper et al., 2019). The protocol for patients in the sham group was identical to the active stimulation, but a plastic block elevated the coil from the scalp by 4 cm. Therefore, the participants still experienced some mechanical vibration and heard the clicking sounds of the device without significant cortical stimulation. To ensure that cortical excitability was comparable between the two groups, the resting motor threshold (rMT) was determined with the visualization method on the day of baseline testing (Pridmore et al., 1998). This procedure is found to reliably measure cortical excitability (Varnava et al., 2011).

Testing of affective symptoms

The primary outcome measure of clinical symptoms was the change of depressive symptoms measured by the 21-item Hamilton Depression Rating Scale. HDRS is a half-structured interview widely used in clinical research (Behera et al., 2017). The HDRS involves the evaluation of a range of depression-related symptoms, including affective state, suicidal thoughts, somatic symptoms, sleeping and eating behavior, and sexual symptoms (Hamilton, 1960).

N-back task

Working memory was tested with the n-back task (Sweet, 2011). One-, two- and three-back tasks were administered consecutively using PsychoPy (version: v1.82.01). At each level, stimuli selected from a set of capital letters (A, C, E, I, K, L, S, O, R, T, U) were presented successively in the middle of the screen. Stimuli were presented for 1500 ms with 500-ms-long interstimulus intervals. For the 1-back task, participants had to press the spacebar if the currently appearing stimulus was the same as the previous one. For the 2-back and 3-back tasks, the spacebar had to be pressed if the second (2-back) or third letter (3-back) prior to the current stimulus was identical to the current stimulus. At each level, a total of 100 trials were completed and 20% of all presented stimuli were target stimuli to which participants were expected to respond. Based on the signal detection theory, we calculated *d'* as an index of sensitivity and performance. *d'* was defined as the subtraction of the hit rate and the false alarm rate expressed in z-scores domain (Haatveit et al., 2010):

$$d' = \mathrm{Z}(\text{hit rate}) - \mathrm{Z}(\text{false alarm rate})$$

Performance on the 1-back task was analyzed in the attention domain, while outcomes of the 2-back and 3-back tasks were averaged and examined in the working

memory (Martin et al., 2016). In addition, median RTs were calculated.

Attention network task

The ANT described by Fan et al. (2002) was administered to evaluate attention processes. First, a fixation cross appeared in the middle of the screen for a random duration between 400 and 1600 ms. Then, a 100-ms-long cue may or may not appear, preceding the target stimulus. Three types of cue were possible: (1) *spatial cue* indicating the position where the target stimulus was presented (2) *center cue* appearing in the position of the fixation cross (3) *double cue* presented both above and below the position of the fixation cross. If *no cue* appeared or the cue had already disappeared, the fixation cross was reintroduced for 400 ms. The stimuli included a target arrow pointing to the left or right to which participants had to respond by pressing the corresponding arrow button on the keyboard. One of the following types of stimuli were presented randomly: (1) in the *neutral condition,* target stimuli contained four lines and the target arrow in the middle (2) the *congruent condition* contained five arrows pointing to the same direction (3) the *incongruent condition* contained four arrows pointing to the same direction and the target arrow in the middle pointing to the opposite way. Stimuli were presented until a response (with a maximum presentation time of 1700 ms), after which a blank screen was presented for the remaining duration. Overall, one trial lasted for 3500 ms, and 300 trials were presented, comprising 24 practice trials and three blocks of 96 trials.

Median RTs of the correct trials were used to formulate three indices that measured different attentional subnetworks. The *alerting attention ratio* measures how one can achieve and maintain an alert state. The *orienting attention ratio* describes the ability to select relevant information from the sensory input. The *executive attention ratio* refers to the ability to resolve conflict among responses. All indices were corrected to the relevant baseline RTs. For alertness and orientation, a higher ratio indicates better attentional processing. On the contrary, a higher executive attention ratio indicates less effectiveness in dealing with interference. For an estimate of psychomotor speed, median RTs across all cue and target conditions were calculated. The indices were calculated as follows:

$$\textit{alerting attention ratio} = (RT_{\textit{double cue}} - RT_{\textit{no cue}})/RT_{\textit{no cue}}$$

$$\textit{orienting attention ratio} = (RT_{\textit{spatial cue}} - RT_{\textit{center cue}})/RT_{\textit{center cue}}$$

$$\textit{executiveattention ratio} = (RT_{\textit{incongruent}} - RT_{\textit{congruent}})/RT_{\textit{congruent}}$$

Statistical analysis

Statistical analysis was conducted using SPSS version 24 (*IBM SPSS Statistics for Windows*, 2016). Age, sex, rMT, handedness, and medication status before the first TBS session were compared between groups using independent t-tests for continuous variables and Fisher's exact tests for categorical variables. Difference scores between baseline and post-TBS HDRS ($HDRS_{pre\text{-}TBS} - HDRS_{post\text{-}TBS}$) were compared using an independent samples t-test. Cohen's *d* was reported as an index of effect size. Moreover, difference scores were entered into an analysis of covariance (ANCOVA) with pre-TBS HDRS score used as a covariate to examine whether baseline scores influence the results.

For the n-back task, *d'* measures of 1-back (interpreted as a measure of attentional processes) and the average of the *d'*s for the 2-back and 3-back tasks (interpreted as a measure of working memory) were analyzed using separate 2×2 mixed analyses of variance (ANOVAs) with TIME (pre-TBS vs. post-TBS) as a within-subject factor and the type of STIMULATION (active vs. sham) as a grouping variable. For ANT, alertness, orientation, and executive attention ratios were entered separately into 2×2 mixed ANOVAs with TIME (pre-TBS vs. post-TBS) as a within-subject factor and the type of STIMULATION (active, sham) as the grouping variable. Effect sizes for each ANOVA were estimated using partial eta squared (η_p^2), and Bonferroni correction was applied to correct for multiple comparisons.

Bayesian statistics were performed using JASP (0.12.2.0 version) (JASP Team, 2020) with default priors. The Bayesian approach can supplement the frequentist approach by providing an estimate of evidence strength. Bayesian analyses quantify the relative evidence in favor of the null (H_0) or alternative hypothesis (H_1) based on the collected data. We calculated and reported the BF_{10}, which is primarily a continuous measure; however, it was interpreted based on the following approximate classification scheme: $BF_{10} < 0.1$ indicates strong evidence for H_0, a value between 0.1 and 0.33 indicates substantial evidence for H_0, while a value between 0.33 and 1 indicates anecdotal evidence for H_0. Anecdotal evidence supports H_1 if BF_{10} is between 1 and 3, a value between 3 and 10 indicates substantial evidence for H_1, and $BF_{10} > 10$ indicates strong evidence for H_1 (Wagenmakers et al., 2018). To make our results more easily interpretable, we report the BF_{01} results (1 divided by BF_{10}) when evidence supports the H_0. For the Bayesian ANOVAs, the inclusion Bayes Factor (BF_{incl}) across matched models is also reported. It quantifies the relative difference between models containing the examined effect and the equivalent models that do not contain it. BF_{incl} is calculated by dividing the sum of the probabilities of the observed data by the sum of the updated probabilities.

RESULTS

Sample characteristics

The active and sham groups were comparable concerning sex, age, handedness, resting motor threshold, baseline HDRS score and medication status (see Table 1). Concomitant antidepressant medication of the participants was: venlafaxine ($n = 4$), mirtazapine ($n = 5$), escitalopram ($n = 2$), duloxetine ($n = 1$), clomipramine ($n = 1$), fluoxetine ($n = 1$), paroxetine

(n = 1), maprotiline (n = 2) and agomelatine (n = 1). Three participants received benzodiazepine treatment, while two participants were prescribed more than one antidepressants.

TBS effects on affective symptoms

A significant effect of TBS was found in the difference scores of HDRS ($HDRS_{pre\text{-}TBS} - HDRS_{post\text{-}TBS}$) between the active and sham group, $t_{18} = -2.522$, $p = .021$, *Cohen's* $d = -1.128$. In light of the collected data, Bayesian analysis indicated moderate evidence for a difference between the change of HDRS scores, $BF_{10} = 3.028$. Based on our results, the data was ~3 times more likely under H_1 (i.e., TBS treatment results in affective changes in the active group) than H_0 (i.e., TBS does not affect affective symptoms) (Supplementary Material S1). Fig. 1(A) shows that a higher reduction of HDRS scores was observed in participants receiving active TBS (mean ± SE scores: active group 8.2 ± 3.360; sham group 4.2 ± 1.172).

ANCOVA controlling for baseline HDRS scores indicated that the effect of baseline HDRS was not significant, $F_{1, 17} = 1.118$, $p = .305$, $\eta_p^2 = 0.062$, $BF_{incl} = 0.726$, whereas a tendency towards the effect of stimulation type on HDRS scores persisted, $F_{1, 17} = 3.415$, $p = .082$, $\eta_p^2 = 0.167$, $BF_{incl} = 2.372$. The Bayesian model comparison yielded that the best model only included the type of stimulation, but not the covariate. Moderate evidence ($BF_{10} = 3.028$) indicated that this model should be chosen over the null model (see Table 2).

For the RTs of the 1-back task, significant TIME × STIMULATION interaction was found, $F_{1, 18} = 7.503$, $p = .013$, $\eta_p^2 = 0.294$, $BF_{incl} = 4.501$. Pairwise comparisons revealed that the RTs of the active TBS group decreased significantly compared to the sham group, $p = .031$. There was a significant difference between the active and the sham group at the post-TBS time point, $p = .046$, while no difference was present at the pre-TBS time point, $p > .05$. The RTs of the active group dropped from (mean ± SE) 592.5 ± 45.3 to 524.5 ± 31.7, while the RTs of the sham group increased from 575.8 ± 45.38 to 620.7 ± 31.7 (Fig. 1 (B)). The main effect of TIME, $F_{1, 18} = 0.318$, $p = .580$, $\eta_p^2 = 0.017$, $BF_{incl} = 0.335$, and STIMULATION, $F_{1, 18} = 0.597$, $p = .450$, $\eta_p^2 = 0.032$, $BF_{incl} = 0.595$, were not significant. The Bayesian analysis revealed that the null model slightly outpredicted the full model ($BF_{10} = 0.908$, $BF_{01} = 1.101$), indicating inconclusive evidence for the null model (Supplementary Material S2).

Regarding the *d'* scores of the 1-back task, the main effect of TIME, $F_{1, 18} = 0.051$, $p = .824$, $\eta_p^2 = 0.003$, $BF_{incl} = 0.312$, STIMULATION, $F_{1, 18} = 1.803$, $p = .196$, $\eta_p^2 = 0.091$, $BF_{incl} = 0.806$, and the TIME × STIMULATION interaction, $F_{1, 18} = 0.006$, $p = .939$, $\eta_p^2 < 0.001$, $BF_{incl} = 0.381$, was not statistically significant. The null model was the best-fitting model, i.e., it outperformed the full model of $BF_{10} = 0.095$, $BF_{01} = 10.476$. The data were ~10 times less likely

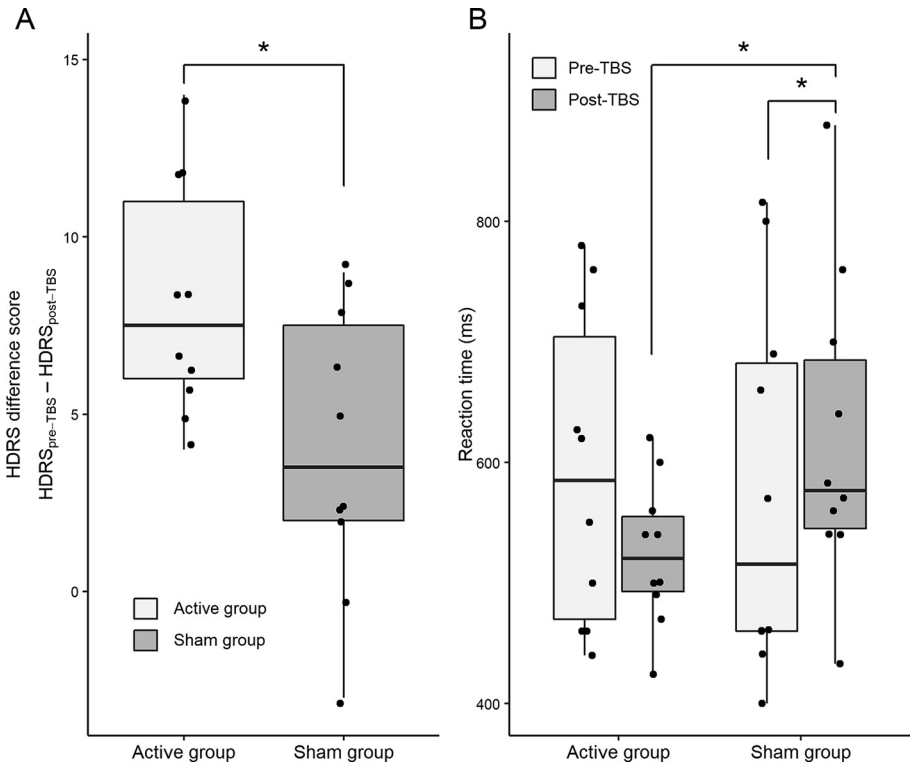

Fig. 1. Cognitive and affective changes in the active and sham group. **(A)** Box plot with individual data points depicting the changes of HDRS difference scores ($HDRS_{pre\text{-}TBS} - HDRS_{post\text{-}TBS}$). **(B)** Box plot with individual data points depicting the reaction time changes on the 1-back task.

Table 2. Model comparison results of Bayesian mixed-model ANOVA

Models	P(M)	P(M|data)	BF_M	BF_{10}	error %
Null model	0.250	0.144	0.504	1.000	
Type of stimulation	0.250	0.436	2.315	3.028	4.367e -4
Type of stimulation + baseline HDRS	0.250	0.268	1.098	1.862	1.182
Baseline HDRS	0.250	0.153	0.541	1.061	0.001

P(M): prior model probabilities, P(M|data): updated probabilities, BF_M: the degree change of the prior model odds after having observed the data, BF_{10}: Bayes Factor in favor of H_1

under H_1 than under H_0 which is considered a substantial evidence supporting the preference of the null model (Supplementary Material S3).

The average of the average RTs of the 2-back and 3-back tasks were entered into a mixed ANOVA which yielded a non-significant main effect of TIME, $F_{1, 18} = 0.520$, $p = .480$, $\eta_p^2 = 0.028$, $BF_{incl} = 0.396$, and STIMULATION, $F_{1, 18} = 1.798$, $p = .197$, $\eta_p^2 = 0.091$, $BF_{incl} = 0.710$. The TIME × STIMULATION interaction, $F_{1, 18} = 1.422$, $p = .249$, $\eta_p^2 = 0.073$, $BF_{incl} = 0.630$, was not significant either. The null model was the best model outperforming the full model of $BF_{10} = 0.180$, $BF_{01} = 5.556$. The data were ~5 times less likely to be observed under H_1 than under H_0. This evidence substantially supports that the null model should be preferred (Supplementary Material S4).

Considering the *d'* scores of the averaged 2-back and 3-back tasks, the main effect of TIME, $F_{1, 18} = 2.078$, $p = .167$, $\eta_p^2 = 0.104$, $BF_{incl} = 0.712$, STIMULATION, $F_{1, 18} = 0.098$, $p = .758$, $\eta_p^2 = 0.005$, $BF_{incl} = 0.447$, and TIME × STIMULATION interaction, $F_{1, 18} = 0.321$, $p = .578$, $\eta_p^2 = 0.018$, $BF_{incl} = 0.433$, was not significant. Bayesian analysis indicated that the best-fitting model was the null model. The results were ~7 times less likely to be observed under H_1 compared to H_0 which is considered as a substantial weight of evidence supporting that the null model should be preferred over the full model, $BF_{10} = 0.146$, $BF_{01} = 6.828$ (Supplementary Material S5).

Attention network task

The mixed ANOVA of the overall RTs yielded that the main effect of TIME, $F_{1, 18} = 3.071$, $p = .097$, $\eta_p^2 = 0.146$, $BF_{incl} = 0.908$, the main effect of STIMULATION, $F_{1, 18} = 0.584$, $p = .455$, $\eta_p^2 = 0.031$, $BF_{incl} = 0.551$, and the TIME × STIMULATION interaction, $F_{1, 18} = 2.138$, $p = .161$, $\eta_p^2 = 0.106$, $BF_{incl} = 1.164$, were non-significant. The null model outpredicted the full model ($BF_{10} = 0.501$, $BF_{01} = 1.995$); however, the data were ~ 2 times less likely to be observed under H_1 compared to H_0 which only indicates anecdotal evidence in support of the null model (Supplementary Material S6).

Results on the alerting attention ratio indicated a non-significant main effect of TIME, $F_{1, 18} = 0.001$, $p = .973$, $\eta_p^2 < 0.001$, $BF_{incl} = 0.306$, STIMULATION, $F_{1, 18} = 0.233$, $p = .635$, $\eta_p^2 = 0.013$, $BF_{incl} = 0.463$, and a non-significant interaction of TIME × STIMULATION, $F_{1, 18} = 0.767$, $p = .393$, $\eta_p^2 = 0.041$, $BF_{incl} = 0.500$. The full model ($BF_{10} = 0.073$, $BF_{01} = 13.718$) was outpredicted by the null model. Strong evidence supported the preference of the null model as the data were ~14 times less likely to be observed under H_1 than under H_0 (Supplementary Material S7).

Regarding the orientating attention ratio, we found that the main effect of TIME, $F_{1, 18} = 0.961$, $p = .340$, $\eta_p^2 = 0.051$, $BF_{incl} = 0.495$, the main effect of STIMULATION, $F_{1, 18} = 0.576$, $p = .458$, $\eta_p^2 = 0.031$, $BF_{incl} = 0.450$, and the TIME × STIMULATION interaction, $F_{1, 18} = 0.173$, $p = .682$, $\eta_p^2 = 0.010$, $BF_{incl} = 0.430$, were not significant. The full model, $BF_{10} = 0.095$, $BF_{01} = 10.545$, was outperformed by the null model. The likelihood of the data being observed under H_1 was ~10 times less likely than under H_0 indicating a strong evidence for the null model (Supplementary Material S8).

The mixed ANOVA of the executive attention ratio revealed a non-significant main effect of TIME, $F_{1, 18} = 0.336$, $p = .570$, $\eta_p^2 = 0.018$, $BF_{incl} = 0.378$, STIMULATION, $F_{1, 18} = 3.320$, $p = .085$, $\eta_p^2 = 0.156$, $BF_{incl} = 0.581$, and a non-significant interaction of TIME × STIMULATION, $F_{1, 18} = 0.017$, $p = .897$, $\eta_p^2 < 0.001$, $BF_{incl} = 0.373$. The full model ($BF_{10} = 0.083$, $BF_{01} = 12.042$) was outperformed by the null model i.e. its interpretation is limited. Compared to H_0, the likelihood of the data being observed under H_1 was ~12 times lower indicating strong evidence favoring null model (Supplementary Material S9).

DISCUSSION

Therapeutic effects of rTMS over the DLPFC on depressive symptoms are steadily gaining recognition. Our results of improved affective symptoms in this randomized, sham-controlled study after ten sessions of bilateral TBS (cTBS over the right DLPFC + iTBS over the left DLPFC) support this notion. Bayesian analysis further corroborated the presence of substantial evidence in support of the antidepressive effects of TBS. However, targeting DLPFC – which is a widely preferred region for non-invasive brain stimulation (Holczer et al., 2020) and a strongly implicated area in MDD (Fitzgerald et al., 2008; Grimm et al., 2008) – might not only affect the affective symptoms but also the cognitive functioning (Diener et al., 2012). Strikingly, the cognitive effects of NIBS in MDD are rarely investigated with inconclusive preliminary results ranging from no effect (Wajdik et al., 2014) to limited efficacy in some subdomains (Iimori et al., 2019; Martin et al., 2017; Scho et al., 2019). Our results indicate that TBS has no or limited effects on the working memory and attentional domains.

The only cognitive measurement on which we found a potential effect of TBS was the overall RT of the 1-back tasks. After active TBS, the frequentist analysis suggested an RT decrease similar to the practice effects experienced in healthy participants (Soveri et al., 2018). On the contrary, in the sham group, pre-TBS and post-TBS RTs were comparable. The perceived shortening of RTs independently of the cognitive load may occur due to improved psychomotor processing speed. Psychomotor speed is often slower in MDD compared to healthy individuals (Liu et al., 2019; Semkovska et al., 2019; Tian et al., 2016) and is associated with reduced cerebral blood flow in the motor cortex in MDD (Yin et al., 2018). However, the Bayesian analysis indicated inconclusive results regarding the reaction time measures of the ANT and the 1-back tasks. Thus, more investigations are required to further verify this finding.

The improvement of psychomotor speed, if replicable, might stem from the fact that TBS effects are propagated to remote brain areas (Singh et al., 2020; Tang et al.,

2015). Furthermore, TBS may modulate motor cortex excitability (Cao et al., 2018) and cerebral blood flow (Cho et al., 2012). Another possible explanation can be that TBS might reduce frontal alpha asymmetry (Pellicciari et al., 2017), which is linked to psychomotor retardation (Cantisani et al., 2015).

More pronounced cognitive changes after TBS were hypothesized as single-session stimulation with identical protocols to ours resulted in TBS-induced theta power modulation (Chung et al., 2017). Although theta power increase is associated with improved working memory performance (Jensen and Tesche, 2002; Lisman, 2010) and cognitive control (Cavanagh and Frank, 2014), in our study, TBS did not lead to such cognitive enhancement. This result is in contrast with previous promising results (Cheng et al., 2016; Scho et al., 2019). However, in the study of Cheng et al. (2016), patients with treatment-resistant depression were recruited, and a higher dose of stimulation with 1800 pulses/session were delivered. Scho et al. (2019) who have found improved working memory performance, administered unilateral TBS to the left DLPFC. Higher doses of TBS have been proposed to exert more pronounced effects (Nettekoven et al., 2014); however, other results have not fully supported this notion (Volz et al., 2013; Williams et al., 2018). Therefore, it is not clear whether the differences across results can be attributed to the difference in dosing TBS or other factors such as sample characteristics. It is also possible that the antidepressive and cognition-enhancing effects of TBS might be independent.

In the present study, several methodological decisions were based on reports of enhanced antidepressant effects (in the lack of similar methodological recommendations on enhancing cognition). For example, TBS was administered as add-on therapy, since concomitant pharmacotherapy might enhance the development of more stable TBS effects on depressive symptoms (Kedzior et al., 2012). However, cognition and affective symptoms might benefit from different stimulation parameters. Distinct patterns of metabolic changes may follow iTBS, cTBS and bilateral TBS (Li et al., 2018). Some TBS effects affecting regions outside the DLPFC relevant to the implementation of executive function (e.g., the medial prefrontal cortex and ACC for cognitive control (Alexander and Brown, 2011)) may be canceled out after bilateral TBS (Li et al., 2018). Thus, it is possible that iTBS, but not the combination of iTBS and cTBS might improve executive functions (Cheng et al., 2016).

One limitation of the present study includes the sham method chosen. While elevating the coil from the scalp hinders significant cortical stimulation (Siebner et al., 2009), other characteristic experiences such as scalp sensations and peripheral nerve stimulation are mostly abolished as well. Although the clicking sounds of the machine and some mechanical vibration can be experienced, the use of a more sophisticated sham method (e.g., a sham coil that produces shallow magnetic fields or weak electrical currents) would further improve the blinding of the participants.

Of note, our results may be slightly underpowered in some cognitive domains, as indicated by the BF_{incl} values. However, BF_{incl} values should be interpreted as a continuous measure (Wagenmakers et al., 2018), and for the ANT indexes and the d' scores of the n-back task, BF_{incl} values of the interactions approached the cut-off score. This indicates that the conclusions drawn are less likely to be misleading regarding executive functions.

Importantly, we did not find evidence for any immediate cognitive adverse effects of TBS. In comparison, electroconvulsive therapy is associated with impaired executive functioning, episodic memory deficit, and deterioration of global cognition (Andrade et al., 2016; Ren et al., 2014) that reverse in a few months (Bodnar et al., 2016), we show that TBS has the advantage of not causing similar temporary impairments while exerting antidepressive effects in patients with MDD.

Taken together, the present study suggests that 10 sessions of bilateral TBS have evident antidepressive effects but have limited cognition-enhancing efficacy. We found that executive functions were not affected by TBS. Hence, TBS might be a good alternative to electroconvulsive therapy as it does not cause transitory cognitive impairment. However, a systematic comparison of the antidepressant and pro-cognitive features (including the magnitude and the duration of the effects) of different brain stimulation paradigms is necessary. Further research is encouraged on the effects of TBS regarding psychomotor speed, as our results suggested a potential effect of TBS on RTs for visual stimuli. Several questions are yet to be answered regarding the optimal parameters of TBS and whether antidepressant and cognitive-enhancing effects require different parameters; thus, comparative studies of bilateral and unilateral stimulation are warranted. Nevertheless, bilateral TBS seems to be an acceptable add-on therapy with promising antidepressant effects, a possible effect on psychomotor speed, and no adverse effects impacting attention or working memory.

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DECLARATION OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORS' CONTRIBUTIONS

AH: Formal analysis, Writing - original draft, review & editing, Visualization, Investigation; VLN: Conceptualization, Methodology, Investigation; TV: Investigation, Writing - Review & Editing; KK: Investigation, Resources; AK: Resources; ZsTK: Conceptualization; Resources; LV: Conceptualization; PK: Conceptualization; AM: Conceptualization, Methodology, Supervision.

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APPENDIX A. SUPPLEMENTARY DATA

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Voxel-based asymmetry of the regional gray matter over the inferior temporal gyrus correlates with depressive symptoms in medicated patients with major depressive disorder

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ABSTRACT

The number of patients suffering from major depressive disorder (MDD) is increasing worldwide. Imbalanced hemispherical brain activity may be an underlying factor of MDD; however, whether structural asymmetry also contributes to the symptoms experienced in MDD has been scarcely investigated. In this study, we aimed to examine cortical asymmetry in association with the severity of depressive and cognitive symptoms observed in MDD during stable medication. The association between the affective and cognitive symptoms and gray matter asymmetry was evaluated in 17 MDD patients using voxel-wise gray matter asymmetry analysis on high-resolution T1-weighted MR images. Asymmetry index values in the inferior temporal gyrus (ITG) correlated with the scores of the 17-item Hamilton Depression Rating Scale (HDRS), but no association was found with the Beck Hopelessness Scale, and performance on the 1-, 2- and 3-back task. Our results indicate that the asymmetry of gray matter content in the ITG might be associated with higher depression severity. Our findings might help to better understand how structural changes contribute to depression severity in patients with MDD.

1. Introduction

Major depressive disorder (MDD) is a debilitating condition affecting mood, cognition, sleep, appetite, and libido (Kennedy 2008). The regulation of these functions involves several brain areas as well as brain circuitries, and consequently, structural abnormalities and functional disruptions have been reported across the entire brain in MDD (Drevets et al., 2008; Suh et al., 2020; Ye et al., 2016). The frontal areas have been implied to show imbalanced brain activity and metabolism with right hemispheric hyperactivity compared to the relative hypoactivity of the left side (for a review see Hecht, 2010). The presence of imbalance has also been supported by EEG (electroencephalography) measures in the alpha frequency range (Grunewald et al., 2018). Moreover, frontal alpha asymmetry seems to correlate with depressive symptoms including symptom severity, psychomotor retardation, and suicidal behavior (Cantisani et al., 2015; Diego et al., 2001; Park et al., 2019). Whether gray matter structural asymmetries are also present in MDD has only been investigated directly in four studies (see Table 1 for a summary), suggesting abnormal frontal and temporal asymmetries (Kumar et al., 2000; Liu et al., 2016; Zuo et al., 2019) or unilateral volume differences compared to healthy controls (Schmaal et al., 2017; van Tol et al., 2014).

A recent large-scale asymmetry analysis conducted by the ENIGMA Consortium comparing gyral-based regions of interest (ROIs), however, has not supported the presence of any cortical asymmetries as compared to healthy participants (de Kovel et al., 2019; Kong et al., 2020). Although this study has high statistical power and sample size, its results do not exclude the possibility that subregions within the examined ROIs and/or subgroups of MDD patients show structural asymmetry that might contribute to the clinical (either cognitive or affective) manifestations of MDD. Convergence of asymmetric cortical volumes has been suggested when analyzing clinical subgroups of patients (distinguished based on medication status or the presence of comorbid disorders) (Gray et al., 2020). Furthermore, voxel-based analyses may be performed to test if certain gray matter subregions (instead of predefined

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ROIs) show abnormal asymmetry.

Structural asymmetries in MDD have been linked to depressive symptoms, indicating their potential relevance in the pathomechanism of MDD. For instance, higher structural asymmetry of the dorsolateral prefrontal cortex (DLPFC) correlated with self-reported depressive symptoms in subclinical and major depression (Liu et al., 2016). Strikingly, associations between structural asymmetry and other core aspects of MDD (e.g., cognitive symptoms or suicidal ideations) have not been explored previously, despite cognitive deficit being a prominent feature of MDD (Gärtner et al., 2018; Mohn and Rund, 2016).

In the present study, we aimed to investigate voxel-based cortical asymmetry in association with the severity of both depressive and cognitive symptoms observed in MDD patients with stable medication status. The interaction of voxel-based asymmetry with depressive symptoms, hopelessness, attention, and working memory were examined to identify brain areas with abnormal cortical asymmetry linked to potential residual symptoms. The voxel-based approach we are using in the current investigation provides higher spatial resolution and does not suffer from the inherent bias of ROI-based methods (Astrakas and Argyropoulou 2010). A protocol for voxel-wise gray matter asymmetry calculation was performed to investigate the association between cortical asymmetries and the cognitive symptoms and MDD severity (Kurth et al., 2015).

2. Methods

2.1 Participants

Seventeen patients with MDD diagnosed by expert clinicians were recruited from the Department of Psychiatry of the Albert Szent-Györgyi Health center, University of Szeged (see Table 2 for sample characteristics). The medication status of all patients was kept stable at least two weeks prior to the neuroimaging recordings. Antidepressant treatment was combined with benzodiazepines in the case of 8 participants, 4 patients received antidepressants only, and 5 participants took benzodiazepines without antidepressant medication. The antidepressants were classified as follows: serotonin and norepinephrine reuptake inhibitors ($n = 4$), selective serotonin reuptake inhibitors ($n = 2$), atypical antidepressants ($n = 2$), tetracyclic antidepressants ($n = 2$), monoamine oxidase inhibitor ($n = 1$), and tricyclic antidepressant ($n = 1$). The study was approved by the Ethics Committee of the University of Szeged (Ref. No.: 165/2014). All participants gave written informed consent in accordance with the Declaration of Helsinki.

Table 2
Sample characteristics.

Age (years, mean ± SD)		49.78 ± 13.12
HDRS score (mean ± SD)		17.58 ± 5.64
Sex	Male	3
	Female	14
Education level	Primary	2
	Secondary	9
	Vocational education	2
	University	4
Medication status	Antidepressant only	4
	Benzodiazepine only	2
	Antidepressant and benzodiazepine combined	11

2.2. Assessment of affective and cognitive symptoms

To assess depression-related symptoms, a half-structured interview, the 17-item HDRS was administered. The HDRS comprises the assessment of several symptoms including affective state, suicidal thoughts, somatic symptoms, sleeping and eating behavior, and sexual symptoms (Hamilton, 1986). The HDRS is a frequently used tool in clinical research (Behera et al., 2017). The short, 4-item version of the Beck Hopelessness Scale (BHS) was also administered to further explore negative expectations and hopelessness (Beck and Steer, 1988).

Three levels of the n-back task (1-back, 2-back, and 3-back) were performed in ascending order by each participant. The task was presented using PsychoPy (version: v1.82.01). Stimuli selected from a set of capital letters (A, C, E, I, K, L, S, O, R, T, U) were presented consecutively on the screen for 1500 ms with 500-ms-long interstimulus intervals. During the 1-back task, participants were asked to press the spacebar if the target stimulus presented on the screen was the same as the previous one. During the 2-back and 3-back tasks, the spacebar had to be pressed if the second or third letter preceding the target stimulus was identical with the letter presented, respectively. At each level, a total of 100 trials were completed, and 20% of all presented stimuli were target stimuli to which participants were expected to respond. Sensitivity index (d' score) was calculated for all levels based on the signal detection theory by subtracting the false alarm rate from the hit rate, both expressed in z-scores: $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ (Haatveit et al., 2010). d' scores of the 1-back task were interpreted in the attention domain, while

Table 1

Study	Sample Patient characteristics	Medication status	Methods Methods, examined regions	Asymmetry index	Results Correlation with symptoms	Asymmetry compared to HCs	Direction of asymmetry
Zuo et al. (2019)	First-episode MDD	Treatment-naïve patients	Cortical thickness	AI = (L–R) × 100 / (L+ R)	No correlation between symptom severity and AIs	Higher AI in the caudal middle frontal cortex, superior frontal cortex and rostral middle frontal cortex in MDD	left-lateralization
Kumar et al. (2000)	Late-onset MDD or late-onset minor depression	N/R	Volume of the cerebral hemispheres, frontal and temporal lobes	AI = (R–L) / (L+ R) × 100	N/A	Smaller left-right frontal AI in minor depression and MDD	less right-lateralized
Liu et al. (2016)	First-episode MDD + responders to antidepressant medication	Treatment-naïve patients + patients receiving antidepressant medication	**ROI analysis:** asymmetry indexes of the DLPFC, hippocampus, amygdala, insula, PFC and the whole brain	AI = R–L	DLPFC AI negatively correlated with self-reported depression	Lower asymmetry index in first-episode, treatment-naïve MDD patients (also in individuals with subclinical depression) Antidepressants normalized AI abnormalities in medicated MDD patients	less right-lateralized
de Kovel et al. (2019)	First-episode + recurrent MDD (in an acute or remitted state)	Treatment-naïve + patients receiving antidepressant medication	**ROI analysis:** thickness and surface area measures for each of 34 bilaterally paired cortical regions	AI = (L–R) / (L+ R)	N/A	Higher superior temporal gyrus thickness AI in MDD (not statistically significant after correction for multiple comparison)	right-lateralization

the results of the 2-back and 3-back tasks were interpreted in the working memory domain (Martin et al., 2016).

2.3. Data acquisition

Magnetic resonance imaging (MRI) was performed using a 1.5 T GE Signa Excite HDxt MR Scanner (GE Healthcare, Chalfont St. Giles, UK). Three-dimensional high-resolution T1-weighted anatomical images were acquired for all participants (3D spoiled gradient echo images with inversion recovery (3D FSPGR IR): echo time [TE]: 4.1 ms; repetition time [TR]: 10.276 ms; matrix: 256 × 256, field of view [FOV]: 25 × 25 cm, flip angle: 15°, in-plane resolution: 1 × 1 mm, slice thickness: 1 mm).

2.4. Data analysis

The image analysis was carried out using the VBM8 Toolbox (http://www.neuro.uni-jena.de/vbm/download/) implemented in Statistical Parametric Mapping 8 (SPM8; Wellcome Trust center for Neuroimaging, London, UK) software (https://www.fil.ion.ucl.ac.uk/spm/software/spm8/). In order to create a symmetric gray matter skeleton containing gray matter asymmetry index (AI) values for each voxel, a step-by-step guideline published by Kurth and colleagues was followed (Kurth et al., 2015). All non-brain parts were removed from the T1-weighted images and then the brain was segmented into gray matter, white matter, and cerebrospinal fluid. All gray and white matter segments were flipped along the midline prior to creating the symmetric Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) template from the original and flipped gray and white matter segments (Ashburner 2007). Afterwards, the images were registered to the mean DARTEL template and averaged, and a binarized right hemisphere mask was created in the symmetric template space to limit statistical calculations to the right hemisphere. Then, we calculated an asymmetry index based on the following equation:

$$AI = \left(\frac{(i1 - i2).}{(i1 + i2). * 0.5}\right) * i3$$

where ($i1$) = warped original gray matter segment; ($i2$) = warped flipped gray matter segment and ($i3$) = binarized right-hemisphere mask image. Positive AI values indicate more gray matter in the right hemisphere (rightward asymmetry), while negative AI value means higher gray matter content in the left hemisphere (leftward asymmetry). After image pre-processing, all AI images were spatially smoothed using an 8 mm smoothing kernel. Finally, a voxel-wise general linear model (GLM) as implemented in the FMRIB Software Library (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM) was performed. Age and sex served as covariates, while positive and negative contrasts were calculated for HDRS, BHS, and d' scores to test bidirectional associations with the AI values. Then, permutation-based non-parametric testing was performed with a thresholding using threshold-free cluster enhancement technique. The images were thresholded at $p < 0.05$ and corrected for multiple comparisons with a family-wise error rate (FWE) correction. The design matrices contained the age, sex, and HDRS, BHS and d' scores for each subject separately.

3. Results

The result of voxel-based gray matter asymmetry analysis was visualized as an overlay on the MNI152 2 mm standard brain. Gray matter asymmetry analysis yielded a significant negative correlation between the gray matter AI values of the inferior temporal gyrus (ITG) and the individual HDRS scores (Fig. 1), as determined by the MNI152 standard space coordinates ($x = 18$, $y = 55$, $z = 17$). No significant association was found between the gray matter AI values and the BHS and d' scores derived from n-back task.

The higher the HDRS scores, the lower or more negative the AI values were, as indicated by the AI values extracted from the significant cluster ($R = -0.879$, $p \leq 0.001$) (Fig. 2). Thus, in patients with more severe depressive symptoms, a higher leftward asymmetry in the ITG (i.e., lower gray matter content in the right hemisphere, higher gray matter content in the left hemisphere) can be observed.

4. Discussion

Brain abnormalities in MDD have been widely investigated to better understand the neural background of this debilitating disorder. The aim of the present study was to examine the association of affective and cognitive symptoms with cortical asymmetries in MDD patients under stable medication. Voxel-based cortical asymmetry calculations were carried out indicating a leftward asymmetry within the ITG in patients with more severe depressive symptoms (i.e., the higher the depression severity, the less gray matter volume in the right ITG as compared to the left homologue area). No similar association or any asymmetry within other brain regions was found with respect to hopelessness and cognitive measures. While previous ROI-based studies have reported no abnormal asymmetry or results limited to specific MDD subgroups (de Kovel et al., 2019; Kong et al., 2020), our analysis showed a cluster of voxel-wise asymmetries within the ITG that were in association with depressive symptoms present in medicated MDD patients. Such small changes might be overlooked if imaging data is analyzed using predefined ROIs.

The ITG has previously been reported to show an asymmetric reduction of gray matter volume (Schmaal et al., 2017), especially in medication naïve (Guo et al., 2014a; Gray et al., 2020) and first-episode

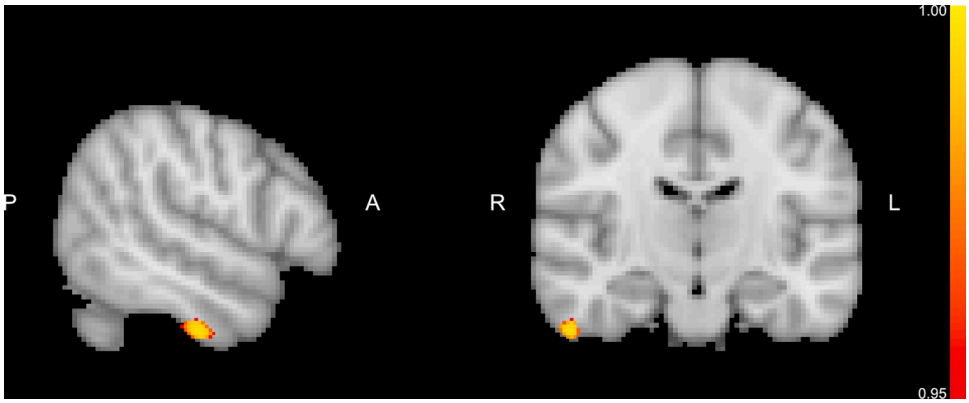

Fig. 1. ***The result of the gray matter asymmetry analysis.*** A significant correlation was found between the AI values of the inferior temporal gyrus and the HDRS scores. MNI152 standard space coordinates of the slices for the significant cluster are ($x = 18$, $y = 55$, $z = 17$). The color bar represents (1 - p) values. (ITG: inferior temporal gyrus, HDRS: Hamilton Depression Rating Scale).

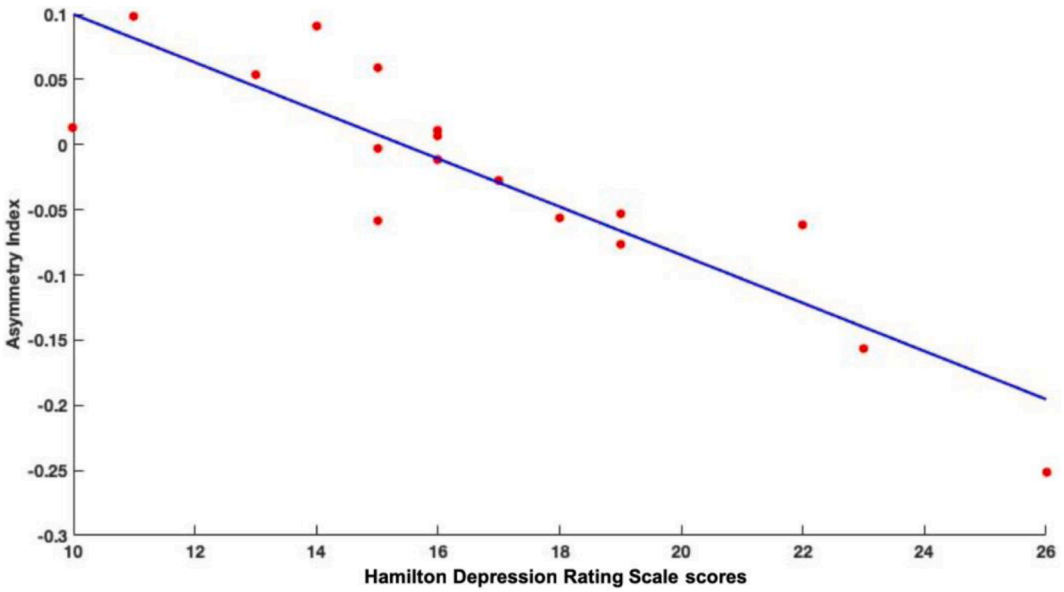

Fig. 2. ***Correlation between the AI values of ITG and the HDRS scores.*** (ITG: inferior temporal gyrus, HDRS: Hamilton Depression Rating Scale).

MDD patients (Peng et al., 2011). Moreover, the volume of the ITG has had a positive correlation with the 17-item HDRS scores and with longer reaction times on an attention task (Li et al., 2010). The ITG has also been found to be affected in other disorders, such as schizophrenia (Onitsuka et al., 2004) and bipolar affective disorder (Gong et al., 2019). Summarizing all these results, the ITG appears to be affected in several disorders including MDD, which casts light on its potential importance in the pathomechanism of these conditions.

The ITG seems to be engaged in cognitive processes such as semantic processing and concept retrieval (Faber et al., 2014), but also contributes to social cognition (Gallagher and Frith, 2003), self-referential processing (Herold et al., 2016) and the processing of affective stimuli (Hu et al., 2017). On a network-level, the ITG seems to be involved in the extended default mode network (DMN) (Allen and Williams 2011; Guo et al., 2014b), which is reported to show an imbalance in MDD (Hamilton et al., 2015). More specifically, an abnormally decreased network homogeneity (Guo et al., 2014b) and reduced amplitude of low-frequency fluctuation (indicating the absolute intensity of spontaneous brain activity) of the right ITG has been observed within the DMN as compared to healthy individuals (Guo et al., 2014b). Our results linking the structural features of the ITG to the clinical symptoms of depression supplement the findings on functional disruptions and suggest that the gray matter content of the ITG might contribute to a larger-scale network-level abnormality relating to negative affect and rumination.

In light of these results, the characteristics of the ITG in MDD should be explored more thoroughly, such as the extent of its white matter network and its relationship with functional or behavioral factors associated with depression. Furthermore, ITG may be suitable as a target for non-invasive brain stimulation (e.g., transcranial magnetic stimulation, transcranial electrical stimulation). These interventions have been utilized to mitigate the affective and cognitive symptoms in MDD (Iimori et al., 2019; Holczer et al., 2021) and to supplement the effects of the ongoing medication (Berlim et al., 2013; Plewnia et al., 2014). By stimulating the ITG, the residual symptoms might be further mitigated; however, this requires empirical support.

Limitations of the present study include sample size and imbalanced sex ratio. However, we corrected for the effects of sex and age by performing a covariate analysis. From the present study, we cannot clearly determine if and which pharmaceutical preparation has an effect on the structural changes of the ITG. In our sample, different types of medication (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) were administered to the patients. Thus, future longitudinal-design studies should explore the antidepressant effects on the gray matter volume of the ITG.

An additional limitation may be the validity of HDRS-17 among patients undergoing different drug therapies as different therapies may induce divergent responses in terms of the final score and its subcomponents. It would be necessary to take additional samples assessed with another psychometric tool measuring depression (e.g., the Beck Depression Inventory). However, antidepressants regardless of the exact type seem to decrease depressive symptoms, and their network-level effect mainly acts on the connection strength between symptom-domains (Berlim et al., 2020). Since our results are cross-sectional, longitudinal studies are needed to examine whether depression severity is consistently associated with the structural changes of the ITG.

Conclusion

In the present study, we examined the association of affective and cognitive symptoms with cortical asymmetries in medicated MDD patients and found that the leftward shift of the ITG was associated with higher depression severity. The understanding of cerebral pathology is essential and may facilitate more targeted approaches for the prevention and management of MDD.

CRediT authorship contribution statement

Krisztián Kocsis: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Adrienn Holczer:** Data curation, Writing – original draft, Writing – review & editing. **Csaba Kazinczi:** Data curation, Writing – original draft. **Katalin Boross:** Data curation, Formal analysis. **Regina Horváth:** Data curation, Formal analysis. **Luca Viola Németh:** Data curation, Formal analysis. **Péter Klivényi:** Conceptualization, Writing – review & editing. **Zsigmond Tamás Kincses:** Conceptualization, Writing – review & editing. **Anita Must:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Frontal two-electrode transcranial direct current stimulation protocols may not affect performance on a combined flanker Go/No-Go task

Adrienn Holczer[1,4]✉, Teodóra Vékony[2,4], Péter Klivényi[1] & Anita Must[3]

Transcranial direct current stimulation (tDCS) has been tested to modulate cognitive control or response inhibition using various electrode montages. However, electrode montages and current polarities have not been systematically compared when examining tDCS effects on cognitive control and response inhibition. In this randomized, sham-controlled study, 38 healthy volunteers were randomly grouped into receiving one session of sham, anodal, and cathodal each in an electrode montage that targeted either the dorsolateral prefrontal cortex (DLPFC) or the fronto-medial (FM) region. Participants performed a combined flanker Go/No-Go task during stimulation. No effect of tDCS was found in the DLPFC and FM groups neither using anodal nor cathodal stimulation. No major adverse effects of tDCS were identified using either montage or stimulation type and the two groups did not differ in terms of the reported sensations. The present study suggests that single-session tDCS delivered in two two-electrode montages might not affect cognitive control or response inhibition, despite using widely popular stimulation parameters. This is in line with the heterogeneous findings in the field and calls for further systematic research to exclude less reliable methods from those with more pronounced effects, identify the determinants of responsiveness, and develop optimal ways to utilize this technique.

Transcranial direct current stimulation (tDCS) has been increasingly tested to modulate a wide range of motor and cognitive functions[1], including interference control and response inhibition, which are among the core aspects of executive functions and are essential for adaptive behavior[2]. However, the mechanisms through which tDCS influences brain activity and behavior are yet to be completely understood and are modulated by several factors, including study design parameters[3]. One key factor influencing tDCS effects is the electrode montage that determines the direction and magnitude of the current passing through the brain[4,5].

A number of tDCS studies have targeted the dorsolateral prefrontal cortex (DLPFC) to modulate interference control (operationalized as performance on the flanker or Stroop tasks[6–10], or response inhibition measured using the Go/No-Go or stop-signal tasks[11–13]) based on its reliable activation while performing these tasks[14–16]. Many studies used an asymmetric electrode montage (i.e. one electrode on the left DLPFC and another over the contralateral supraorbital area)[6–8] that is frequently used when studying the cognitive effects of tDCS in other domains (e.g.[17–20]). Recent studies have found that anodal tDCS over the DLPFC was associated with improved interference control or enhanced response inhibition[6–8,11,21], in accordance with the assumption that anodal tDCS depolarizes the neuronal membrane and, thus, increases spontaneous brain activity[22]. However, the efficacy of cathodal tDCS has been questioned regarding the modulation of cognition[23], and more specifically, interference control and response inhibition[6,13]. Additionally, some reports have found no cognition-modulating effects of either anodal or cathodal tDCS when targeting the DLPFC[9,24,25].

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Importantly, the implementation of both interference control and response inhibition results from the dynamic interplay between several cortical areas[26,27]. Apart from the DLPFC, the anterior cingulate cortex (ACC) is considered a hub for monitoring and detecting interference[28–30] via engaging with the DLPFC which is associated with interference resolution[15,16]. Increased activity in the fronto-medial areas has also been reported with respect to response inhibition on a Go/No-Go task[27]. Accordingly, studies have targeted different brain sites with various electrode montages with the common aim of improving interference control and response inhibition[8,10,12,31]. Nevertheless, the results have been ambiguous: while only a limited impact on response inhibition has been reported, electrophysiological evidence has suggested that tDCS modulates error-related measures and conflict detection[12,31,32]. The effects of fronto-medial tDCS on stimulus-stimulus interference resolution have not been investigated. Still, considering that interference control also involves an evaluative (i.e. conflict monitoring) phase[33], fronto-medial tDCS may result in increased conflict monitoring and associated behavioral changes.

To date, montages targeting the DLPFC alone and fronto-medial montages have not been directly compared despite both being commonly used in the field[32,34]. For a clinically meaningful effect, systematic comparisons (with stimulation parameters that are not of interest kept constant) and replication studies are of paramount importance in identifying the most effective parameters[35]. Excluding those sets of parameters that yield inconclusive effects may aid the exploration of methods that are more reliable. In addition, it is also recommended to test polarity specificity, that is, to include both anodal and cathodal stimulation in the experimental paradigm[13]. The present randomized, sham-controlled study compared the effects of anodal, cathodal, and sham tDCS on interference control and response inhibition using a combined flanker Go/No-Go task while contrasting the cognition-modulating effects of two prefrontal electrode montages: a conventional DLPFC and a fronto-medial montage. In addition to cognitive changes, we also monitored adverse effects and compared them across the two montages.

Materials and methods

Experimental design. A randomized, sham-controlled mixed-design study was conducted on healthy volunteers. The experiment consisted of three sessions of tDCS (anodal, cathodal, and sham) with a counterbalanced stimulation order that was randomized at the beginning of each participant's first session using computer-generated allocation. With the same method, participants were randomly assigned to one of two remaining experimental groups. They received stimulation either over the left DLPFC (DLPFC Group) or the fronto-medial (FM) areas (FM Group). The target area was kept constant for a given participant. Immediately after starting the stimulation, participants performed a combined flanker Go/No-Go task detailed below. After each session, participants filled out a questionnaire to assess the presence of any adverse effects. The interval between the different sessions was at least 48 h to avoid potential carryover effects. The study was conducted in accordance with the declaration of Helsinki, and the experimental protocol was approved by the Ethics Committee of Albert Szent-Györgyi Clinical Centre, University of Szeged (Ref No.: 174/2018).

Participants. 40 healthy young subjects (M_{age} = 23.28; years; SD_{age} = 3.46 years R_{age} = 18–31 years) were recruited in our study (20 females). Two participants withdrew participation after the first session: one participant dropped out due to a headache after the first (sham) session, and one participant due to logistical issues after receiving anodal stimulation. As these dropouts were deemed random, the data of 38 participants (complete cases) were analyzed (see Table 1). Overall, 38 participants completed all sessions with a mean of 8.3 days apart. The minimum group size was predefined to include at least 15 participants in accordance with previous studies with similar interventions and outcome measures with significant findings[6,11,36,37]. The participants were naïve to the purpose of the study and were debriefed after the last session ended. All participants had normal or corrected-to-normal vision and met the safety restrictions of tDCS (e.g. lack of history of epilepsy, previous head injury, the presence of metallic implants in the cephalic region, or any implanted electronic devices). None of the participants reported a history of any neurological or psychiatric disorders or the use of any drugs affecting the function of the central nervous system. All participants were informed about the potential side effects of the stimulation and signed an informed consent form prior to the experiment.

Experimental task and procedure. A combined version of the Eriksen flanker and the Go/No-Go tasks was used to examine cognitive control performance (Fig. 1), based on the task used by Zmigrod et al.[11]. Combined tasks like ours have been shown to yield comparable behavioral results as well as brain activation patterns as the traditional flanker and Go/No-Go tasks[38–41]. The task was presented using E-Prime version 2.0[42]. An arrow (target stimulus) pointing to the left or the right appeared on the screen, surrounded by four other

	DLPFC group (n = 19)	FM group (n = 19)	*p*	BF_{01}
Age (mean years of age ± SD)	23.63 ± 3.62	24.00 ± 3.50	0.752	3.048
Sex (m/f)	11/8	13/6	0.737	2.173
Handedness (r/l)	15/4	17/2	0.557	3.058

Table 1. Demographic characteristics of the subgroups. Between-group analyses were carried out using independent *t* tests for continuous variables and Fisher's exact tests for categorical variables. BF_{01} indicates the Bayes factor in favor of the null hypothesis over the alternative hypothesis.

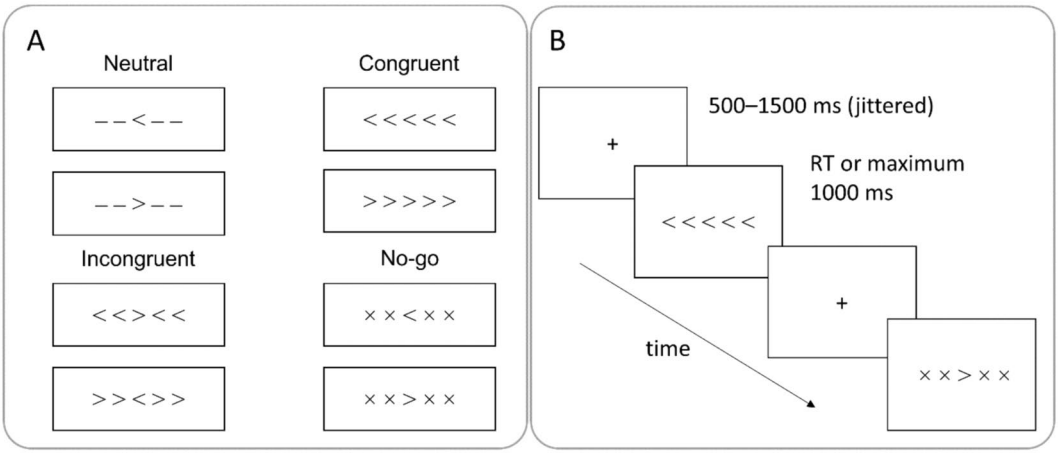

Figure 1. The trial types (**A**) and task flow (**B**) of the combined flanker Go/No-Go task.

stimuli. Participants were asked to respond to the middle (target) stimulus with the left or right arrow button of the keyboard with their left or right index finger of each hand, respectively. Based on the characteristics of the surrounding stimuli, four trial types could be differentiated: *congruent* (surrounding stimuli trigger the same response as the target stimulus), *incongruent* (surrounding stimuli trigger a different response as the target stimulus), *neutral* (surrounding stimuli do not indicate orientation), and *no-go* trials (surrounding stimuli indicate response inhibition). In *no-go* trials, participants were instructed to withhold their response when "×" symbols surrounded the target stimulus. The stimuli remained on the screen until response or up to 1000 ms. The inter-stimulus interval varied pseudo-randomly between 500 and 1500 ms. The mean inter-trial interval was 625.94 ms (SD = 232.9).

The order of the trials was randomized, and the number of trials for each trial type was counterbalanced. The task was preceded by a practice block containing 16 trials when participants received immediate feedback on their accuracy. After that, six blocks of 96 trials were completed by the participants (576 trials). Between each block, participants could rest and continue the task at their pace.

tDCS stimulation parameters. Stimulation was delivered using the Eldith DC Stimulator Plus (NeuroConn GmbH, Ilmenau, Germany). The stimulation parameters including the electrode size, current intensity, stimulation duration, and sham protocol were chosen based on the most common settings in the literature[34]. Rubber electrodes covered in 35 cm^2 saline-soaked sponges were fixed on the scalp with plastic traps. Current strength of 2 mA was used. For anodal stimulation of the left DLPFC, the anode was placed over the F3 according to the international 10–20 EEG localization system, while the cathode was positioned over the contralateral supraorbital area. For the anodal fronto-medial stimulation, the anode was applied over the AFz and the cathode over the Pz. Simulation of electric fields generated by tDCS for both electrode montages was also performed to ensure targeting. When applying cathodal stimulation, the position of the anode and cathode electrodes was reversed. To simulate the current flow (Fig. 2), we created three-dimensional head models with a finite element method using SimNIBS v3.2 with the 'Ernie' head model[43]. Isotropic conductivities were adopted from the SimNIBS GUI. Twenty minutes of stimulation with 10 s of fade-in and fade-out was carried out for both groups. Sham stimulation was identical to the active protocol of the given group, except that the stimulation length was reduced to 30 s. The position of the anode and cathode during sham stimulation was randomized and counterbalanced across groups.

Procedure. Participants started the flanker task immediately after the start of the stimulation. The expected length of the cognitive control task was matched with the length of the stimulation. After finishing the task, participants completed a questionnaire regarding the subjective effects and sensations experienced during the stimulation.

Adverse effects. A self-reported questionnaire recommended by Brunoni et al. was administered to evaluate and compare the adverse effects of both montages[44]. The following symptoms were included in the questionnaire: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, and immediate mood changes. Participants were also asked to report if they experienced any symptoms not listed. Symptoms were rated based on presence with a 4-point rating scale (1 = absent, 4 = severe) and certainty (whether the sensation was related to the stimulation or not) with a 5-point rating scale (1 = none, 5 = definite).

Statistical analysis. Data were analyzed using JASP (version 0.17.2.1.[45]) and the figures were made in R (version 4.0.3[46]). Median reaction times (RTs) of correct trials were entered into a mixed-model analysis of

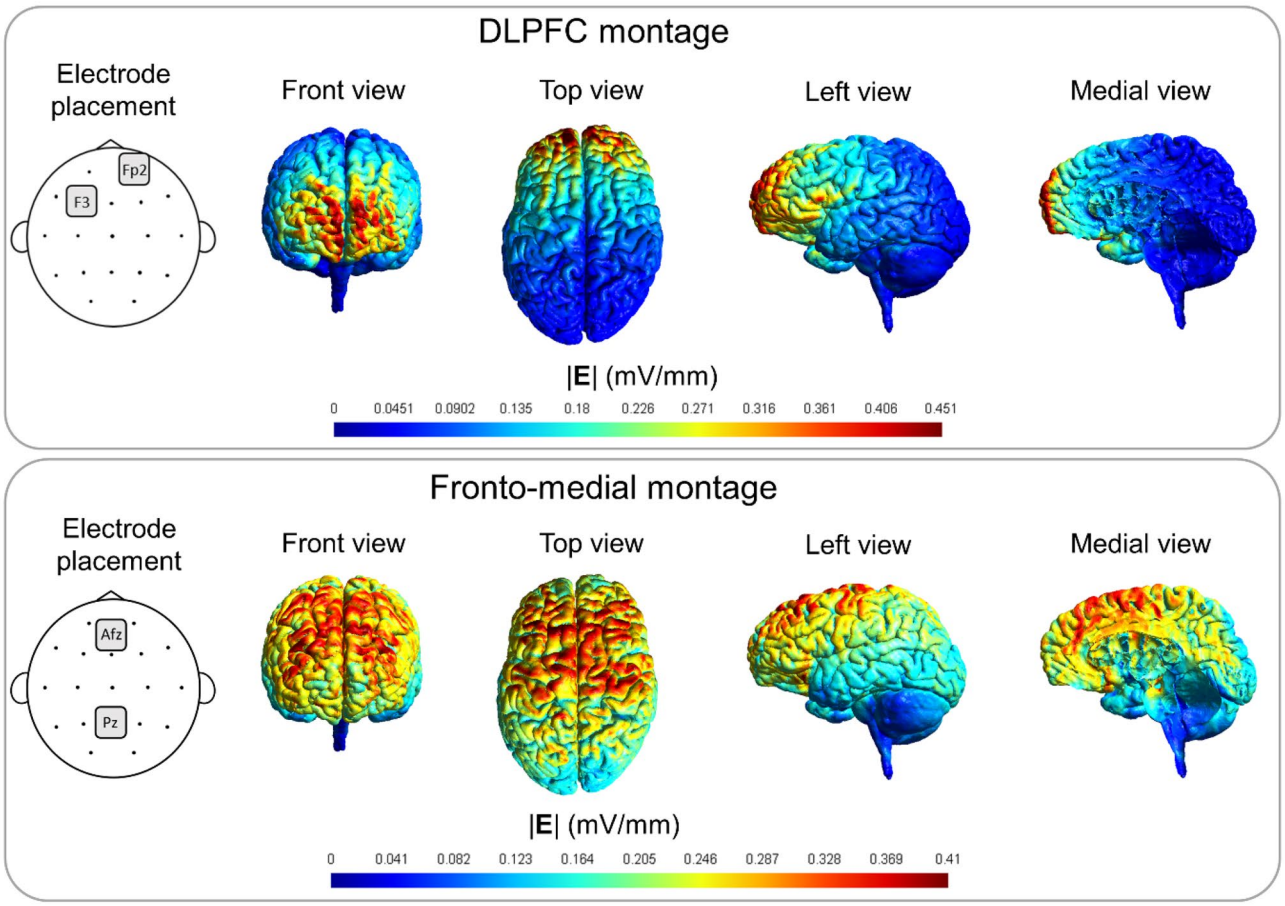

Figure 2. Simulation of normalized electric field distribution (|E|) for both montages. Field strengths were similar between electrode montages. For the anodal fronto-medial stimulation, the anode was applied over the AFz and the cathode over the Pz. For anodal stimulation of the left DLPFC, the anode was placed over the F3 according to the international 10–20 EEG localization system, while the cathode was positioned over the contralateral supraorbital area. When applying cathodal stimulation, the position of the anode and cathode electrodes was reversed.

variance (ANOVA). A 2 × 3 × 3 ANOVA was used with Montage (DLPFC, FM) as a between-subject factor and with Stimulation Type (sham, anodal, cathodal) and Trial Type (neutral, congruent, incongruent) as within-subject factors. No-go trials could not be included in the RT analysis as these required the suppression of motor response.

Interference effects were calculated for all stimulation types by extracting the median RTs of the congruent trial type from the median RTs of the incongruent trial type (Interference effect = $RT_{incongruent} - RT_{congruent}$). Lower interference effect score indicates better recruitment of cognitive control. Next, a 2 × 3 ANOVA was performed on the interference effect scores with montage (DLPFC, fronto-medial) as a between-subject factor and Stimulation Type (sham, anodal, cathodal) as a within-subject factor. To further explore tDCS effects, congruence sequence effect was analyzed using a 2 × 3 × 2 × 2 ANOVA with Montage (DLPFC, FM) as a between-subject factor and with Stimulation Type (sham, anodal, cathodal), Trial n congruence (congruent, incongruent), and Trial n-1 congruence (congruent, incongruent) as within-subject factors. Due to the low number of trials, CSE was only calculated for the congruent and incongruent trials, and not the Go/No-Go trials. Erroneous trials, the first trials with no previous congruency, and trials preceded by neutral or Go/No-Go trials were removed from the analysis. Thus, four possible categories were possible based on Trial n-1 and Trial n congruence: congruent trials preceded by congruent trials (cC), congruent trials preceded by incongruent trials (iC), incongruent trials preceded by congruent trials (cI) and incongruent trials preceded by incongruent trials (iI).

Accuracy data were analyzed similarly to median RTs, except that accuracy scores of no-go trials were also included in the Trial Type factor (neutral, congruent, incongruent, no-go).

The presence of adverse effects was analyzed in separate mixed analyses of variance with Stimulation type (anodal, cathodal, sham) as within-subject factors and Montage (DLPFC, FM) as a between-subject factor. To assess whether adverse effects were comparable, we evaluated the Stimulation type × Montage interaction for each symptom.

For all ANOVAs, Greenhouse–Geisser correction was used if necessary to correct for non-sphericity, and Bonferroni-corrected post-hoc tests were performed for statistically significant results.

Bayesian statistics with default priors were also performed to supplement the frequentist approach by providing an estimate of evidence strength. Bayesian analyses quantify the relative evidence in favor of the null (H_0) or alternative hypothesis (H_1) based on the collected data. We calculated the BF_{10}, which is primarily a continuous measure; however, it was interpreted based on the following approximate classification scheme: $BF_{10} < 0.1$ indicates strong evidence for H_0, a value between 0.1 and 0.33 indicates substantial evidence for H_0, while a value between 0.33 and 1 indicates anecdotal evidence for H_0. Anecdotal evidence supports H_1 if BF_{10} is between 1 and 3, a value between 3 and 10 indicates substantial evidence for H_1, and $BF_{10} > 10$ indicates strong evidence for H_1[47]. For the Bayesian ANOVAs, the inclusion Bayes Factor (BF_{incl}) across matched models is also reported. It quantifies the relative difference between models containing the examined effect and the equivalent models that do not contain it. BF_{incl} is calculated by dividing the sum of the probabilities of the observed data by the sum of the updated probabilities and is interpreted in line with the convention of BF interpretation. The exclusion BF (BF_{excl}) can be calculated from the BF_{incl} scores by dividing 1 by the BF_{incl}. In order to improve the interpretation of our results, we report both the BF_{10} and BF_{01} scores, as well as the BF_{incl} and the exclusion BF (BF_{excl}) scores.

Results

Reaction times. We performed a $2 \times 3 \times 3$ ANOVA with Montage (DLPFC, FM) as a between-subject factor and with Stimulation Type (sham, anodal, cathodal) and Trial Type (neutral, congruent, incongruent) as within-subject factors. The Trial Type main effect was significant, $F(1.364, 49.111) = 212.611$, $p < 0.001$, $\eta_p^2 = 0.855$, $BF_{incl} > 10$, $BF_{excl} = 0.1$. Post hoc tests showed that RTs were significantly slower in the incongruent trial type as compared to the neutral ($p < 0.01$) and congruent trial types ($p < 0.01$). This result indicates that the flanker task was successful in evoking an interference effect. Bayesian analysis also revealed that Trial Type was the best to predict the data with the highest BF_{incl} score suggesting strong evidence to include the effect. The main effect of Stimulation Type and Montage did not reach significance (both $ps > 0.05$; $BF_{incl} = 0.401$ [$BF_{excl} = 2.493$] and 0.395 [$BF_{excl} = 2.531$], respectively). No interactions were significant by the frequentist analysis methods (all $ps > 0.05$). Bayesian statistics mostly supported these results as the best model only included the main effects of Trial Type and Stimulation type, along with the interaction of Stimulation type and Trial Type. Data were better explained by this model than under the null model ($BF_{10} > 10$, $BF_{01} < 0.1$). The BF_{incl} score of Trial Type × Stimulation type indicated only anecdotal evidence to include the interaction effect ($BF_{incl} = 1.926$, $BF_{excl} = 0.519$). Post hoc tests also revealed that RTs did not differ significantly between different stimulation types and montages; although, the median RTs collapsed across the flanker task's trial types were somewhat elevated in the FM group compared to the DLPFC group (Fig. 3). Please refer to Table 2 for the descriptive data.

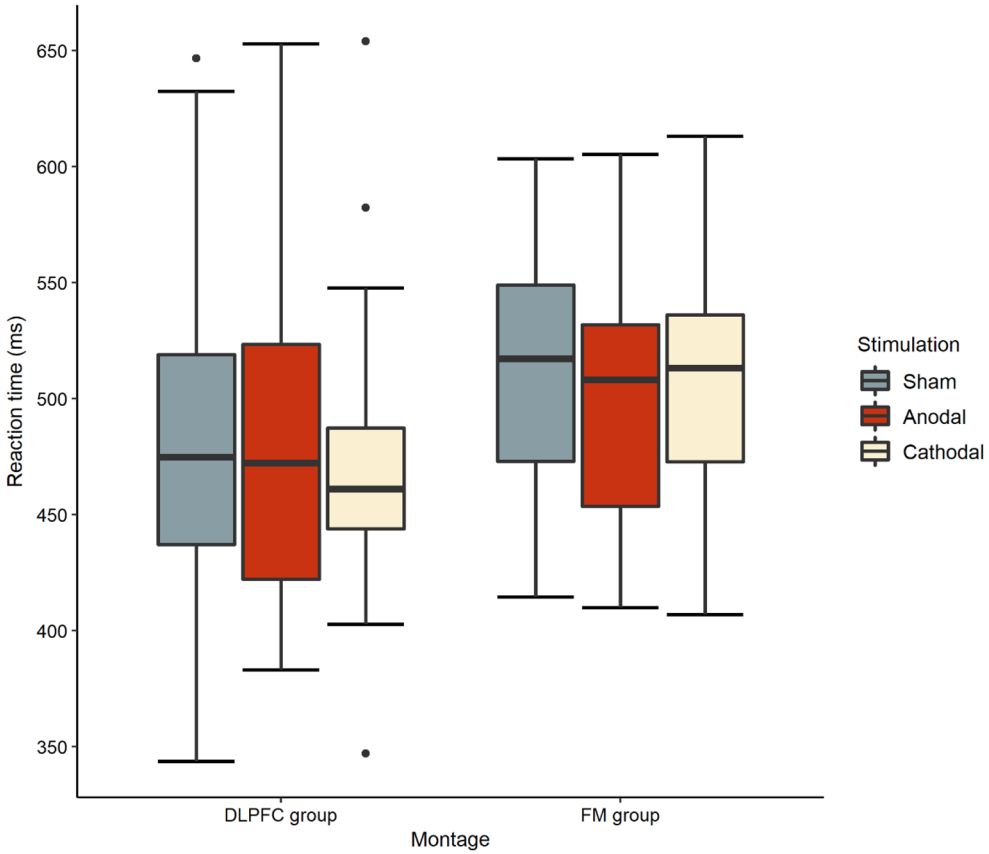

Figure 3. Reaction times per stimulation type in the DLPFC and FM group.

	DLPFC montage			Fronto-medial montage		
	Anodal	Cathodal	Sham	Anodal	Cathodal	Sham
Reaction time						
Congruent	468.97 (79.7)	458.84 (69.1)	466.34 (76.5)	482.05 (53.2)	490.23 (51.3)	496.23 (53.7)
Incongruent	509.10 (73.0)	498.42 (64.4)	510.97 (77.4)	522.81 (60.9)	534.63 (55.4)	540.76 (59.3)
Neutral	471.13 (78.4)	464.13 (67.0)	474.92 (79.6)	481.44 (48.2)	498.81 (55.9)	500.26 (51.3)
Congruency sequence effect						
cC	476.987 (82.680)	469.46 (81.8)	473.37 (84.8)	489.46 (55.8)	501.85 (55.7)	506.96 (61.5)
cI	519.48 (76.3)	513.63 (71.5)	524.42 (85.5)	534.77 (71.0)	548.07 (63.1)	563.27 (65.5)
iC	482.25 (89.7)	470.293 (78.3)	480.35 (89.4)	493.37 58.3)	498.72 (54.6)	512.45 (61.6)
iI	513.33 (80.0)	502.15 (68.6)	517.60 (81.5)	521.16 (64.2)	534.97 (53.3)	537.95 (61.9)
Accuracy						
Congruent	0.988 (0.016)	0.988 (0.023)	0.986 (0.026)	0.990 (0.010)	0.988 (0.014)	0.992 (0.008)
Incongruent	0.975 (0.024)	0.975 (0.020)	0.981 (0.015)	0.980 (0.017)	0.981 (0.015)	0.983 (0.015)
Neutral	0.985 (0.025)	0.985 (0.026)	0.989 (0.018)	0.991 (0.014)	0.986 (0.014)	0.992 (0.010)
No-go	0.951 (0.048)	0.962 (0.034)	0.961 (0.045)	0.967 (0.020)	0.970 (0.020)	0.956 (0.031)

Table 2. Median RTs in milliseconds and accuracy rates (with standard deviations in parentheses) as a function of electrode montage, tDCS condition and trial type. *DLPFC* dorsolateral prefrontal cortex, *cC* congruent trials preceded by congruent trials, *iC* congruent trials preceded by incongruent trials, *cI* incongruent trials preceded by congruent trials, *iI* incongruent trials preceded by incongruent trials.

Interference effect. The main effect of Stimulation type, $F(1.996, 71.846) = 1.882$, $p = 0.160$, $\eta_p^2 = 0.050$, $BF_{incl} = 0.380$, $BF_{excl} = 2.617$, and the main effect of Montage, $F(1, 36) = 1.704$, $p = 0.704$, $\eta_p^2 = 0.004$, $BF_{incl} = 0.446$, $BF_{excl} = 2.242$, were nonsignificant with BF_{incl} scores in favor of H_0. The interaction of Stimulation type and Montage was also nonsignificant, $F(1.996, 71.846) = 0.760$, $p = 0.471$, $\eta_p^2 = 0.021$, $BF_{incl} = 0.246$, $BF_{excl} = 4.065$. The Bayesian ANOVA suggested that the null model was the best model also supporting that the included variables did not have a significant effect on the interference scores (Fig. 4).

Congruency sequence effect. The analysis indicated a main effect of Trial n congruency, $F(1, 36) = 11.573$, $p < 0.002$, $\eta p^2 = 0.243$, $BF_{incl} > 10$, $BF_{excl} < 10$, as well as a main effect of Trial n-1 congruency, $F(1, 36) = 175.134$, $p = 0.001$, $\eta p^2 = 0.829$, $BF_{incl} = 9.802$, $BF_{excl} = 0.102$, both supported by substantial evidence according to the $BF_{incl/excl}$ scores. The former is indicative the presence of the flanker effect in trial n that is also in line with our analysis of the interference effects, while the latter supports that the congruence of trial n-1 has an impact on RTs of trial n. Specifically, RTs were shorter if trial n was congruent as compared to being incongruent ($p < 0.001$), and shorter RTs were recorded when the n-1 trial was incongruent as compared to congruent ($p = 0.002$). The two-way interaction of Trial n-1 congruency × Trial n congruency was also significant (see Fig. 5) which suggests a congruency sequence effect, $F(1, 36) = 44.125$, $p < 0.0001$, $\eta p^2 = 0.551$, $BF_{incl} = 83{,}599.050$, $BF_{excl} = 1.196$. Participants were the fastest on cC trials, and these RTs significantly differed from cI and iI trials ($ps < 0.001$), but not from iC ($p = 0.509$). In turn, RTs on iC were shorter than RTs on either cI or iI ($ps < 0.001$). When incongruent trials were preceded by incongruent trials as compared to congruent trials, RTs were slower ($p < 0.001$). Another significant two-way interaction was found between Trial n-1 congruency and Montage, $F(1, 36) = 4.188$, $p = 0.048$, $\eta p^2 = 0.104$, $BF_{incl} = 0.466$, $BF_{excl} = 2.145$. This interaction was primarily linked to the difference of RTs between congruent and incongruent trials on Trial N-1 in the FM group ($p = 0.003$). The rest of the two-way interactions, three-way interactions, and the four-way interaction did not reach significance (all $ps > 0.005$, all $BF_{incl}s < 1.375$, $BF_{excl}s < 0.727$). The Bayesian analysis supported leaving out these higher-order interactions as the best model only included the main effects, namely, Montage, Stimulation Type, Trial n congruency, and Trial n-1 congruency along with the interaction of Trial n congruence × Trial n-1 interaction. The best model outperformed the null model which supports the inclusion of these factors.

Accuracy. We detected a near-ceiling effect of performance on the combined flanker Go/No-Go task. The mean overall accuracy was 97.97% (range = 94.73–99.71%). An explanatory ANOVA revealed a significant main effect of Trial Type, $F(1.166, 41.992) = 14.659$, $p < 0.01$, $\eta_p^2 = 0.289$, $BF_{incl} > 10$, $BF_{excl} < 0.1$, with higher number of errors in the no-go trial type as compared to the neutral, congruent, and incongruent trial type ($p < 0.05$) and no difference between the three latter ($p > 0.05$). No significant interactions were found ($ps < 0.05$, $BF_{incl}s < 0.500$, $BF_{excl} < 2.000$).

Adverse effects. All participants completed the tDCS sessions without major complaints. Participants receiving sham, anodal, and cathodal tDCS in different montages were comparable regarding headache, neck pain, scalp pain, tingling, burning sensation, skin redness, sleepiness, trouble concentrating, and mood changes as the interaction of Montage × Stimulation type was not significant ($ps > 0.05$, $BF_{incl}s < 0.900$, $BF_{excl} > 0.795$) (see Supplementary Material). A significant Stimulation type × Montage interaction was found for itching sensa-

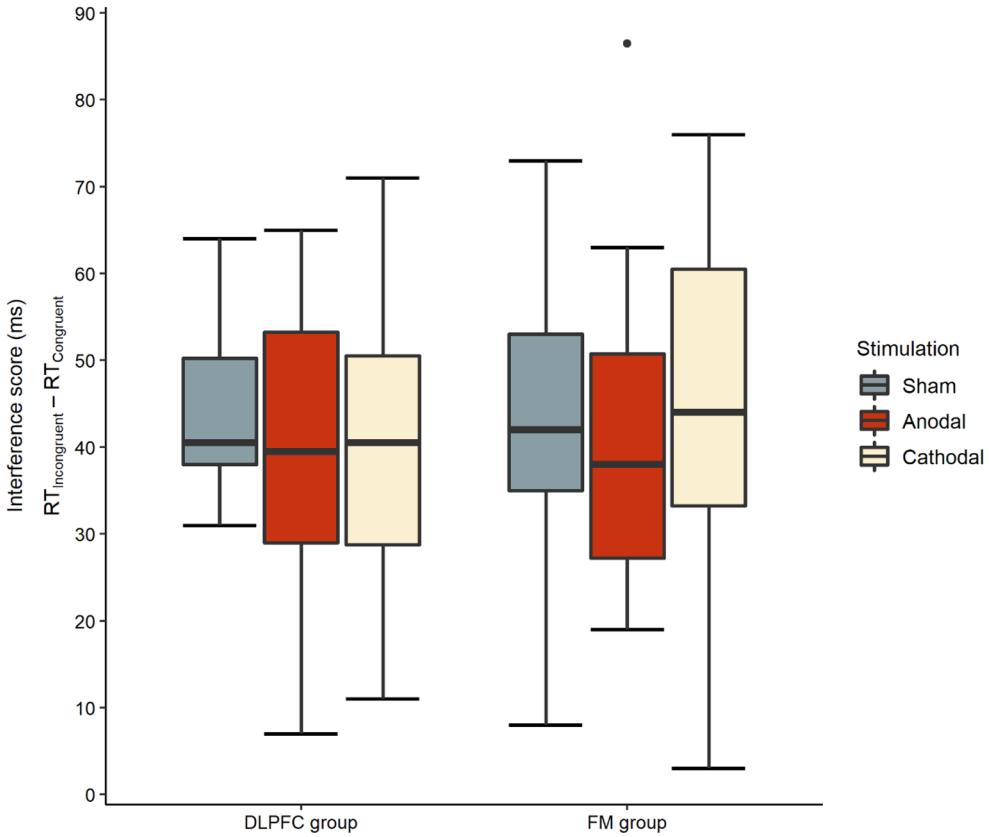

Figure 4. Interference scores per stimulation type in the DLPFC and FM group.

tion, $F_{2, 72} = 3.605$, $p = 0.032$, $\eta_p^2 = 0.091$, $BF_{incl} = 0.729$, $BF_{excl} = 1.371$. Post-hoc tests revealed a tendency towards higher levels of itching following anodal stimulation compared to sham stimulation only in the DLPFC group ($p = 0.011$).

Discussion

Various tDCS electrode montages targeting either the DLPFC or the fronto-medial regions have been utilized to modulate interference control or response inhibition. However, such montages have not been directly compared in terms of efficacy and adverse effects, even though this approach offers insight into their applicability for specific cognitive targets and could aid future study designs. Here, we chose commonly used stimulation parameters[34] and directly compared a conventional asymmetric DLPFC montage with a fronto-medial montage in a randomized, single-blind, sham-controlled study. We investigated tDCS effects on cognitive control and response inhibition along with adverse effects. Neither anodal nor cathodal stimulation of either montage was found to influence the correct response latency, interference scores, or CSE compared to sham stimulation, when tDCS was delivered for a single session to healthy young adults with the given parameters.

Our findings (supported by both conventional and Bayesian statistical methods) are in line with the incomprehensive results of the literature[3,9,25,48]. We also failed to replicate those results that have indicated that tDCS over the left DLPFC in this specific asymmetrical montage results in performance changes during a cognitive control task[7,8]. This might suggest that conventional tDCS methods that are still widely used in the field[49] yield inconsistent results in modifying cognitive control, and attention might be steered towards novel electrode montages and optimizing parameter settings.

A possible issue with the two-electrode montages when both electrodes are placed on the head (such as those we used here) is that the partial contribution of the return electrode in reducing cortical excitability over the area below the electrode cannot be completely ruled out. The use of extracephalic montages (i.e. when the return electrode is not placed on the head) might eliminate the effect of the return electrode on cortical modulation[50]. Of note, changing the position of the return electrode to an extracephalic location might affect the current flow and result in the stimulation of areas other than the target region[4]. Moreover, increasing the distance between the electrodes might reduce the neuromodulatory effects of tDCS in some montages[4]. Interestingly, changing the return electrode's position from the contralateral mastoid to the contralateral supraorbital area (while keeping the anode at the same position) has not been found to affect tDCS effects on cognitive control in a previous study[10] indicating the possibility that the return electrode's position might be less pronounced in some cases. Another novel method, the use of high-definition tDCS (HD-tDCS) has yielded promising results regarding its modulatory effects on cognitive control and response inhibition on a behavioral or electrophysiological level[36,51–54].

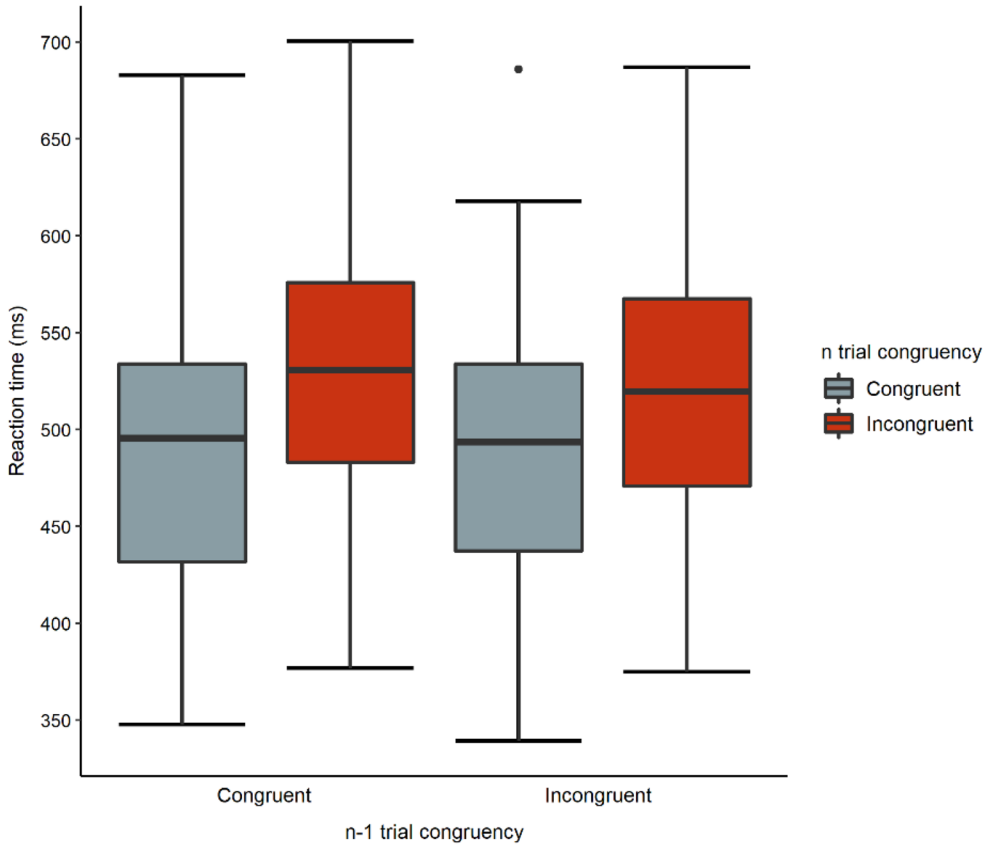

Figure 5. Congruency sequence effects on the combined flanker Go/No-Go task.

The parameter space of other stimulation parameters, including currents strength, electrode size, and stimulation timing should also be revisited and systematically tested due to the lack of consensus regarding their effectiveness[13], especially since some of them seem not to follow a linear trend in exerting an effect on cognition[55]. While it has been suggested that higher intensity is associated with larger cortical excitability enhancement of the primary motor cortex[56], in another study, no effect of tDCS has been reported on excitability, not even when the intensity was adjusted to the individual baseline excitability[57]. In the domain of working memory, stimulation intensity had no effect on the enhancement caused by tDCS[58]. Although there are numerous tDCS studies by now, a consistent pattern of an optimal constellation of stimulation parameters is yet to emerge. Of note, the parameters in the present study were set based on previous examples of the literature and are among the most common settings[34]. Moreover, a complete within-subject design with both anodal, cathodal, and sham stimulation was performed on the same subjects in order to reach more reliable conclusions.

The choice of target area has also been a parameter of considerable diversity in the field. Although the asymmetric stimulation of the left DLPFC is fairly popular, and the role of the DLPFC is also supported by evidence from neuroimaging and non-invasive brain stimulation studies[51,59], growing evidence has been suggesting that the right instead of the left DLPFC might be more involved in response inhibition[13,60]. In addition, the right DLPFC has been also linked to interference resolution at the electrophysiological level which, however, was not expressed on a behavioral level[53]. On the other hand, transcranial magnetic stimulation has been found to enhance performance on a Stroop task only when targeting the right DLPFC, not the left DLPFC[61]. In support of the potential involvement of the bilateral DLPFC, an empirical study involving 120 healthy participants concluded that both left and right DLPFC are involved in interference resolution during a Flanker task as tDCS delivered to both sites has resulted in performance improvement compared to both sham stimulation and active tDCS over a control site[51]. It has been proposed that the left and right DLPFC might play different roles in interference resolution. It has also been suggested that the left DLPFC is involved in anticipatory regulation of control, while the right DLPFC is responsible for adaptive control or interference resolution during response selection. These findings highlight the importance of conducting systematic comparisons between stimulation of the left and right DLPFC[60,61].

Several other brain areas have been proposed as targets for neuromodulation. A neuroimaging study has indicated that the left anterior insula is a region involved in both response inhibition and cognitive control, making this area another potential target for non-invasive brain stimulation in future studies[62]. Importantly, the dorsal anterior cingulate cortex has also been found active during both interference resolution and response inhibition[15,16,27]. However, it is possible that our attempt to stimulate the fronto-medial areas was not effective in reaching the medial surface of the frontal lobe despite our simulation. Alternatively, the lack of behavioral

changes is due to the limited focalization of tDCS effects. The current challenge lies in selecting the right electrode montage to target the fronto-medial cortices (and more broadly, the intended target region) due to the diverse and inconsistent findings in the existing literature.

With the advancement of computational modeling, the simulation of electric fields has become more accessible. Recent evidence contradicts the notion that tDCS has the most pronounced effect directly beneath the electrodes[63]. In our study, we employed a conventional asymmetric montage, which has been recently suggested to generate high electric field magnitudes not only over the DLPFC but also over the frontopolar regions[64]. Stimulation of the orbitofrontal cortex was also implicated in another study[65]. Consequently, the modulation of these areas may have contributed to our null results. The frontopolar cortex has been linked to adaptive resolution of interference on a flanker task[66], while the orbitofrontal cortex is believed to play a role in response inhibition[67]. The potential excitation of these areas may have also contributed to the positive findings of previous studies utilizing the conventional asymmetric DLPFC montage[6–8]. However, in our study, this did not translate into observable behavioral changes.

It is also worth noting that interference resolution and response inhibition have been operationalized in numerous ways in the literature including the Stroop, flanker, Simon, and anti-saccade, as well as the stop-signal and the Go/No-Go tasks, respectively[68]. Despite the clear presence of interference effect at the behavioral level, only a weak association has been identified between performance on tasks believed to measure interference control[69] and their correlation with real-life activities and self-reported measures[70]. This suggests that task-specific cognitive processes are likely to play a significant role contrary to a domain-general cognitive control. Additionally, it has been demonstrated that changing the task design such as replacing the stimulus type (e.g. letters, arrows) in the flanker task can lead to differences in reaction time and error rate, despite both exerting the flanker effect. Moreover, some modified tasks might not even be producing a reliable interference effect[71–73]. To enhance the ecological validity of these tasks, several novel tasks have been developed, and despite measurable behavior results, the comparability of these tasks with the classical versions is yet to be established[74–76]. Possibly, these tasks differ to some extent regarding the activation of intra- and interregional networks[68]. For example, less lateralized processing of interference has been suggested on the flanker task than on the Stroop task which might indicate the limited comparability of them[68,77]. Notwithstanding, consistent activation of specific brain regions (including the prefrontal and fronto-medial areas which also served as the target regions in our study) across tasks measuring response inhibition and interference control has been demonstrated[62]. However, future studies should consider that not only the task choice but also the specific details of the task might influence tDCS effects. Besides, non-invasive brain stimulation might act on specific indices of cognitive control (such as the interference score or the CSE) differently within the same task corresponding to the fact that some regions are more involved in interference resolution or adaptive control. Although we did not observe the effect of tDCS on any of these indices, it has been previously reported that on a Stroop task, only transcranial magnetic stimulation differentially affected the CSE and not the interference effect[61].

In the present study, we chose a combined task in order to measure both interference control and response inhibition. This task has been found comparable to the flanker and Go/No-Go tasks with a moderate correlation of convergence validity[38]. Furthermore, training for four consecutive days using a letter version of a combined flanker Go/No-Go task has resulted in a transfer effect on a traditional Go/No-Go task indicating that at least a partial overlap exists[78]. Combined tasks similar to ours have been also found to elicit electrophysiological and MRI activation patterns that are consistent with previous studies using the flanker and Go/No-Go tasks separately[39–41]. However, one limitation of the present task is that combining the two tasks may impact the way participants interact with the task. In the original flanker task, responses to the flanking stimuli are to be inhibited and the target is supposed to be in the center of attention. Whereas in the combined flanker Go/No-Go task, attention should be allocated to the flanking stimuli as well[79]. Participants also need to keep in mind the differing instruction for no-go trials which may increase the working memory demand of the task as compared to the original flanker and Go/No-Go tasks[38].

Despite the additional cognitive load, the current task design might not be sensitive enough to detect subtle changes or electrophysiological changes that do not reach the behavioral level. This might be especially true considering accuracy which was consistently high in all participants and trial types in the present study. The ceiling effect might be related to null results in healthy subjects as it might prevent tDCS effects from manifesting. By applying both anodal and cathodal stimulation, the latter classically intended to inhibit the target area temporarily, we aimed to disentangle the effects of current polarity and capture the potential performance deteriorating effects of tDCS as opposed to the improvements that might reach an upper limit. Importantly, our results derived from healthy adults (with performance potentially reaching a ceiling effect) cannot necessarily be expanded to other potential groups of participants. Our null results may be attributed to the possibility of compensatory activations occurring in both the stimulated areas and their contralateral counterparts, or within functional networks. It has been proposed that tDCS is rather a tool to improve deficient cognitive processes, and indeed, encouraging results exist indicating that tDCS can reverse the abnormal activity of several networks in mild cognitive impairment and that this change in brain activation was associated with improved performance[80].

Finally, another source of inconsistencies of tDCS effects has been attributed not only to methodological differences but also subject variables (such as age, sex, certain cognitive status, and genetics), neurophysiological (e.g. cortical excitability), and other factors (time of day)[81]. In this study, an effort was made to recruit a homogenous sample and groups in terms of sex, age, education, and handedness. Participants were also asked to attempt to schedule all sessions at the same time of day for all three sessions. Our results, coupled with the mixed findings of the literature, might also point towards the relevance of these factors and that tDCS effects are more strongly dependent on brain state and inter-individual responsiveness than on the above-listed parameters; however, more research is warranted to disentangle the complex multifactorial influences of various factors on tDCS effects[82].

Future lines of research should address these speculations by systematically studying individualized parameters and individual predictors of tDCS efficacy on large samples of participants. Provided that some conventional tDCS methods keep yielding inconclusive results, novel electrode montages might also be considered. Studies with such scope could not only significantly contribute to the understanding of the mechanisms of tDCS and its clinical applicability but also the understanding of the neural background of cognitive control and response inhibition.

Conclusion

In conclusion, here we began to investigate the role of a less examined stimulation parameter, namely, electrode montage, along with current polarity, on interference resolution and response inhibition in a sample of healthy young adults and found no effects of tDCS. As null results are accumulating in the field, there is still room for further systematic research to identify the determinants of responsiveness and optimal ways to utilize this technique to improve cognition.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

A.H. participated in the conceptualization of the study, conducted the data collection and analysis, prepared the figures, and wrote the manuscript. T.V. participated in the conceptualization of the study and in the data collection. P.K. and A.M. supervised the study process. All authors reviewed the manuscript.

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Co-author certification

I, myself as a corresponding author of the following publication(s) declare that the authors have no conflict of interest, and Adrienn Holczer Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in her thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

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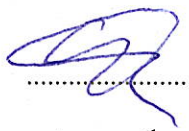

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