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Understanding the Neural and Behavioral Correlates of Mind Wandering Through Transcranial Direct Current Stimulation

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Abstract

The mind's tendency to wander is an integral part of the human experience. Recent studies suggest that high-level cognitive functions such as mind wandering (MW) can be modulated by non-invasive brain stimulation (NIBS) techniques such as transcranial direct current stimulation (tDCS). However, the effectiveness of tDCS in the cognitive domain remains an issue of debate. This thesis aimed to understand if tDCS is effective in modulating MW, either on the behavioral or neural levels, by employing rigorous, transparent, open science practices that include open availability of data and materials, such as analysis scripts. In a high-powered (N = 192) preregistered replication attempt in **Paper I**, we fail to replicate the finding that anodal tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) increases MW propensity. In contrast, a small effect was found in the opposite direction, though this was not robust. Further, tDCS did not impact any of our task performance measures. In **Paper II**, we showed that bipolar montages targeting the left DLPFC induce widespread effects extending far beyond the target site by simulation of tDCS-induced electric field (E-field) in the brain. However, E-field elicited by multi-electrode 4×1 HD-tDCS montages tended to be more focal, generally confined within the ring created by the four return electrodes. In **Paper III**, 4×1 HD-tDCS targeting the left DLPFC combined with our novel task showed reduced MW propensity for the group receiving active stimulation when compared with the sham group, without impacting task performance. These results highlight the value of preregistered replications in tDCS research in general, and the effectiveness of 4×1 HD-tDCS in modulating MW in particular. A NIBS method that can reliably regulate MW will have implications for conditions that are associated with the unfavorable behavioral effects of MW.

List of Abbreviations

AE	Approximate Entropy
BV	Behavioral Variability
CRT	Choice Reaction Time
DAN	Dorsal Attention Network
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
E-field	Electric Field
EEG	Electroencephalography
EF	Executive Function
EF$_{fa}$	Executive Failure View
EF$_{fu}$	Executive Function View
fMRI	Functional Magnetic Resonance Imaging
FPCN	Frontoparietal Control Network
FT-RSG	Finger-Tapping Random Sequence Generation
HDI	Highest Density Interval
LPFC	Lateral Prefrontal Cortex
MAAS	Mindful Attention and Awareness Scale
mPFC	Medial Prefrontal Cortex
MW	Mind Wandering
NIBS	Non-Invasive Brain Stimulation
OSF	Open Science Framework
PANAS	Positive and Negative Affect Schedule
PCC	Posterior Cingulate Cortex
rIPL	Right Inferior Parietal Lobule
RT	Reaction Time
SART	Sustained Attention to Response Task
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TUTs	Task-Unrelated Thought
WMC	Working Memory Capacity

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Paper I

Boayue, N. M., Csifcsák, G., Aslaksen, P., Turi, Z., Antal, A., Groot, J., ... Mittner, M. (2020a). Increasing propensity to mind-wander by transcranial direct current stimulation? a registered report. *European Journal of Neuroscience*, *51*(3), 755–780. doi:10.1111/ejn.14347

Paper II

Csifcsák[1], G., **Boayue[1], N. M.**, Puonti, O., Thielscher, A., & Mittner, M. (2018). Effects of transcranial direct current stimulation for treating depression: A modeling study. *Journal of Affective Disorders*, *234*, 164–173. doi:10.1016/j.jad.2018.02.077

Paper III

Boayue, N. M., Csifcsák, G., Kreis, I., Carole, S., Finn, I. C., Vollsund, A. E., & Mittner, M. (2020b). The interplay between cognitive control, behavioral variability and mind wandering: Insights from a HD-tDCS study. *Submitted for publication*. doi:10.31234/osf.io/d9ngb

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Boayue, N. M., Csifcsák, G., Puonti, O., Thielscher, A., & Mittner, M. (2018). Head models of healthy and depressed adults for simulating the electric fields of non-invasive electric brain stimulation. *F1000Research*, *7*, 704. doi:10.12688/f1000research.15125.2

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Groot, J. M.**, Boayue, N. M.**, Csifcsak, G., Boekel, W., Huster, R. J., Forstmann, B., & Mittner, M. (2020). Probing the neural signature of mind wandering with simultaneous fMRI-EEG and pupillometry. *Submitted for publication*. doi:10.31234/osf.io/24v3r

1

Introduction and thesis aims

1.1 Introduction

The mind's ability to stray away from current activities is a relatable experience (e.g., thinking about an upcoming vacation while trying to read a book). This mental phenomenon may have potential cognitive benefits for creativity and autobiographical planning (Baird et al., 2012; Baird, Smallwood, & Schooler, 2011). In addition, it has been linked with mental health disorders (Deng, Li, & Tang, 2014; Seli, Risko, Purdon, & Smilek, 2017b; Seli, Smallwood, Cheyne, & Smilek, 2015). Mind wandering (MW) research has developed significantly in the last two decades; it has gone beyond purely behavioral measures to a greater understanding of its neural underpinnings. Electroencephalography (EEG; Broadway, Franklin, & Schooler, 2015a; Jin, Borst, & van Vugt, 2019; Kam et al., 2011; Smallwood, Beach, Schooler, & Handy, 2008a; van Son et al., 2019), functional magnetic resonance imaging (fMRI; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mittner et al., 2014; Turnbull et al., 2019) and pupillometry (Mittner et al., 2014; Pelagatti, Binda, & Vannucci, 2018) have made significant contributions to this wealth of knowledge.

In particular, the advent of fMRI has been very influential in advancing our knowledge about the brain mechanisms underlying MW. FMRI studies have implicated the recruitment of brain regions and large-scale brain networks,

including the default mode network (DMN) and frontoparietal control network (FPCN) (see Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016, for a review). Methodological approaches, such as EEG, pupillometry, and fMRI, have elucidated the neural underpinnings of MW; however, their correlational nature does not allow causal inferences into the direct engagement of specific brain regions.

To establish the causal role of individual brain regions, studies have investigated MW in patients diagnosed with brain lesions to the ventromedial prefrontal cortex, a node in the DMN (Bertossi & Ciaramelli, 2016), and the lateral prefrontal cortex (LPFC), a part of the FPCN (Kam, Solbakk, Endestad, Meling, & Knight, 2018) compared with healthy controls. However, these studies lack a proper control group to account for the occurrence of diaschisis, which might result from these lesions. Invasive methods are not usually considered for ethical reasons; however, MW has been investigated using human intracranial EEG recordings from the DMN and FPCN regions of patients with epilepsy (Kam et al., 2019).

The non-invasive manipulation of individual brain regions identified from fMRI studies can assess their direct influence on MW. Using these methods, the brain-behavior relationship is constrained to a predefined target; therefore, a causal link can be established. Brain regions can be manipulated via non-invasive brain stimulation (NIBS) techniques, such as transcranial direct current stimulation (tDCS; Filmer, Dux, & Mattingley, 2014; Nitsche & Paulus, 2000). This is a cheap, non-invasive technique with minor adverse effects (e.g., itching and tingling beneath the electrodes) (Antal et al., 2017; Bikson et al., 2016; Woods et al., 2016). Meta-analyses have shown that the results of tDCS studies are mixed; therefore, this intervention may only have a negligible effect on cognition (Horvath, Forte, & Carter, 2015a, 2015b; but see Filmer, Mattingley, & Dux, 2020). However, this variability might be due to the small sample sizes usually employed in tDCS research (Minarik et al., 2016), which will influence the ability to extrapolate or replicate their findings. Additionally, there are other factors, including differences in individual head and brain anatomy, electrode placements, electrode shapes, current intensity, and brain states (Boayue et al., 2018; Horvath, Carter, & Forte, 2014), which might also influence tDCS findings. These mixed results, the large parameter space for tDCS investigation, and the problems of reproducibility in psychological studies (Open Science Collaboration, 2015) indicate that a high-powered, registered report would be the best way to establish the true effects of tDCS.

Computational modeling can assist with understanding the spatial distribution of tDCS-induced E-field in the brain to select the proper electrode montage for cortical targeting. The effect of tDCS on MW and associated psychological processes can be investigated in a single experimental setup by selection of the appropriate tDCS montage. In addition, novel cognitive tasks are necessary to induce more specific and robust excitability changes in brain regions linked to MW, which would potentially be susceptible to the effect of tDCS.

1.2 Aims and objectives of the thesis

This thesis investigated the modulatory effect of tDCS on the behavioral and neural correlates of MW using rigorous, transparent, open-science practices that include open availability of data and materials, including analysis scripts in a publicly available repository (such as the OSF, https://osf.io/). **Paper I** is a multi-lab, registered report that attempted replication of a seminal study by Axelrod and colleagues (2015) who reported increased self-reported MW propensity as a result of anodal stimulation of the left DLPFC. This replication attempt was necessary due to the relatively small sample size (10–14 participants/group) used in the original study, coupled with the lack of clear evidence of the cognitive effect of tDCS (Horvath et al., 2015b; Tremblay et al., 2014). Therefore, we sought to establish the reliability of these findings. **Paper II** is a simulation study that compared the focality of tDCS-induced E-field for seven conventional bipolar montages targeting the left DLPFC with two more specific, so-called 4×1 HD-tDCS montages (one targeting the left DLPFC and the other targeting the mPFC). **Paper III** used a 4×1 HD-tDCS protocol targeting the left DLPFC that was very similar to the one identified in the simulation study in **Paper II**, combined with a novel finger-tapping random sequence generation (FT-RSG) task to investigate the influence of tDCS on executive function (EF), behavioral variability (BV), MW, and their interactions.

2

Literature review

2.1 Mind wandering in everyday life - importance, implications and its measurement

When watching a movie or reading a novel, our attention can spontaneously drift to thoughts about an upcoming vacation or plans for dinner later. This ubiquitous mental phenomenon has been described as MW and is thought to consume up to half of our waking lives (Killingsworth & Gilbert, 2010). These momentary attentional shifts are integral parts of our conscious experience and have intrigued scientists' interests for years, and there has been a surge in the investigation of MW over the last decade (Callard, Smallwood, Golchert, & Margulies, 2013; Mills, Raffaelli, Irving, Stan, & Christoff, 2018). When the mind wanders, our attention involuntarily or voluntarily decouples from the external environment or primary task to internal thoughts and feelings (Barron, Riby, Greer, & Smallwood, 2011; Smallwood, 2013; Smallwood & Schooler, 2015).

Previous studies have shown that MW has potentially beneficial outcomes. Baird et al. (2011) have found an increased production of creative ideas when the task precedes an incubation period with an undemanding task that facilitates MW when compared with a difficult task, no resting or resting period.

One possible function of MW is autobiographical planning (Baird et al., 2012) because it is predominantly future-oriented; therefore, these thoughts usually relate to personally relevant future-oriented goals. However, MW has been linked to symptoms of depression (Deng et al., 2014), obsessive-compulsive disorder (Seli et al., 2017b) and attention deficit hyperactivity disorder (Seli et al., 2015). Additionally, it is prevalent in automated environments or environments that require low cognitive demands, such as modern-day aviation that uses autopilots (Wiegmann et al., 2005). In this respect, it poses safety concerns due to its negative impact on performance, for example, while driving (Yanko & Spalek, 2014).

Research investigating MW is typically performed in a controlled manner in laboratory settings (Christoff et al., 2009; McVay, Kane, & Kwapil, 2009; Smallwood, McSpadden, Luus, & Schooler, 2008b) or in daily-life (Kane et al., 2007; Kane et al., 2017; Killingsworth & Gilbert, 2010; Klinger, 1978; McVay & Kane, 2009; Song & Wang, 2012) for ecological validity.

Daily-life studies use experience sampling methodology that probe study participants randomly to complete brief questionnaires using an electronic device cued by a beep sound a couple of times daily to access their subjective experience (Kane et al., 2007; Kane et al., 2017; Smallwood, Riby, Heim, & Davies, 2006). The content of the questionnaire can include questions to assess whether or not participants were focused on their current activity or MW (yes or no), the contents of their thoughts (e.g., "I was thinking about normal, everyday things" on a 7-point Likert scale; 1 = not at all, 4 = moderately, 7 = very much) or the emotional context in which these thoughts occur (e.g., "What I'm doing right now is stressful" on a 7-point Likert scale; 1 = not at all, 4 = moderately, 7 = very much) (Kane et al., 2007; Kane et al., 2017).

In laboratory settings, participants perform a cognitive task while their MW propensity is intermittently assessed as they respond to thought-probes. These thought-probes are questions presented to participants periodically throughout the task. For example "To what extent have you experienced task-unrelated thoughts (TUTs) prior to the thought-probe?" with a Likert scale ranging from 1 – 4 (1 = minimal TUTs and 4 = maximal TUTs; therefore, indicating MW) (Axelrod, Rees, Lavidor, & Bar, 2015). There are two main experience sampling methods used in the laboratory context in the MW literature (Smallwood & Schooler, 2006). The most common is the probe-caught method, which randomly samples participants' thoughts throughout the task. The other is the self-caught method wherein participants press a button when they catch themselves MW. The probe-caught thought-probes answer alternatives range from

binary options ("on-task" or "off-task") and Likert scales (Levinson, Smallwood, & Davidson, 2012), multiple alternatives meant to capture the heterogeneity of the participant's thoughts just before the thought-probe appears. These alternatives include questions about external distractions from environmental stimuli and task-related interference (such as thoughts about performance on the task) (Robison, Miller, & Unsworth, 2019). One advantage of the probe-caught method is that participants do not have to be aware of their MW for it to be caught since they are intermittently probed. A drawback of this method is that it may interfere with the ongoing thoughts. Likewise, the self-caught method's advantage is that participants are not interrupted during the ongoing task; however, they have to be aware of MW to report it (Schooler et al., 2011; Schooler, 2002; Seli et al., 2017a). Therefore, the self-caught method may be better suited to capture the deliberate form of MW, while the probe-caught method may capture both deliberate and spontaneous MW.

2.2 Heterogeneity in conceptualization & phenomenology of mind wandering

Neuroscientific and psychological investigations of MW over two decades have provided significant insights into the wandering mind. These have been aided by technological and methodological advancements. The advent of fMRI (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992), which measures hemodynamic responses that are coupled with changes in neural activity, has enabled the extraction of neural activity in pre-defined regions and large-scale networks. The high spatial resolution of fMRI has provided insights into the network of cortical regions implicated in MW. However, the heterogeneity in the conceptualization and phenomenology of MW poses a challenge to the comparability of findings derived from fMRI studies. For example, intentional and unintentional MW seem to have distinct neural correlates (Golchert et al., 2017).

2.2.1 Heterogeneity in conceptualization

There is an ongoing debate on the conceptual definition of MW (Christoff et al., 2018; Seli et al., 2018a; Seli et al., 2018b). At first glance, MW, when thought about as an attentional drift away from a task-related cognitive activity as presented so far, may seem to be a unitary construct. However, researchers have

conceptualized this phenomenon differently over the years, which is reflected in the variety of terms that have been adopted in the literature. For example, stimulus-independent thoughts (e.g., Antrobus, 1968; Teasdale et al., 1995; Teasdale, Proctor, Lloyd, & Baddeley, 1993), are defined as thoughts that are unrelated to the actual stimuli in an experimental task and are closely related to subconscious attentional fluctuations in laboratory settings; TUTs (e.g., Giambra, 1989) are defined as thoughts that include content independent of the ongoing task and provide insight into a failure in attentional focus; and spontaneous thoughts (Christoff et al., 2016) describe thoughts that are inherently unguided/unconstrained. Therefore, MW encompasses a wide range of mental phenomena with these different types capturing various aspects.

Seli and colleagues have proposed a family-resemblances framework for MW. In a natural family, specific criteria are met to be a member, and there are close and distant relatives. From the family-resemblances point-of-view, MW is a heterogeneous construct with graded membership based on prototypicality (where some MW experiences are more characteristic of the experience than others). As such, all MW varieties are a part of a family with commonalities and differences. In more concrete terms, the determination of more or less prototypical MW thought experiences is less clear; however, the authors suggested sampling the views of laypeople, researchers, or both to generate MW exemplars (Seli et al., 2018b). These researchers argue that a graded structure based on prototypicality would be appropriate to ensure that different conceptualizations can be included within the MW family. Interestingly, Christoff and colleagues (2018) disagree with the idea of the family-resemblances framework. They argued that a MW field should exist with defining feature(s) that distinguishes it from other forms of thought. In a dynamic framework (Christoff et al., 2016) they situate MW on two dimensions (automatic and deliberate), each ranging from weak to strong constraints. Automatic constraints are caused by affective and sensory salience, whereas deliberate constraints are implemented through cognitive control. According to this framework, the defining feature of MW is the lack of strong automatic and deliberate constraints which differentiates it from other types of thoughts.

Regardless of the disagreement about whether MW should have a necessary defining feature(s) or should be seen as a broader term encompassing different mental phenomena capturing different aspects of the experience, there is consensus that researchers define the particular kind of MW they are assessing. In this thesis, MW is conceptualized and operationalized as TUTs: all thoughts that are unrelated to performing the cognitive task at hand. This operationalization of MW includes task-related interference (Smallwood et al.,

2006) and external distraction (Stawarczyk, Majerus, Catale, & D'Argembeau, 2014).

2.2.2 Heterogeneity in phenomenological features

MW has several phenomenological features (for review see Stawarczyk, 2018), such as the temporal orientation of thoughts (i.e., thoughts of the present, past, or future). There is a prospective bias in thoughts generated during MW (i.e., they tend to be future-oriented; Smallwood and Schooler (2015), Stawarczyk (2018)). This bias is independent of task context and has been demonstrated in the laboratory (Smallwood, Nind, & O'Connor, 2009b) and daily life (Song & Wang, 2012). Moreover, it is moderated by task difficulty (Smallwood et al., 2009b). In this study, participants performed a series of three tasks (CRT, working memory task, and passive viewing task), each interspersed with thought-probes to assess whether they were focused on the here-and-now, past, or future. The results showed that most TUTs are future-oriented during the less demanding tasks (CRT and passive viewing) when compared with the more demanding working memory task. These findings suggest that when task demand is low, there are more available attentional resources dedicated to future-oriented thoughts.

Another phenomenological feature of MW is intentionality. It is usually assumed that MW occurs without explicit intent; however, MW can be both spontaneous or deliberate (for review see Seli, Risko, Smilek, & Schacter, 2016). For instance, prior studies have found that spontaneous, not deliberate MW is associated with obsessive-compulsive disorder and attention deficit hyperactivity disorder symptomatologies (Seli et al., 2017b; Seli et al., 2015).

Finally, meta-awareness, which is the explicit knowledge of one's ongoing thought (Schooler et al., 2011), is a phenomenological feature that is considered in the context of MW. Interestingly, an early neuroimaging study showed more pronounced activity in the executive network and DMN when participants were unaware of their MW than when they were aware of their off-focus attention (Christoff et al., 2009) indicating that in the context of MW, activity in these networks is not critical for meta-awareness.

2.3 Cognitive tasks in mind wandering research

MW research has employed different cognitive tasks depending on the aim of the particular study, including the stop-signal task (Mittner et al., 2014), sustained attention to response task (SART; Christoff et al., 2009), the n-back task (Turnbull et al., 2019) and choice reaction time (CRT; Seli, Konishi, Risko, & Smilek, 2018c) task. For example, the CRT task, and the n-back tasks have been used to investigate the impact of task difficulty on MW (Seli et al., 2018c). This study showed that the undemanding CRT task induces more MW than the 1-back task, which is more attention-demanding, implying a negative correlation between MW and task difficulty (Seli et al., 2018c).

The most commonly used task in MW research is the SART, which was employed in **Paper I** of this thesis. The SART is a go/no-go task that requires a motor response on most trials (go-trials) except a very low proportion of no-go trials (e.g., 10%). The monotonous nature of the task tends to induce a lot of MW because of its low cognitive demand.

MW research largely relies on self-reports using the experience sampling methodology; however, several behavioral measures of the SART have been investigated as indices of MW. **Paper I** investigates the impact of tDCS on four of these SART performance measures (commission errors, omission errors, mean reaction time (RT) for go-trials, and RT coefficients of variation). MW is associated with reduced task performance and mean RT for go-trials preceding off-task thought-probes tend to be faster when compared with on-task reports (Hawkins, Mittner, Forstmann, & Heathcote, 2019; McVay & Kane, 2009). Similarly, a shorter mean RT for go-trials prior to commission errors when compared with correct responses to target (no-go) trials has been reported (McVay & Kane, 2009). The RT coefficients of variation is higher when participants mind-wander when compared with focusing on the task (Bastian & Sackur, 2013; Cheyne, Solman, Carriere, & Smilek, 2009; Hawkins et al., 2019). In addition, the error rates for go-trials (omission errors) correlate with self-reported MW (Cheyne et al., 2009) and mean error rates for no-go trials (commission errors) are higher before off-task thoughts when compared with on-task thoughts (Hawkins et al., 2019). Finally, time-on-task effects have been reported, describing an increased tendency to mind-wander in later trials of the task at hand (Stawarczyk, Majerus, Maj, der Linden, & D'Argembeau, 2011a).

We used a novel FT-RSG task in **Paper III**. Briefly, this task requires participants to generate a random movement sequence with both right and left index fingers

on pace with an ongoing metronome (see Methods for details).

2.4 Mind wandering and executive function

EFs are high-level cognitive processes, often associated with the frontal lobes, involved in top-down control of goal-directed behavior (Friedman & Miyake, 2017). Accumulating evidence shows emerging consensus about the implication of EFs in MW (Kam & Handy, 2014; McVay & Kane, 2009, 2010, 2012; Smallwood, 2010; Smallwood & Schooler, 2006). MW is associated with worse performance on executive-control tasks. For example, Kam and Handy (2014) instructed participants to perform tasks related to core EFs: the Stroop task, which requires response inhibition of a prepotent response, and n-back task, which requires updating information in working memory. RTs were longer preceding the MW state when compared with the on-task state during incongruent trials in the Stroop task. Furthermore, response accuracy was lower in the MW state when compared with on-task for the 1-back task. However, the exact nature of involvement of EF remains debatable (McVay & Kane, 2010; Smallwood, 2010) because it is unclear whether MW consumes the same executive control resources as the primary task at hand or is an outcome of executive control failure.

The executive failure view (EF_{fa}; Kane et al., 2016; McVay & Kane, 2009; McVay et al., 2009; McVay & Kane, 2010, 2012) posits that MW occurs due to the inability of the executive control system to maintain task goals and avoid interference from automatic thoughts that are elicited by external and mental cues. Maintaining executive control is resource-consuming; therefore, it fluctuates over time. Performance drops during lapses in control, and if shielding from these distractive stimuli fails simultaneously, thoughts may become focused elsewhere. Evidence in support of this view comes from studies investigating MW and individual differences in working memory capacity (WMC), which is defined as the ability to maintain task relevant information in memory while simultaneously performing an unrelated task (such as during the Automated Operation Span task). High-WMC individuals exhibited less MW and had fewer errors and RT variability during the SART when compared with low-WMC individuals (McVay et al., 2009; McVay & Kane, 2012). This suggests that high-WMC individuals can suppress these attentional lapses that lead to MW while maintaining better task performance. The EF_{fa} hypothesis posits that MW occurs spontaneously in a resource free manner; however, suppression of these intrusive thoughts requires working memory resources.

High-WMC individuals have more resources available; therefore, they can effectively suppress MW and maintain better performance.

In contrast, the executive function view (EF_{fu}; Smallwood, 2010; Smallwood & Schooler, 2006; Teasdale et al., 1995) postulates that MW is resource demanding; therefore, it requires the same executive resources as the primary task for its maintenance. For instance, when the content of MW is future-focused, individuals require the use of memory traces that are recombined in a novel way. This can be highly demanding and rely on the same executive system as the mental operations underlying a cognitive task. Behavioral and neuroimaging studies have supported this hypothesis. Levinson et al. (2012) have shown that individuals with higher WMC report greater MW during low perceptual load tasks but not for high perceptual load tasks. This indicates that there are resources available for MW during low perceptual load tasks. Furthermore, regions in the executive network are active during MW (Christoff et al., 2009), indicating that executive resources are recruited during MW.

The EF_{fa} and the EF_{fu} create contrasting hypotheses about the association between executive resources and MW. The EF_{fa} predicts that high-WMC individuals should exhibit less MW because they monitor the ongoing task more efficiently; therefore, EF failure is less likely. Further, low-WMC individuals would exhibit more MW because they are less likely to block out distractions from the primary task. Conversely, the EF_{fu} predicts that high-WMC individuals would mind-wander more because MW depends on the same executive resources as the primary task; therefore, MW should increase when the task is not very difficult and does not consume all working memory resources. It is essential to empirically test these two predictions based on an experimental paradigm that examines the validity of both theories. Our experimental setup in **Paper III** was meant to achieve this goal.

2.5 Neural mechanisms of mind wandering

FMRI indirectly measures neural activity *in vivo* by measuring low-frequency spontaneous blood oxygenation level-dependent activity with radiofrequency coils and high-field magnets. FMRI scanners record these signals as high dimensional images. Blood oxygenation level-dependent activity patterns are presented as activation and deactivation maps and give insight into brain function. FMRI scans can be acquired with study participants laying passively in the scanner without performing an external experimental task (resting-state

fMRI) or acquired while participants perform an experimental task (task-based fMRI). Studies have employed fMRI in clinical and healthy populations (Lang, Duncan, & Northoff, 2014). Furthermore, this method allows researchers to not only look at activation patterns in discrete brain regions, but also at connectivity between brain regions (Raichle et al., 2001).

Activation within the DMN has been linked to MW via fMRI studies (Mason et al., 2007). Regions within this large-scale network are consistently engaged during resting-state fMRI compared with task-based fMRI (Greicius, Krasnow, Reiss, & Menon, 2002; Raichle et al., 2001). The DMN consists of two core hubs and at least two sub-systems with a distinct functional contribution to cognition that interact (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Andrews-Hanna, Smallwood, & Spreng, 2014). The two core hubs of the DMN are the posterior cingulate cortex (PCC) and the anterior mPFC. The two sub-systems are the dorsal mPFC and the medial temporal lobe.

Between-network functional connectivity is used to understand the interactions between large-scale brain networks. Connectivity patterns between the DMN and other large-scale networks have been investigated (e.g., Mittner et al., 2014). For example, the dorsal attention network (DAN) (M. D. Fox et al., 2005), shows regional engagement when attention is focused externally (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). The core DAN consists of the intraparietal sulcus, superior parietal lobule, dorsal frontal cortex along the precentral sulcus near, or at the frontal eye field, and the middle temporal complex. Functional connectivity studies have reported an anticorrelation between nodes of the DMN and DAN (M. D. Fox et al., 2005). However, the negative relationship between "task-positive" (DAN) and "task-negative" (DMN) networks seems simplistic. Firstly, the DMN is a large-scale heterogeneous network with different sub-systems serving different functions. Secondly, the global signal regression used in these initial studies could have potentially biased the results (K. Murphy, Birn, Handwerker, Jones, & Bandettini, 2009).

A recent meta-analysis of 20 studies investigated the anticorrelation between the aforementioned networks. Dixon et al. (2017) analyzed the empirical effect sizes and how studies that included or did not include global signal regression in their preprocessing pipeline influenced the results. The results showed a strong anticorrelation for studies that used global signal regression and a weak anticorrelation for studies that did not use global signal regression. Further, Dixon et al. (2017) have investigated functional connectivity between individual sub-systems of the DMN and the DAN. Their results have demonstrated

that functional connectivity between DMN and DAN varies significantly across DMN sub-systems; the DAN shows a modest anticorrelation with the core hub-like sub-system, shows no correlation with the dorsal mPFC sub-system, and exhibits a very weak but reliable anticorrelation with the medial temporal lobe sub-system. This result is in line with M. D. Fox et al., 2005, who observed that the anticorrelation with the DAN was based on seed regions in mPFC and PCC. These regions are the core hub-like sub-system of the DMN (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014).

Another large-scale brain network associated with MW is the FPCN, which is primarily involved in cognitive control. Nodes in this region and the DMN are active when participants report MW (Christoff et al., 2009). A recent quantitative meta-analysis of MW showed similar patterns of co-activation of the DMN and FPCN (K. C. Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015). It has been postulated that the FPCN might exhibit positive functional connectivity with the DAN to support external cognition, or positive functional connectivity with the DMN, to support internally focused cognition (Smallwood, Brown, Baird, & Schooler, 2012; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). This is consistent with the EF_{fu} model of MW.

2.6 Non-invasive brain stimulation

Four decades ago, Merton and Morton (1980) showed that the intact human brain could be transcranially stimulated with an electrical stimulus using two scalp electrodes. To date, the most common NIBS techniques are transcranial magnetic stimulation (TMS) and tDCS. TMS works by applying magnetic stimulation to the target cortical area using magnetic coils that produce magnetic fields, which in turn induce electric currents in the underlying neural tissue (Miniussi, Harris, & Ruzzoli, 2013). For tDCS, a weak electric current (typically 1–2 mA) is applied by two or more scalp electrodes, which modulates the resting membrane potential (Filmer et al., 2014). Shifting the resting membrane potential of neurons in a polarity-dependent manner has been reported in early animal studies (Bindman, Lippold, & Redfearn, 1964; Purpura & McMurtry, 1965); anodal and cathodal stimulation applied to the cortical surface increases and decreases cortical excitability, respectively. In contrast to TMS, tDCS-induced polarizations are weak and do not directly lead to action potentials. These NIBS techniques have been used to study the link between regional brain activity and underlying cognitive processes (Bestmann, de Berker, & Bonaiuto, 2015; Polania, Nitsche, & Ruff, 2018). NIBS

directly induces changes in the excitability of the underlying neural tissue (Stagg & Nitsche, 2011). Therefore, it lends itself when used appropriately for making inferences about how particular cortical regions are implicated in a range of different cognitive functions, such as attention (Coffman, Trumbo, & Clark, 2012), working memory (Fregni et al., 2005), and perception (Antal et al., 2004).

The inter-individual variability in tDCS-induced E-field is well known (Datta, 2012; Li, Uehara, & Hanakawa, 2015). This can be attributed to differences in anatomy, brain states, cognitive strategies, and other factors. The electrical current applied is mostly shunted by the skull; however, the amount of current shunted is partly dependent on the thickness of the skull: the thicker the skull, the more shunting (Opitz, Paulus, Will, Antunes, & Thielscher, 2015). Another area of variability is cortical folding, with differences creating a significant impact on the tDCS-induced E-field (Opitz et al., 2015). The degree of depolarization or hyperpolarization is highly contingent on the orientation of the neuronal population relative to the electric field (Rahman et al., 2013a). Different cellular effects are induced dependent on whether the component of the E-field is radial or tangential to the cortex.

Modeling tDCS-induced E-field to assess their spatial distribution can provide insight into inter-individual variability. A model of the head is required to achieve this and the creation of individual head models for each study participant is costly because individual structural magnetic resonance images are required. To overcome this, researchers use a reference head model, such as the almi5, which is included with SimNIBS, an open-source tool for simulating the E-field induced by NIBS (Windhoff, Opitz, & Thielscher, 2011) or The New York Head (Huang, Parra, & Haufe, 2016). The use of these reference head models assumes that all brains are identical.

There are now freely available fully integrated tools, such as ROAST (Huang, Datta, Bikson, & Parra, 2019) and SimNIBS (Saturnino et al., 2019; Thielscher, Antunes, & Saturnino, 2015) to create head models and simulate tDCS-induced E-field. These tools segment the structural magnetic resonance images into different tissue types (for example, scalp, bone, cerebrospinal fluid, gray matter, white matter, and eyes), generate high-quality volume meshes, and assign the appropriate tissue conductivities. Ongoing brain activity appears to be important for the observed tDCS effects (Shahbabaie et al., 2014). This is defined as the state dependence of tDCS. Furthermore, different behavioral effects have been reported when tDCS is concurrently applied while participants complete a task (online) or task completion after tDCS (offline) (Stagg

et al., 2011).

2.7 tDCS and mind wandering

TDCS can establish a causal brain-behavior relationship, which can be leveraged to understand MW. Brain regions or networks identified from correlational methods, such as fMRI, serve as stimulation targets. Previous studies have reported facilitatory and inhibitory modulatory effect of tDCS on MW in healthy participants (see Chaieb, Antal, Derner, Leszczyński, & Fell, 2019, for a review). These studies used different montages (electrodes setup and sizes), current intensities, cognitive tasks, and stimulation durations.

In a series of two experiments, Axelrod et al. (2015) set out to test the causal role of the frontal lobe in MW. More specifically, the involvement of the executive control network in MW. The first experiment was a within-subjects design with two experimental sessions separated by at least a week. Participants received either sham tDCS (control condition same montage as the anodal setup, 2 minutes stimulation) or 1 mA anodal tDCS of the left DLPFC (cathode at the right supraorbital position). In the anodal tDCS group, participants performed the SART for approximately 40 mins with stimulation for the first 20 mins. Next, they tested whether the observed effect was region-specific using the same experimental parameters as in the first experiment but with a between-subjects design (three conditions: anodal tDCS of the left DLPFC, anodal tDCS of the occipital cortex, and sham stimulation of left DLPFC). The authors found increased self-reported MW propensity in the anodal left DLPFC tDCS condition when compared with the two control conditions (sham and occipital cortex stimulations). These results suggest that the observed effects may not have been due to any lack of specificity in the tDCS montage. Recently, Axelrod and colleagues replicated their findings and further showed that the observed increase in MW is independent of meta-awareness (Axelrod, Zhu, & Qiu, 2018). However, Filmer, Griffin, and Dux (2019) used a similar montage to that of Axelrod et al. (2015) and found that MW propensity increases using 2 mA cathodal stimulation of the left DLPFC. This finding brings into question the polarity specific effect of tDCS on MW because both cathodal and anodal stimulation led to increased MW.

Interestingly, there was no significant impact on SART performance measures in either the original or replication study (Axelrod et al., 2015; Axelrod et al., 2018). Although neither studies discussed this in detail, these results of

unchanged SART performance measures together with increased MW points towards the EF_{fu} model of MW - available WMC resources in the anodal left DLPFC stimulation group was used for MW without impacting performance.

Following the publication of Axelrod et al. (2015), Kajimura and Nomura (2015) sought to investigate whether tDCS decreases MW propensity. This effect could support individuals with MW-associated disorders and other impairments that result in reduced task performance, such as human errors in aviation and automobile accidents. They used the left LPFC (a key node of the executive control network) and right inferior parietal lobule (rIPL, a key node of the DMN) as stimulation targets. A between-subjects design with participants allocated to one of three tDCS groups (anodal, cathodal, and sham) was used. The anodal condition had an anode and cathode placed above the rIPL and left LPFC, respectively, and the cathodal group had the polarities reversed. The current intensity was 1.5 mA and lasted 20 min in the active stimulation conditions and 30 seconds in the sham condition. Participants performed a perceptual load task (Lavie & Cox, 1997) after tDCS (offline). There was a significant reduction in MW propensity in the anodal group when compared with the cathodal group (cathodal vs. anodal rIPL stimulation), which indicates that the effect of stimulation is polarity-dependent. There were no significant differences between the sham condition and either active stimulation condition (anodal or cathodal). Similar to Axelrod et al. (2015), tDCS did not significantly modulate task performance.

Kajimura and colleagues conducted a follow-up study (Kajimura, Kochiyama, Nakai, Abe, & Nomura, 2016) designed to assess the precise neural mechanisms of the tDCS-induced stimulation effects observed in their previous study (Kajimura & Nomura, 2015). In this tDCS-fMRI study, the same stimulation protocol and experimental paradigm was used but with only two thought-probe responses (on-task vs. off-task). They acquired resting-state fMRI pre- and post-tDCS before the experimental task which were later used to access stimulation-induced functional connectivity (non-directed) and stimulation-induced effective connectivity (directed) within the DMN. Kajimura and colleagues (2016) showed that there was less MW in the anodal group (anode rIPL and cathode left LPFC) when compared with the cathode group (cathode rIPL and anode left LPFC) with no effect on task performance. This replicated their earlier findings. Interestingly, the functional connectivity analysis did not detect tDCS-induced stimulation effects; however, the authors reported decreased effective connectivity from the mPFC and rIPL to the PCC in the anodal group, which was reversed in the sham group. In addition, they found

an increase in effective connectivity from the mPFC to the PCC in the cathodal group. In a subsequent mediation analysis, they showed that the connection from the rIPL to the PCC inhibited MW in the anodal group. In contrast, mPFC to PCC connection facilitated MW. These results indicate the critical roles of both the rIPL and mPFC in influencing MW by altering PCC function.

Left LPFC and rIPL stimulation may be responsible for a reduction in MW. Another study used an extracephalic montage with the anode over the rIPL, which resulted in decreased MW (Kajimura, Kochiyama, Abe, & Nomura, 2018). This finding indicates that reduced MW propensity (Kajimura et al., 2016; Kajimura & Nomura, 2015) is likely due to rIPL stimulation and not left LPFC stimulation. The rIPL is part of the DMN; therefore, these effects might be related to changes within the DMN, not the FPCN.

Recently, Coulborn, Bowman, Miall, and Fernández-Espejo (2020) failed to replicate the findings of Kajimura et al. (2018) using similar montage and task. Both studies used a within-subjects design with N = 12 and 23 for Kajimura et al. (2018) and Coulborn et al. (2020), respectively. This failed replication stresses the need to design well-powered studies and more replications of the modulatory effect of tDCS on MW.

The mPFC is another key node of the DMN and has been the target of investigation in MW-tDCS studies. Cathodal stimulation of the mPFC with an extracephalic electrode over the right deltoid led to decreased MW in men only when compared with stimulation of the occipital cortex or sham stimulation (Bertossi, Peccenini, Solmi, Avenanti, & Ciaramelli, 2017). This finding suggests that 1) the tDCS effect is not polarity-dependent in DMN stimulation because anodal stimulation also reduces MW (Kajimura et al., 2018) or 2) stimulating different hubs of the DMN (rIPL vs. mPFC) will result in the same effect for the reversed polarity alone. This suggests that the rIPL reduces MW and the mPFC increases MW. This explains the finding of reduced MW in the study by Bertossi et al. (2017) because they used cathodal stimulation.

The MW-tDCS studies that have been reviewed in this thesis used conventional bipolar montages. Simulation studies have shown that the E-field induced by these bipolar montages reach far beyond the targeted region, with relatively strong E-field magnitudes reaching regions far away from the target (Boayue et al., 2018). This lack of spatial specificity opens the interpretation of these findings to multiple possibilities. For example, increased MW propensity can be interpreted in terms of the EF_{fu} model of MW in that those receiving anodal stimulation have more available executive resources; therefore, more MW

capacity (Axelrod et al., 2015). However, Broadway and colleagues (2015b) argue that the brain regions implicated in meta-awareness are within the path of the electric current in the montage used by Axelrod et al. (2015). This finding may indicate that participants receiving anodal stimulation were more aware of their MW. While their follow-up study demonstrated that the observed increase in MW was independent of meta-awareness (Axelrod et al., 2018), the fact that their montage was largely non-focal cannot rule out that the behavioral effect was due to the stimulation of regions other than the left DLPFC, such as the mPFC.

A multi-electrode setup, with one anode surrounded by four cathodes (4 × 1 ring montage), can be used to eliminate the ambiguity in interpretation caused by conventional bipolar montages (Boayue et al., 2018; Datta et al., 2009). This setup produces a more targeted, focused, and confined stimulation than the conventional bipolar montage. This reduces the possibility of other brain regions being implicated in confounding psychological phenomena, such as meta-awareness.

2.8 Pre-registration and registered reports

Over the past decade, it became increasingly clear that there are issues with the credibility of psychological science as it has been practiced, with the significant lack of reproducibility for many studies (Open Science Collaboration, 2015). Scientific rigor is now stressed as a mainstay of undertaking scientific research to counter some of these practices. For example, pre-registration and registered reports have been proposed to prevent some of these practices (Nosek et al., 2019; Nosek & Lakens, 2014). These have been used within the context of this thesis.

Publication bias (Fanelli, 2011) is a significant challenge in scientific research. Most published works show statistical significance, while null findings have a lower probability of being published. Furthermore, journals prefer to publish novel findings instead of replicating the results of a previous study with a negative or inconclusive result. When the hypothesis of a study is conceived before collecting results, it becomes confirmatory. However, the practice of HARKing (K. R. Murphy & Aguinis, 2017), where hypotheses are developed post hoc but presented as *a priori*, is problematic because it might lead researchers to develop very narrow hypotheses that best fit their data. Exploratory analysis can be conducted when it is identified and distinguished from confirmatory

analysis. Additionally, researchers' degrees of freedom or p-hacking (Simmons, Nelson, & Simonsohn, 2011), which refers to the flexibility of researchers when conducting statistical analyses, can lead to the inclusion/exclusion of certain participants or experimental conditions. These questionable research practices may have flooded the scientific literature with false-positive results (Simmons et al., 2011), i.e., by giving flexibility in the analysis and flexibility in formulating the hypothesis, the target can be moved so that wherever it went, will be dead on-center.

Pre-registration (Nosek et al., 2019) can remedy these issues. This requires that both the analysis proposal and experimental hypotheses are registered before a study is conducted. In addition, registered reports (Nosek & Lakens, 2014) have the extra layer of submitting the introduction and methods sections of a research article for peer review (stage 1). Data can only be collected, analyzed, and re-submitted (stage 2), irrespective of the results, following stage 1 acceptance.

In summary, the cost and ease of use of tDCS led to an initial explosion of research employing this technique to understand brain function; however, a recent meta-analysis investigating the cognitive effects of tDCS revealed varying outcomes from stimulation (Horvath et al., 2015a, 2015b; Tremblay et al., 2014). The results show varying outcomes of stimulation. Pre-registration and registered reports could be a vital tool to help establish the real effects of tDCS. This will create a more rigorous and transparent scientific process in the field of tDCS.

3

Materials and methods

This chapter presents a summary of the materials and methods employed in the three papers. Detailed descriptions for each paper are found in the individual papers contained in the thesis.

3.1 Participants

For the multi-lab study (**Paper I**), a total of 192 healthy young participants were recruited at the Arctic University of Norway, University of Amsterdam, the Netherlands, and Georg August University of Göttingen, Germany. Structural neuroimaging data for the simulation-based study (**Paper II**) were downloaded from the OpenfMRI database (accession number:ds000171). These freely available high-resolution T1-weighted anatomical images were collected in a separate fMRI study (Lepping et al., 2016). The dataset includes structural magnetic resonance imaging scans of 19 healthy adult participants with no history of depression or other psychiatric disorders. In addition, we used individuals diagnosed with major depressive disorder and experiencing a depressive episode at the time of the scanning. All 60 participants of the tDCS experiment of **Paper III** were recruited at the Arctic University of Norway.

3.2 Ethics

Ethical approval was granted at all three labs (Tromsø, Amsterdam, and Göttingen) in the multicenter study conducted in **Paper I**, and in Tromsø for **Paper III**. All studies adhered strictly to the Declaration of Helsinki on the conduct of research involving research participants.

3.3 Cognitive tasks and questionnaires

3.3.1 Cognitive tasks

Figure 3.1 shows the two experimental tasks used in this thesis. **Paper I** used the SART and **Paper III** used our novel FT-RSG task. The SART dis-

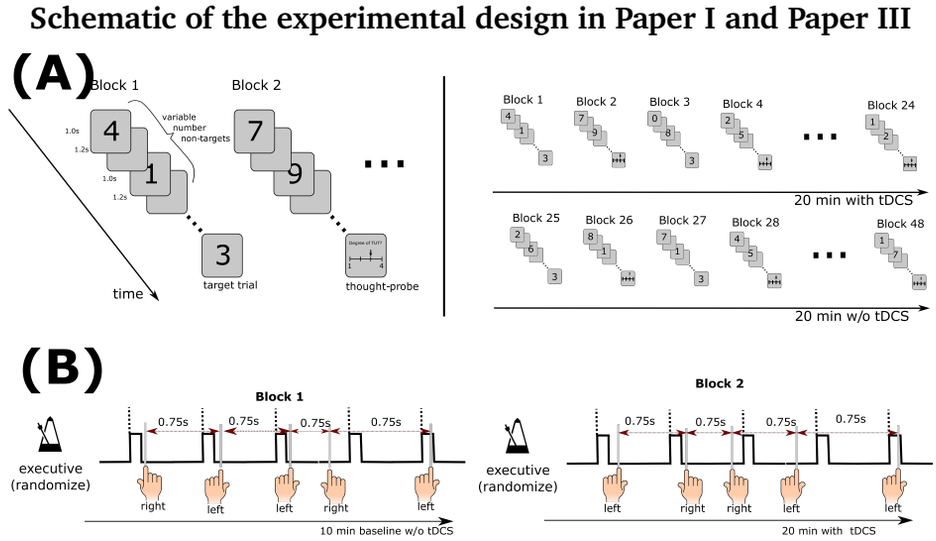

Figure 3.1: **A)** The SART was used in **Paper I**, which consisted of two halves where tDCS stimulation was turned on and off in the first and second halves, respectively. In the first half, the task was performed with 20 min or 15 s of tDCS for the active stimulation or sham groups, respectively. Each half consisted of 24 blocks of trials ending in either a target or a thought-probe. The number of non-target trials was variable in each block. **B)** The FT-RSG task was used in **Paper III**, which consisted of two halves. In the first half, the task was performed for 10 min without stimulation in all groups. In the second half, the task was performed with 20 mins of tDCS for the active stimulation group and sham stimulation for the sham groups.

cussed in section 2.3 is frequently used in the context of MW studies because of its monotonous nature (Smallwood et al., 2006). Previous studies have used it to assess the neural and behavioral correlates of MW (Cheyne et al., 2009; Christoff et al., 2009; Smallwood et al., 2008b; Stawarczyk et al., 2014; Stawarczyk et al., 2011a). To quantify the frequency of MW, participants are intermitently presented with a thought-probe where they report their MW propensity on a Likert scale, "1" (minimal) to "4" (maximal). The question used in **Paper I** for the thought-probe was, "To what extent have you experienced task-unrelated thoughts before the thought-probe?". The experimental design is shown in Figure 3.1A, which is based on Axelrod et al. (2015). Each stimulus lasted for 1 s with an inter-stimulus interval set to 1.2 s. There were two experimental halves each lasting 20 min with tDCS on (online tDCS) in the first half and tDCS off (offline tDCS) in the second half. Each half consisted of 24 blocks of variable numbers of non-targets. Each block ended either with a target trial or a thought-probe.

The FT-RSG task is a novel experimental paradigm designed to dynamically investigate the interplay between EF, BV, and MW (**Paper III**). The experimental design is shown in Figure 3.1B. The task requires participants to respond with random left-right button presses in synchrony with a fast-paced metronome. The inter-stimulus interval was set to 750 ms, which was determined in a pilot study as part of **Paper III**. Participants were required to match their finger taps as closely as possible to the timing of the metronome while at the same time maintaining randomness in their finger taps. There were two experimental blocks. The task was performed in the first 10 min block without tDCS stimulation. In the second block, the task was performed with 20 min tDCS (active tDCS group) or no stimulation (sham group). In addition, participants were intermittently presented with thought-probes to measure the frequency of MW on a scale from "1" (minimal) to "4" (maximal). Randomness in the finger-tapping sequence, which is linked to executive control, was operationalized using Approximate Entropy (AE; Pincus & Kalman, 1997). BV was calculated as the standard deviation of the inter-tap-intervals, which were measured between successive finger taps.

The FT-RSG task has some similarities with other tasks used previously in the MW literature, such as the Metronome Response Task (Seli, Cheyne, & Smilek, 2013) and a standard Finger Tapping task (Kucyi, Hove, Esterman, Hutchison, & Valera, 2016), including the use of a metronome. The Metronome Response Task and FT-RSG use the metronome at a constant interval throughout the task. In contrast, the Finger Tapping task uses the metronome for 10 s only, after which the participants have to keep time without its prompt. Participants

have two response alternatives that should be randomized in our novel FT-RSG task, which is different from the Metronome Response Task and Finger Tapping task. Our task is similar to the Random Number Generation task, which is reported to recruit central executive resources and has previously been used to study stimulus-independent thoughts (Teasdale et al., 1995). In our task, participants generate random left-right finger taps instead of random sequences of numbers or letters. A pilot study showed high correlation between the degree of randomness in the Random Number Generation task and the FT-RSG task as measured by AE.

3.3.2 Questionnaires

Two questionnaires were used in this thesis. First, the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was used to measure participants' mood states because a link has been reported between MW and negative mood states (Killingsworth & Gilbert, 2010; Smallwood, Fitzgerald, Miles, & Phillips, 2009a). The PANAS is a 20 items scale (10 describing positive and 10 describing negative emotional states), that are rated from 1 (very slightly or not at all) to 5 (extremely). Both positive and negative mood scores are calculated independently, and their values are used to assess the participants' current or past mood states. This questionnaire was used in **Paper I**, which was a multicenter study. Therefore, it was important that the PANAS scale were also available in Dutch (Engelen, Peuter, Victoir, Diest, & Van den Bergh, 2006) German (Janke & Glöckner-Rist, 2012) and Norwegian (Gullhaugen & Nøttestad, 2011). Second, participants completed the Mindful Attention and Awareness Scale (MAAS; Brown & Ryan, 2003) in **Paper I** and **Paper III**. This is a 15-item scale designed to measure an individual's disposition to attend to the current experience and overcome prepotent stimuli or internal states. The MAAS was used in Dutch (Schroevers, Nykliček, & Topman, 2008), German (Michalak, Heidenreich, Ströhle, & Nachtigall, 2008) and Norwegian (Verplanken, Friborg, Wang, Trafimow, & Woolf, 2007) in **Paper I**. Only the Norwegian version was used in **Paper III**. However, this data was not analysed for **Paper III**.

3.4 Simulation of the tDCS-induced electric field

In **Paper II**, we simulated the E-field induced by tDCS in a healthy and a clinical population. The clinical population consisted of patients diagnosed with

major depressive disorder. This paper sought to understand the distribution of the E-field induced by commonly used tDCS montages in the treatment of depression in terms of their focality. The montages used were largely based on a meta-analyses by Brunoni et al., 2016. TDCS-induced E-field was simulated for nine montages. They included seven bipolar montages targeting the left DLPFC and two 4×1 HD-tDCS ring montages (one targeting the left DLPFC and one targeting the mPFC). As detailed in our data descriptor (Boayue et al., 2018) and **Paper II**, tissue segmentation was performed automatically in SPM12 (Friston et al., 1994) for skin, skull, eyeballs, CSF and major air cavities, and in FreeSurfer 5.3.0 (Fischl, Sereno, & Dale, 1999) for gray and white matter. Subsequently, segmented images of each participant were visually inspected and manually corrected with FreeSurfer 5.3.0 (Fischl et al., 1999). During manual corrections we verified that the segmentation of the cortical gray matter corresponded to the anatomical scans, except for medial temporal lobe structures (i.e., the parahippocampal gyrus and hippocampus proper). Head models were created with a custom version of SimNIBS 2.1 (Saturnino et al., 2019; Thielscher et al., 2015), which is a freely available software package for simulating the effects of NIBS techniques. The final head mesh of each participant consisted of approximately 3,200,000 tetrahedral elements, assigned to six tissue types (Figure 3.2). The initial segmentation included more than 6 tissue compartments; we used separate tissue types for cerebellar gray and white matter that were later combined into one of 6 tissue types: skin, skull, cerebrospinal fluid, gray matter, white matter, and eyeballs in the final head models for simulation purposes. In addition, air cavities were modeled by not inserting tetrahedra to these locations, such as the air surrounding the head. Tissue conductivities were set as follows: 0.465 S/m (skin), 0.01 S/m (skull), 0.5 S/m (eyeballs), 1.654 S/m (cerebrospinal fluid), 0.275 S/m (gray matter), and 0.126 S/m (white matter). The accuracy of tissue segmentation and correspondence between anatomical scans and the resulting head models for 4 individuals are shown in Figure 3.3.

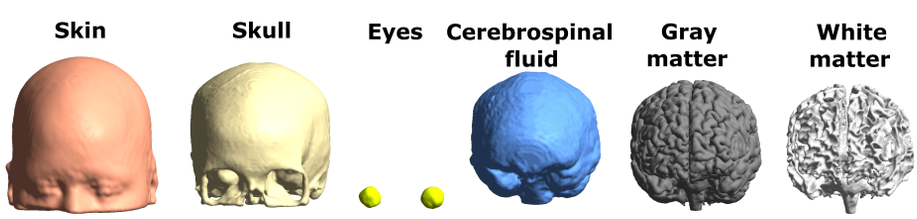

Figure 3.2: The six tissue compartments of the head models.

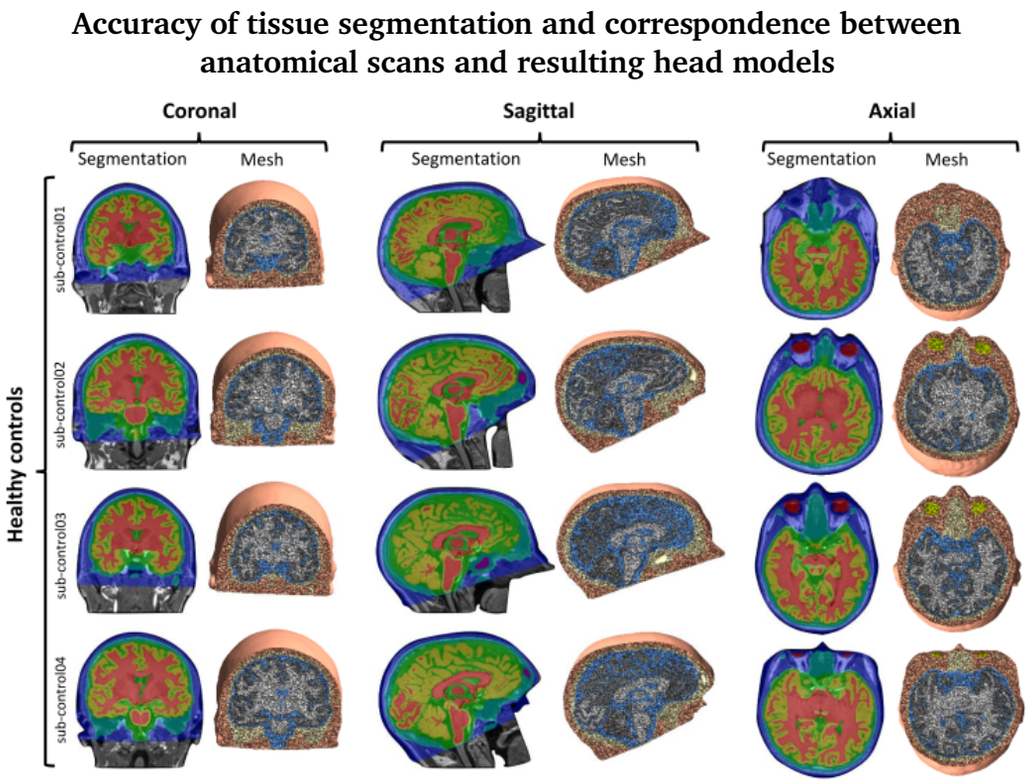

Figure 3.3: Cross-sections showing the correspondence between anatomical scans overlaid with results of the tissue segmentation (skin: dark blue; skull: turquoise; cerebrospinal fluid: green; gray matter: yellow; white matter: red; air cavities: purple, eyeballs: dark red) and the head models (meshes) for 4 individuals. Adapted from Boayue, Csifcsák, Puonti, Thielscher, and Mittner (2018).

Electrodes (each of of appropriate size depending on the montage) of thickness 1 mm were used for the bipolar montages with sponge pocket thickness of 2.5 mm. Circular connectors of 0.5 cm diameter were positioned at the middle of the electrode pads. For the 4×1 montages, we used electrodes with diameter of 1.2 cm and thickness of 1 mm with a gel layer of 2.5 mm. Electrode positions were based on the International 10/10 system. Electrodes were fitted to each individual head by using a modified version of a published script (Huang et al., 2013). This script required one manual step of entering the coordinates of six fiducials from the MRI images (nasion, inion, left and right preauricular points, back and front neck). The International 10/10 coordinates for each subject were obtained using these points. Anode stimulation intensity was set to 2 mA, with equal distribution of return currents for the 4 cathodes (-0.5 mA

for each) in the 4 × 1 protocols. The bipolar montages had the stimulation intensity of 1 – 2 mA and -1 – -2 mA for the anode and cathode, respectively, depending on the montage. The results of the simulations were visualized using Gmsh (Geuzaine & Remacle, 2009).

Bipolar versus HD-tDCS

Paper I and **Paper III** used bipolar and 4 × 1 HD-tDCS montages, respectively. In our recent data descriptor (Boayue et al., 2018), we compared a bipolar montage and 4 × 1 protocol targeting the left DLPFC. The results showed more widespread E-field distribution in the conventional bipolar montage when compared with the 4 × 1 HD-tDCS. Figure 3.4 shows the distribution of the E-field magnitude (vector norm) both for the 4 × 1 montage similar to the montage used in **Paper III** and the bipolar montage used in our study (**Paper I**) and by Axelrod et al. (2015). Similar to our data descriptor (Boayue et al., 2018), strong E-field are induced by both montages in the left DLPFC. Interestingly, the distributions were symmetrical and unilateral for the bipolar and 4 × 1 HD-tDCS montage, respectively.

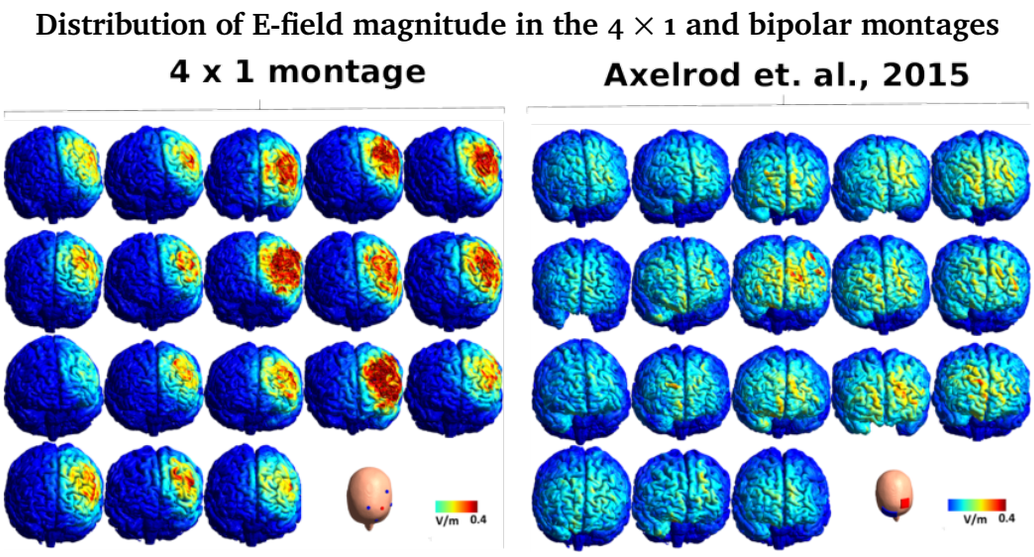

Figure 3.4: Simulation of tDCS-induced E-field in the cortex of 18 head models for the 4 × 1 montage (adapted from Boayue, Csifcsák, Puonti, Thielscher, and Mittner (2018)) similar to **Paper III** and the bipolar montage used in **Paper I** and by Axelrod, Rees, Lavidor, and Bar (2015).

Figure 3.5 shows the normal component of the E-field shown in Figure 3.4, which are thought to drive the tDCS-induced effect with positive and negative values representing the inward and outward flowing excitatory and inhibitory components, respectively (Rahman et al., 2013b), which are averaged across 18 individual datasets. The simulation showed that the 4×1 montage is more focal and stronger in intensity than the bipolar montage.

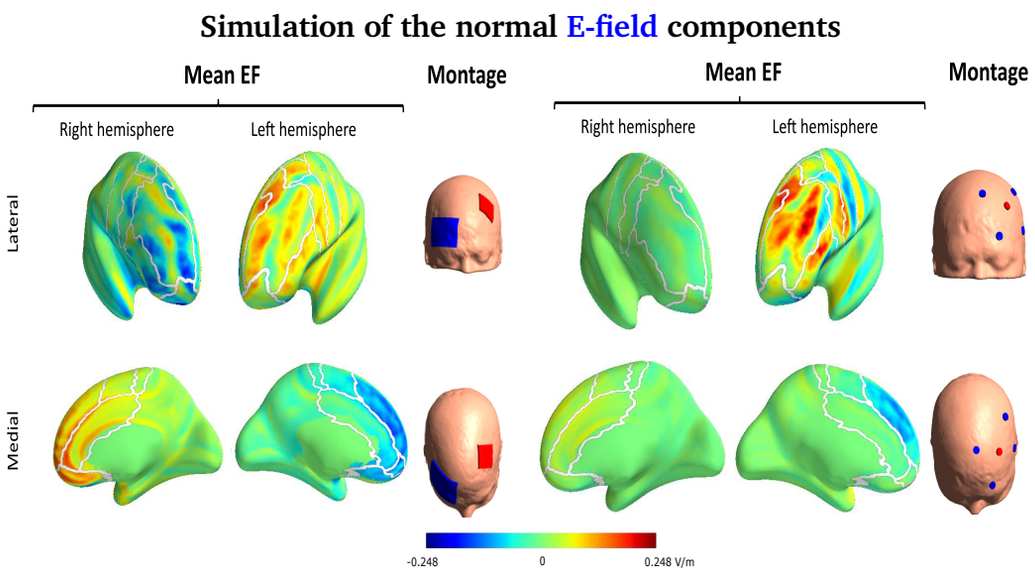

Figure 3.5: Simulation of the normal component of the E-field induced using the set-up of Axelrod, Rees, Lavidor, and Bar, 2015's (left) and the 4×1 (right), averaged over N=18 individual datasets. The traditional protocol features a broad and non-focal distribution of the E-field featuring both strong anodal (inward flowing) and cathodal (outward flowing) currents across both DLPFCs and mPFCs (left). In contrast, the 4×1 HD-tDCS protocol shows a stronger amplitude and is more focal.

3.5 tDCS apparatus and stimuli presentation

Paper I used the Neuroconn DC stimulator in study mode to enable the minimum allowable stimulation duration of 15 s in the sham protocol. The double-blind mode of the Neuroconn stimulator defaults at 40 s, which was not desirable. In **Paper III**, a Neuroelectrics Starstim stimulator was used. All stimuli in **Papers I** and **III** were presented using Psychopy (Peirce, 2007).

3.6 Stimulation protocol used in Paper I and Paper III

The stimulation protocols used in **Paper I** and **Paper III** are summarized in Table 3.1 below. The electrode coordinates presented here are based on the international 10-20 EEG system. The anode (4 × 4cm) for **Paper I** was positioned at F3 with a current intensity of 1mA. In **Paper III**, the same position was used with a circular electrode (diameter, 12 mm) and current intensity of 2 mA. In **Paper I**, the cathode (7 × 5cm) electrode was placed over the right supraorbital (RSO) with current intensity of -1mA. The cathodes (diameter, 12 mm) in **Paper III** were spread in a ring with the coordinates: C3, T7[1], Fp1, and Fz, and a current intensity of -0.5 mA (summing up to -2mA). The conducting medium used in **Papers I** and **III** was the Ten20 paste and Signa Gel, respectively. **Paper I** did not use local anaesthetics to conform with our replication aims. In contrast, we used a local anaesthetic (EMLA Cream) in **Paper III**. Both studies used two sessions: **Paper I** included online tDCS (20 min) followed by offline tDCS (20 min); **Paper III** included a baseline phase (10 min) followed by online tDCS (20 min). Blinding efficacy was assured in **Paper I** by a 30 s fade-in period followed by 15 s stimulation and a 30 s fade out period for the sham group. **Paper III** used a fade-in, fade-out period at the start of the session and a fade-in, fade-out period after the stimulation duration for the sham group.

Table 3.1: Summary of stimulation protocols

Study	Anode	Cathode	current	session I	session 2	conducting medium	local anaesthetics
Paper I	F3	RSO	1 mA	20 min online	20 min offline	ten20	
Paper III	F3	C3, T7 Fp1,Fz	2 mA	10 min baseline	20 min online	signa gel	EMLA Cream

3.7 Blinding

Effective tDCS blinding protocols are essential to be confident that the observed effects are due to stimulation but not a placebo effect, such as participants' expectancy. Recently, we showed based on data from subjective ratings of participants in **Paper I** that the commonly used blinding protocol, "fade-in,

1. Though our simulation result was based on FT7, we have used T7 in the atual experiment because the Neuroelectrics cap did not have an FT7 electrode location. We, however, do not believe that this will substantially affect the distribution of E-field.

short-stimulation, fade-out" sham control protocol does not ensure complete blinding when compared with active tDCS at 1 mA for 20 mins (Turi et al., 2019). **Paper I** and **Paper III** used double-blind, sham-controlled protocols. In **Paper I** we used the Neuroconn DC stimulator running in study-mode with each stimulation protocol randomly linked to a letter and secured with a 5-digit code. The mapping between the stimulator code and stimulation mode was accessible to a single researcher from each lab. This researcher was responsible for programming the device but not involved in data-acquisition. In **Paper III** the Neuroelectrics starstim was used and the device was programmed by a single researcher who was not involved in data acquisition. In **Paper I** participants were asked to guess if they had received the sham or active stimulation on a 7-point Likert scale, ranging from sham(1) to active (7). In **Paper III**, participants were asked to guess whether they received active or sham stimulation. The responses in both studies were collected at the end of each experiment.

3.8 Data management and open science

We have made all data, materials (such as the experimental instructions and questionnaires), and scripts from these experiments available on the OSF database. Data were uploaded continuously as they were acquired. Participants were assigned a random subject identification number. Data were stored as comma-separated values files with thought-probe responses, RTs, and stimulation group. They contained no sensitive information to retain participant anonymity. Therefore, all behavioral data, materials, and analysis scripts are publicly shared in adherence to open science practices. This allows other researchers to reproduce our findings and possibly extend them in other creative ways. For example, we relied on freely available public data for our simulation study in **Paper II**. The availability of datasets enables efficient data use that could alternatively have a significant acquisition cost. In addition, most research is funded by the public; therefore, the availability of these data ensures more efficient use of their resources. Table 3.2 below summarizes the availble data, materials and analysis scripts from **Paper I**, **Paper II** and **Paper III**.

Table 3.2: Summary of available data, materials and scripts

	Paper I	Paper II	Paper III
Project home	osf.io/dct2r/	osf.io/u5brq/	osf.io/nm2sz/
Pre-registration	osf.io/bv32d		osf.io/4hvdf
Preprint	psyarxiv.com/dfex3/	psyarxiv.com/erwvu/	psyarxiv.com/d9ngb/
Stimuli-presentation	osf.io/ctfjk/		osf.io/qt5g6/

3.9 Statistical methods

This thesis uses Bayesian statistics exclusively. We used Bayes factors and Bayesian parameter estimation using posterior distributions because of their benefits (Kruschke & Liddell, 2017; Wagenmakers et al., 2017b).

Classical inferential statistics with hypothesis testing using p values, and parameter estimation with confidence intervals have been the default for statistical inference in most empirical sciences. In the classical/frequentist domain, p values below a significance level of 0.05 are usually used to reject a null hypothesis, however this approach is suseptible to p-hacking. Bayesian statistics has begun to emerge as a viable alternative to frequentist statistics as freely available user-friendly open-source software package such as JASP become accessible with accompanying detailed tutorials that have been developed for Bayesian estimation and hypothesis testing (Love et al., 2019; Marsman & Wagenmakers, 2016; van den Bergh et al., 2019; Wagenmakers et al., 2017a). In the Bayesian framework, prior belief is updated based on the available data.

Wagenmakers et al. (2017b) have reported the benefits of Bayesian parameter estimation over frequentist parameter estimation with a confidence interval. First, Bayesian parameter estimation can incorporate prior knowledge to constrain the data in a meaningful way. For example, height measurements are known to be positive; therefore, it would be prudent to choose an appropriate prior distribution that is positively bound. This prior knowledge is updated as data accumulate to give us a posterior distribution. It is expected that the posterior distribution would be relatively peaked with informative data. Second, unlike the confidence interval, the Bayesian parameter estimation using posterior distribution allows quantifying confidence that a parameter lies within a particular interval. Therefore, the posterior distribution can show the

likelihood that a parameter has a particular value (e.g., 0.1) or lies within an interval (e.g., 0.7 - 0.9). For instance, in this thesis, 95% highest density interval (HDI) for effect sizes and regression coefficients are reported. Third, unlike classical frequentist statistics that rely on sampling distributions, Bayesian estimation relies on the data at hand for inference. Fourth, Bayesian estimation is coherent, meaning the final result should not change whether it was done as a single batch or sequentially. For example, in **Paper I**, where we have used a sequential sampling design, the final result should not change whether it was done as a single batch or sequentially. Finally, Bayesian estimation can be used in complicated models irrespective of model complexity, such as hierarchical or mixed models; the outcome is always the posterior distribution of the desired parameter. When this posterior distribution cannot be obtained analytically, it can be estimated numerically by Markov chain Monte Carlo method. In this thesis, the posterior distribution was estimated using the Markov chain Monte Carlo method employed in Stan (Carpenter et al., 2017).

Wagenmakers et al. (2017b) have reported the benefits of Bayesian hypothesis testing using Bayes factors when compared with null hypothesis significance testing. First, the Bayes factor quantifies evidence for both H_0 and H_1 given the data . This means that the Bayes factor directly compares the two competing hypotheses. In contrast, the null hypothesis significance testing only tests whether H_0 can be rejected. Second, the Bayes factor can quantify evidence for H_0. Both H_0 and H_1 are specified in the Bayesian framework; therefore, both models can be tested to assess which more accurately predicts the available data. Third, the Bayes factor allows evidence to be monitored as data accumulate as is evident in our sequential sampling design in **Paper I**. Fourth, data can still be analyzed and interpreted independent of a sampling plan using the Bayes factor. Lastly, the Bayes factor is not biased against Ho. It quantifies how predictive both Ho and H1 are based on their model specifications. Furthermore, an inadequate fit for Ho does not suggest a preference for H1; both models are compared equally.

3.9.1 Replication Bayes factors

In **Paper I**, different Bayes factors were used to assess the different hypotheses. Axelrod et al. (2015) showed increased self-reported MW propensity for participants who received anodal left DLPFC stimulation when compared with sham stimulation of the same region based on the mean thought-probe responses of participants during the whole experiment. To test this prediction, we used a directed Jeffreys-Zellner-Siow (JZS) Bayes Factor (Rouder,

Speckman, Sun, Morey, & Iverson, 2009). This tests the hypothesis that the mean thought-probe difference between the group receiving active (anodal) and sham (placebo) stimulation will be greater than zero to the hypothesis that this difference is zero or negative (Morey & Rouder, 2015). Since Bayes factor is a ratio, a value greater than one would support the hypothesis that anodal stimulation increases MW and a value less than one would support the hypothesis that this effect is zero (no effect on MW) or negative (reduces MW). A stimulation effect of zero would not be captured by $BF_{directed}$; therefore, we supplemented this Bayes factor by two other Bayes factors to detect zero effect. In summary, the Bayes factor BF_{null+} tests the hypothesis that the observed effect is zero to the hypothesis that this effect is positive. The Bayes factor BF_{null-} tests the hypothesis that observed effect is zero to the hypothesis that this effect is negative. In either case, a Bayes factor greater than one quantifies evidence for a zero effect and a value less than one quantifies evidence for a negative effect in the case of BF_{null-} and evidence for positive effect in the case of BF_{null+}. Finally, we tested the hypothesis that there is zero effect against the hypothesis of any effect (positive or negative), BF_{null}. Of these four Bayes factors, only $BF_{directed}$ tests the prediction of the original study, the rest quantify evidence for the absence of the effect of stimulation. Two additional Bayes factors, the replication and meta-analytic Bayes factors were calculated based on code provided by (Verhagen & Wagenmakers, 2014, http://www.josineverhagen.com/?page_id=76). The replication Bayes factor, $BF_{replication}$, compares the hypothesis that the replication effect size will concur with that of the distribution of the original study to the hypothesis that the effect size can be attributed to random fluctuations from zero. This Bayes factor directly tests the success of the replication attempt. Finally, the fixed-effect meta-analytic Bayes factor BF_{meta} (Rouder & Morey, 2012) pools data from the original and replication study to quantify evidence for an overall effect. Table 3.3 summarizes the six Bayes factors discussed here.

Table 3.3: Summary of the Bayes factors used in **Paper I**

$BF_{directed}$	positive vs zero or negative effect of stimulation
BF_{null+}	zero vs positive effect of stimulation
BF_{null-}	zero vs negative effect of stimulation
BF_{null}	zero vs negative or positive effect of stimulation
$BF_{replication}$	successful replication vs null result
BF_{meta}	pooled data from original and replication study vs null result

3.9.2 Hierarchical ordered probit regression model

We incorporated an analysis method designed to analyze rank ordered data for the thought-probe responses in **Papers I** and **III**. Many areas of research rely on the Likert scale, which generates ranked ordered data. For instance, one might be asked how strongly one agrees with something on a scale of 1-7. These kinds of data are not metric (interval or ratio) data. Instead, they are ranked ordered data that has to be handled in a specialized way. Most scientific literature treat these as metric data, which can increase the type I and II error rates (Liddell & Kruschke, 2018). A normal distribution is used as a model of both metric and ordinal data, which can be described by their mean and standard deviation. However, the probability of each outcome is given by the probability density of the normal distribution at a particular point for metric data. The ordinal probit model is described by the mean and standard deviation. Furthermore, the probability density distribution is thresholded and the accumulative density (area under the curve) is calculated as the probability of each response option. The thresholds at the ends are fixed for ensuring identifiability. For example, the number of thresholds will be four on a 7-item scale. Furthermore, we used a Bayesian estimation of the hierarchical order probit model because of its benefits. First, the Bayesian framework allows flexible specification of our model. Second, there is no waste of data using a hierarchical model because participants' data inform group-level parameters. This is in contrast to other MW literature where MW probe data are typically averaged within-subject before being used in the final between-subject analysis.

4

Summary of Results

This chapter summarizes the main results of the original papers. The individual papers provide detailed results.

4.1 Paper I

Title: *Increasing propensity to mind-wander by transcranial direct current stimulation? A registered report*

Following the preregistered sequential-sampling plan, the criterion for optional stopping was that 95% HDI of the posterior distribution of the effect size excludes zero in the positive direction. This criterion was checked after 120 participants (60 participants/group) to alleviate spuriously rejecting a null effect of stimulation and subsequently after each batch of 18 participants (9 participants/group). The final analyses included the full prespecified maximum of 192 participants broken down into 64 participants per lab (3 labs in total) because the intermittent results did not meet the criterion for optional stopping. Analysis at each point in our sequential-sampling plan resulted in a consistently negative mean posterior effect size, and all HDIs included zero. This resulted in a final effect size of $d = -0.11$, HDI$= [-0.38, 0.17]$. This

indicated that participants receiving anodal stimulation were less likely to report being off-task than those receiving sham stimulation; however, this was not reliably different from zero. The directional Bayes factor, $BF_{directed}$, showed support for the hypothesis that the effect is more likely to be negative or zero.

Furthermore, different Bayes factors quantifying evidence for null effect of stimulation were tested against non-zero (positive or negative), BF_{null}, positive, BF_{null+}, and negative, BF_{null-} effects respectively, all of which to various degrees showed support for a null effect of stimulation. Additionally, the replication Bayes factor, $BF_{replication}$, showed extreme evidence that the original study was not replicated. Next, when data was combined from both the original and the replication studies, BF_{meta} showed strong evidence against an effect of anodal stimulation on self-reported MW. Detailed results are presented in Table 4.1 and Figure 4.1. Exploratory analysis showed that stimulation was not associated with either on-line or off-line task performance.

N	Cohen's d	BF_{null+}	BF_{null-}	BF_{null}	$BF_{directed}$	$BF_{replication}$	BF_{meta}
120	-0.09 [-0.44, 0.24]	7.46	3.21	4.48	0.43	0.002	0.071
138	-0.06 [-0.38, 0.25]	7.27	3.91	5.08	0.54	0.003	0.081
156	-0.05 [-0.35, 0.25]	7.30	4.44	5.52	0.61	0.003	0.088
174	-0.07 [-0.36, 0.22]	8.65	3.93	5.41	0.45	0.003	0.074
192	-0.11 [-0.38, 0.17]	10.65	3.09	4.79	0.29	0.002	0.059

Table 4.1: Results at the pre-registered stopping points. The criterion for stopping data-collection was that the 95% HDI around the effect-size would exclude zero in the positive direction. The effect-size was consistently negative and all HDIs included zero and therefore the complete sample was collected.

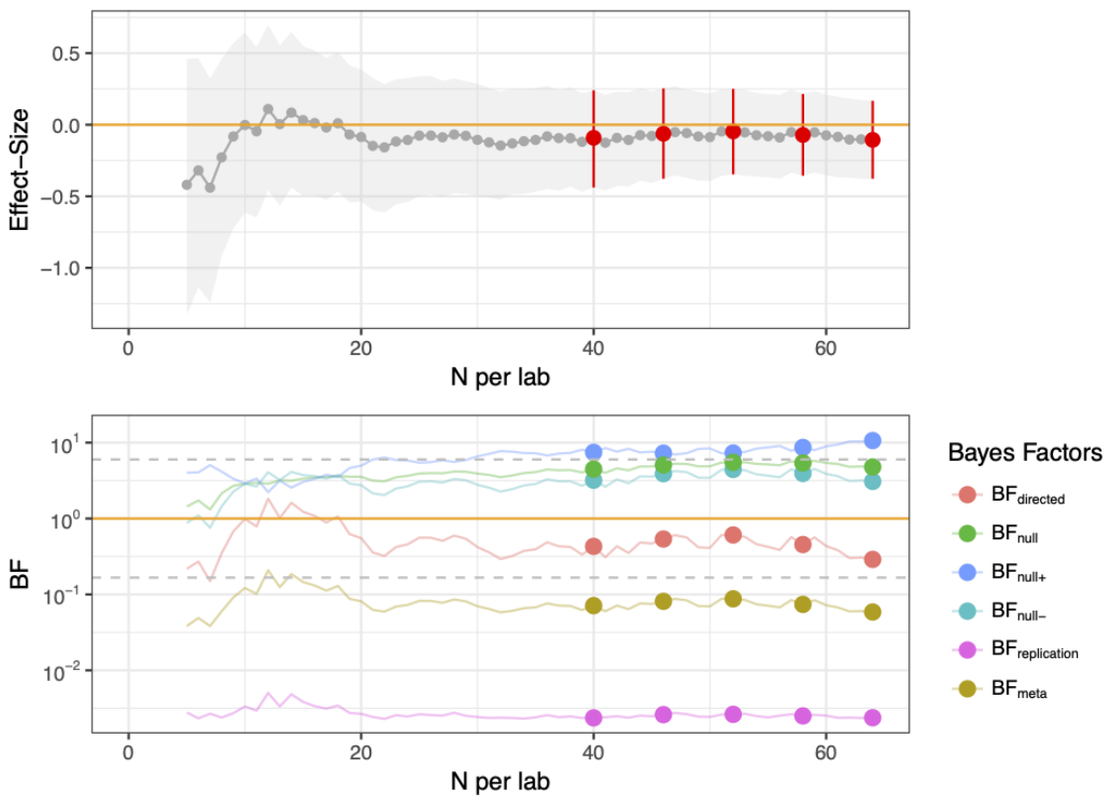

Figure 4.1: Results of the sequential sampling plan. Target statistics for increasing sample size (per lab) are plotted. Dots represent the pre-registered time-points at which data-collection could be stopped should the HDI exclude zero in the positive direction. (a) Effect-size and 95% HDI for the effect of anodal stimulation on mean thought probes. All HDIs include zero at any time. The final effect-size was in the opposite direction than hypothesized. (b) Bayes factors quantifying evidence in support of various hypotheses (see text for details). Horizontal dashed lines indicate Bayes factor = 6 or 1/6

4.2 Paper II

Title: *Effects of transcranial direct current stimulation for treating depression: A modeling study*

Paper II investigated tDCS-induced E-field for 7 bipolar and two 4×1 mon-

tages. Here, we highlight the differences between a typical bipolar and the 4 × 1 DLPFC montage. Simulated tDCS-induced E-field for the conventional bipolar montages showed E-field of comparable magnitude in the left DLPFC and the mPFC (e.g., see Figure 3.5). In addition, there was substantial interindividual variability in the E-field cortical maps depending on the stimulation parameters of the particular montage (e.g., see Figure 3.4). The 4 × 1 montages were more localized but had weaker E-field. Focality-indices (percentage of top 1% nodes in a target region) that were calculated separately for inward (anode-like effect) and outward (cathode-like effect) flowing E-field normal to the cortical surface showed the highest focal excitatory effect in the left DLPFC for the 4 × 1 DLPFC montage (see Figure 4.2).

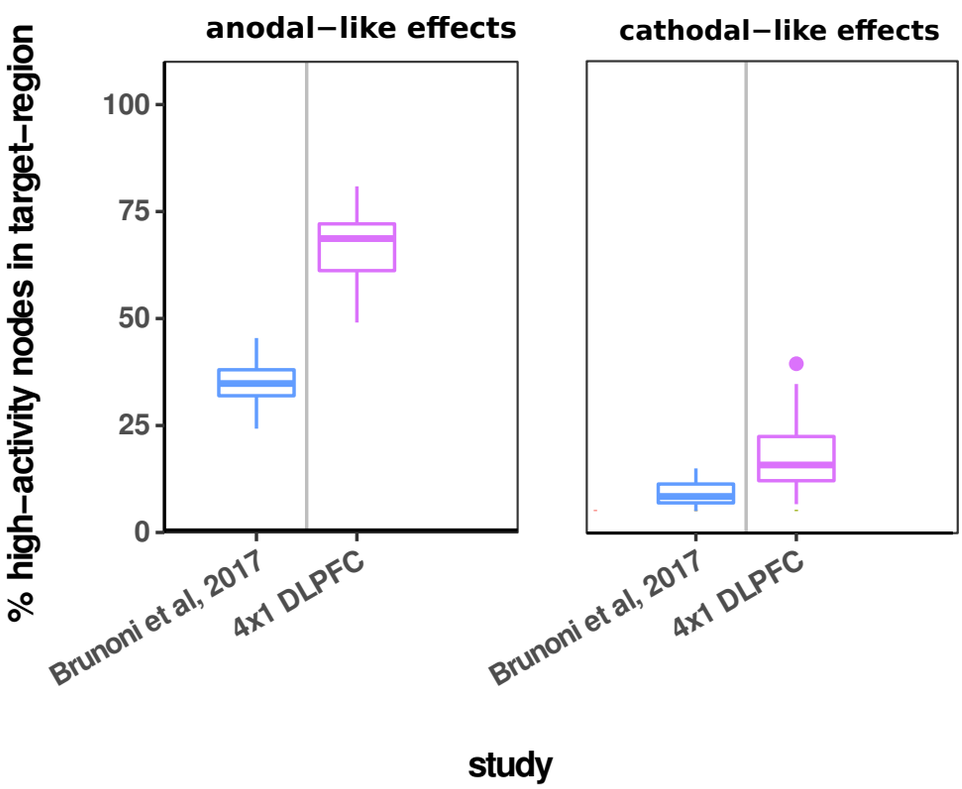

Figure 4.2: Focality-indices (percentage of top 1% nodes in the left DLPFC), calculated separately for positive and negative E-field normal values for two montages. Horizontal lines within boxes represent median values, whereas lower and upper box hinges correspond to the first and third quartiles (25th and 75th percentiles, respectively). Upper/lower whiskers extend to the largest/smallest values that do not exceed 1.5* the inter-quartile range; data beyond the end of whiskers are outliers.

4.3 Paper III

Title: *The interplay between cognitive control, behavioral variability and mind wandering: Insights from a HD-tDCS study*

Our preregistered analysis plan (osf.io/4hvdf) rested on the assumption that AE (proxy for executive control) measure would differ significantly between the two groups (anodal vs. sham) as a precondition for testing our other hypothesis; however, this was not the case, therefore, rendering our preregistration void. All results herein are exploratory. In contrast to **Paper I**, blinding was effective probably because in this study, we used a local anesthetic to alleviate skin sensations related to active tDCS.

Bayesian estimation of the hierarchical ordered probit regression model with participants' self-reported MW as the outcome variable showed that MW was associated with high BV and decreased randomness (AE) in the FT-RSG task. A positive interaction between BV and randomness (BV × AE) in the FT-RSG task was associated with MW, indicating that the positive association between MW and BV gets stronger for higher AE. In addition, there was a time-on-task effect within (effect of Trial) and between sessions (effect of Block; baseline vs. stimulation) but no main effect of stimulation. Crucially, there was a negative Block × Stimulation interaction effect indicating reduced MW in the real relative to the sham stimulation group. These results were robust against a model that included AE, BV, and the crucial Block × Stimulation interaction (see Figure 4.3).

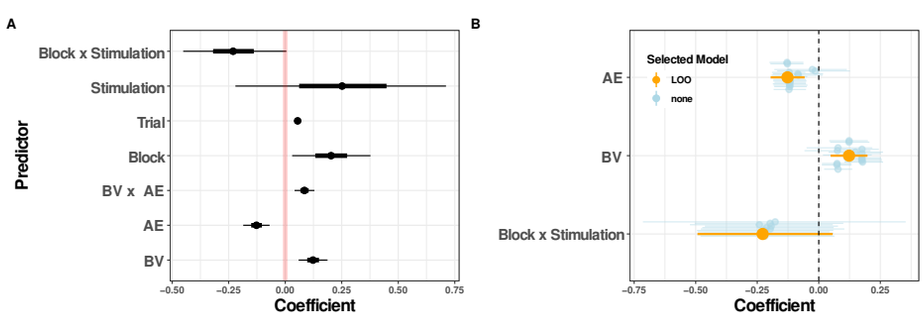

Figure 4.3: Model-coefficients in study 3. A: All coefficients of the winning model. B: The coefficients for AE, BV and the crucial Block × Stimulation interaction for all of the tested models that included them. LOO indicates the winning model based on leave-one-out cross-validation criterion and none indicate the rest of the other models.

5

Discussion

This thesis sought to investigate the behavioral and neural correlates of the pervasive mental phenomenon, MW, using tDCS. We aimed to establish the causal role of the left DLPFC in MW and the impact of stimulation on behavioral performance using transparent, rigorous open science practices. MW was assessed using the probe-caught method. In **Paper I**, a high-powered, multi-lab, preregistered report protocol, and robust Bayesian statistics were used to quantify evidence for and against an effect using a sequential sampling design. We failed to replicate the findings of Axelrod et al. (2015) that anodal tDCS applied to the left DLPFC leads to increased self-reported MW when compared with a sham tDCS to the left DLPFC. Through computational modeling using realistic head models, **Paper II** demonstrated that bipolar montages similar to that used by Axelrod et al. (2015) and **Paper I** elicit widespread stimulation extending far beyond the stimulation site. In contrast, a 4×1 montage targeting the left DLPFC was more focal with the induced E-field staying within the ring created by the four return electrodes. Based on the insight from **Paper II** on the diffuse nature of bipolar montages, **Paper III** used a 4×1 montage targeting the left DLPFC. Additionally, the task was also changed from SART in **Paper I** to our novel FT-RSG task in **Paper III**. With this new montage and task, **Paper III** showed that participants receiving anodal stimulation of the left DLPFC tended to report less MW as compared to the sham stimulation group. In addition, MW was associated with high BV and less randomness (a

proxy for executive control) in the FT-RSG task. TDCS had no impact on task performance in both **Papers I** and **III**, which was in line with other studies (Axelrod et al., 2015; Filmer et al., 2019).

5.1 Paper I

In **Paper I**, we failed to replicate the results of (Axelrod et al., 2015) using different Bayes factors to quantify evidence for the null-effect. These Bayes factors supported a null-effect to varying degrees. Further, the $BF_{replication}$, meant to test replication success showed strong evidence that the original study did not replicate. An additional Bayes factor, BF_{meta}, meant to quantify evidence for combined data from both the original and the replication studies showed strong evidence against an effect of anodal stimulation on self-reported MW. In contrast, analyses based on the effect-size estimate and Bayesian estimation of a hierarchical ordered probit regression model showed that the effect was in the opposite direction, although it was not reliably different from zero. This result indicates that participants receiving anodal stimulation were less likely to report MW when compared to the sham group, although this result was not robust.

Our null finding is not particularly surprising given the "crisis of confidence" (Pashler & Wagenmakers, 2012) facing psychological science in general due to low replicability (Open Science Collaboration, 2015) and lack of strong evidence for the cognitive effect of single session tDCS more specifically (Horvath et al., 2015b). The discrepancy between our findings and that of the original study of Axelrod et al. (2015) can be attributed to reasons addressed in **Paper I** and our commentary (Csifcsák et al., 2019). Firstly, the original study used a small sample size (10–14 participants/group). Such underpowered studies lead to an overestimation of the true effect size due to the significance filter (Gelman & Carlin, 2014; Minarik et al., 2016). This seems apparent in the large effect size of $d = 1.24$ reported by Axelrod et al. (2015), which is atypical in the psychological literature. Secondly, small sample sizes lead to mixed findings as we have shown previously using computational modeling of tDCS induced E-field (Boayue et al., 2018), individual response to tDCS shows large variability due to anatomical differences. This means that large sample sizes should be employed to ascertain the stability and reliability of tDCS to elicit a particular behavioral response given a particular montage in a healthy population. If pooling a large sample size is not feasible for a single lab, a multi-lab study should be adopted with preferably robust Bayesian statistics

and a pre-registered protocol similar to **Paper I**.

Our finding of no effect could be due to the following reasons. Firstly, it is likely that the bipolar protocol used in our study does not provide strong enough stimulation to modulate activity in any underlying region implicated in MW, such as the mPFC and the left DLPFC. Secondly, these regions may have been stimulated effectively, which could be shown by measuring neural responses with EEG or fMRI, but they do not contribute to MW at all. However, this seems unlikely based on previous literature on the DLPFC/DMN involvement in MW (Christoff et al., 2009; Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011b). Lastly, our protocol may produce widespread effects by up-regulating the left DLPFC and down-regulating (some parts of) the mPFC; therefore, these effects may have cancelled each other out. This latter is very speculative of course, but considering the result of **Paper III**, both the first and last still hold, as the 4 × 1 montage produced more focal effects (supporting the last possibility since stimulation of the mPFC is alleviated), but also stronger stimulation of the left DLPFC (supporting the first possibility that E-field might not have been potent enough to modulate either mPFC or left DLPFC).

Therefore, we concluded that the data from Axelrod et al. (2015) should not be used as evidence of the utility of left DLPFC tDCS in modulating MW propensity.

5.2 Paper II

Paper II focused on the use of computational modeling to gain insight into the distribution of tDCS induced E-field of different tDCS montages. Both conventional bipolar and 4 × 1 montages were assessed. We showed that simulated tDCS-induced E-field for seven conventional bipolar montages (some very similar to the montage used by Axelrod et al. (2015) targeting the left DLPFC elicited diffuse E-field distribution with comparable E-field magnitude in the left DLPFC and the mPFC. In addition, there was substantial interindividual variability in the E-field cortical maps depending on the stimulation parameters of the specific montage. The bipolar montages induced a higher intensity of E-field, with widespread distribution beyond the stimulation target. This lack of spatial specificity is a challenge for conducting hypothesis-driven research because it stimulates multiple brain regions concurrently. This can complicate the attribution of any observed effect to either the mPFC or left DLPFC and lead to multiple interpretations. In contrast, the 4 × 1 montages

were more localized with weaker E-field at the same stimulation intensity. Focality-indices calculated separately for the E-field normal to the cortical surface associated with excitatory and inhibitory effects showed a more focal excitatory effect in the left DLPFC (see Figure 4.2) for the 4×1 montage. This is in line with previous studies (Datta et al., 2009). Taken together, **Paper II** shows that we created a 4×1 montage explicitly targeting the left DLPFC, which seems appropriate for our purpose used further in **Paper III**. It should be pointed out that the increased focality for the 4×1 montage was at the expense of E-field intensity in **Paper II**; however, this did not hold when compared with Axelrod et al. (2015) because their protocol (also used in **Paper I**) used 1 mA, whereas the bipolar montages used for comparison in **Paper II** used 2 mA. Thus, our 4×1 montage was both more focal and intensive when compared with Axelrod et al. (2015).

5.3 Paper III

In **Paper III**, we showed that MW is associated with high BV and decreased executive control, which is measured by the degree of randomness (AE) in a generated sequence in the FT-RSG task. This finding indicates that when the mind wanders, behavioral performance becomes less stable and therefore, manifests in highly variable behavior. In addition, there is less cognitive control to focus on generating random sequences as the brain fluctuates between different attentional states. Further, we found an interaction between BV and randomness (BV $\times$ AE) associated with MW, which suggests a more pronounced positive relationship between MW and BV as randomness increases. In addition, we found a time-on-task effect within (from trial to trial) and between sessions (baseline vs. stimulation), indicating that participants were more likely to mind wander as the task progressed. There was no main effect of stimulation (that is, when baseline and stimulation sessions are combined); however, there was a negative Block $\times$ Stimulation interaction effect. This indicated reduced MW in the active relative to the sham stimulation group. Therefore, active tDCS seems to be effecitve in reducing the between-session time-on-task effect. Importantly, these results were robust against the choice of statistical model that included BV, AE, and the crucial Block $\times$ Stimulation interaction (see Figure 4.3). However, This effect should be treated with caution as the HDI included zero.

Our finding of reduced MW with no effect on task performance (AE) can be viewed from at least two perspectives. Firstly, this provides some support for

the EF_{fa} model of MW in that stimulation of the left DLPFC, a vital node of the FPCN (Christoff et al., 2009; Stawarczyk et al., 2011b) provided executive control resources that enabled participants in the active stimulation group to avoid any internal or external distractions. In contrast, the EF_{fu} model of MW, argues that the same executive resources are required for the on-going task and MW. Therefore, the availability of more resources would have led to more MW with a negligible effect on task performance. Secondly, neuroimaging studies have indicated an anticorrelation between the DMN and FPCN (M. D. Fox et al., 2005). Therefore, increased activity in the FPCN might have indirectly triggered reduced activity in the DMN, leading to less MW.

Our results are in contrast to Axelrod et al. (2015) who found an increased MW propensity in the active stimulation group. Interestingly, both montages induced inward flowing (excitatory) E-field in the left DLPFC as can be seen in Figure 3.5. The montage used by Axelrod and colleagues elicits broad E-field extending to the mPFC, which is a core hub of the DMN (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014). Direct stimulation of this core region could as well explain their results. Notably, mPFC stimulation is not dependent on the polarity of DLPFC stimulation, because regardless of polarity, the mPFC in one hemisphere receives inward-currents, and the other receives outward-currents (see Figure 3.5 left). Interestingly, the polarity of DLPFC stimulation determines which mPFC hemisphere receives the outward-current; however, hemispheric lateralization for the DMN in terms of its relationship to cognitive processes hasn't been shown so far. It would be interesting to assess the same effect of reduced MW after the electrode polarities in our 4 × 1 HD-tDCS montage are reversed. An active control group, for example, targeting the occipital cortex, would ascertain the specificity of the observed tDCS effect on MW. Furthermore, a combined HD-tDCS - fMRI study with effective connectivity analysis would be warranted to tease apart the neural mechanism of the induced E-field elicited by HD-tDCS.

5.4 General Discussion

Papers I and **III** provide some evidence for reduced MW as a result of anodal stimulation of the left DLPFC; however, this finding was less robust in **Paper I**. There are essential differences between these studies. The montage used in **Paper III** targets the left DLPFC more accurately while the E-field are much more diffuse in **Paper I**. The specificity of the montage in **Paper III** reliably implicates the causal role of the left DLPFC in MW when compared with

Paper I because the E-field are more focused. In addition, both studies employ different tasks that might play a role in the observed effects. The SART used in **Paper I** is designed to be relatively easy even though it requires the use of executive resources since participants have to inhibit prepotent responses for the No-Go stimuli. Therefore, some level of executive control is needed, but it is rather weak. In contrast, the FT-RSG task is challenging at a fast pace. This suggests that the FT-RSG task may generate higher activity than the SART in the executive networks, including the DLPFC. Consequently, a higher 'baseline' activity of the left DLPFC during the FT-RSG task than during the SART may make it more susceptible to the active stimulation that was applied. However, this hypothesis of an increase in susceptibility to neuromodulation during higher activity needs to be verified using concurrent neuroimaing.

There are important differences between the studies in this thesis: we used different montages, tasks, and current intensities. For example, **Papers I** and **III** used 1 and 2 mA respectively. Further experiments are required to address whether electrode arrangement, current intensity, task, or some combination thereof are responsible for the observed differences in outcomes between these two studies. To test the effect of current intensity, a study using the bipolar montage and increased intensity of 2 mA in both groups (SART vs. FT-RSG task) receiving active stimulation would be necessary. To measure the effect of the task, an experiment using two groups (SART vs. FT-RSG) receiving the same active anodal 4×1 left DLPFC stimulation should be implemented. Furthermore, the 4×1 montage should be switched with the bipolar montage to assess the effect of electrode arrangement.

Current intensity might influence the effect of tDCS on MW, which determines tDCS dosage together with the duration of the stimulation. Further studies should be conducted to assess the effect of increased tDCS current intensity on MW when all other stimulation parameters are held constant. Filmer et al. (2019) recently tested this empirically with cathodal stimulation of the left DLPFC and three current intensities (1, 1.5, and 2 mA). These findings showed a linear relationship between MW propensity and current intensity; however, only the 2 mA cathodal condition differed significantly from the sham condition.

Some authors reported increased MW propensity as a result of anodal stimulation of the left DLPFC (Axelrod et al., 2015; Axelrod et al., 2018). In contrast, other authors (Kajimura et al., 2016; Kajimura & Nomura, 2015) found decreased MW propensity due to cathodal stimulation of the same region; however, different experimental designs and methodologies were used. This

would seem to support the initial view of anodal excitatory and cathodal inhibitory effects, based on previous studies (Nitsche & Paulus, 2000) investigating the effect of tDCS on the motor cortex. However, these may not apply to the cognitive domain. A recent preregistered study showed a facilitatory effect (increased MW propensity) of 2 mA cathodal left DLPFC stimulation on MW relative to sham stimulation (Filmer et al., 2019). This is in contrast to previous studies (Kajimura et al., 2016; Kajimura & Nomura, 2015); however, there were critical methodological differences, including the choice of anodal electrode location (right supraorbital region (Filmer et al., 2019), parietal cortex (Kajimura et al., 2016; Kajimura & Nomura, 2015)) and experimental paradigms. The montage used in prior studies (Kajimura et al., 2016; Kajimura & Nomura, 2015) targeted regions of the DMN (parietal cortex anode) and FPCN (prefrontal cortex cathode); therefore, it is challenging to assess which area might have been responsible for the observed MW effect. In a recent study, Kajimura et al. (2018) showed that anodal tDCS applied to the right parietal cortex using the contralateral cheek as reference led to decreased MW propensity. This finding confirmed a causal role of the rIPL in modulating MW. More recently, a study employing a similar experimental design did not show any effect (Coulborn et al., 2020).

The choice of proper reference for conventional bipolar montages is essential because both electrodes induce E-field in the brain (Kajimura et al., 2016; Kajimura & Nomura, 2015). The use of an extracephalic reference electrode might help to alleviate any ambiguity in interpretation (Kajimura et al., 2018).

One potential explanation for the reduction in MW propensity in **Paper III** when compared with **Paper I** might be due to the different blinding protocols adopted. Our earlier work based on data from **Paper I** (Turi et al., 2019) demonstrated that the "fade-in, short-stimulation, fade-out" sham control protocol compromised blinding efficacy. In contrast, we showed that blinding was successful in **Paper III**. This might be due to the combination of the local anesthetic (EMLA cream) and conductive gel. In addition, compromised blinding might explain the findings in Axelrod et al. (2015), but not our null finding (**Paper I**). Numerically we found reduced MW in **Paper I**, however this result is not reliable because participants likely reported more MW because the electrodes itched a little such that in total no effect was found. Another explaination could be that Axelrod et al. (2015) might not have used naive participants as we did in **Paper I**. Consequently, participants would more likely know they have been stimulated as they recognize the sensation of active tDCS.

5.5 Benefits and challenges of open and reproducible science

Reproducibility is an essential part of empirical science. Open science practices must be adhered to facilitate this. These include open access to raw data and the availability of analysis scripts, including all necessary materials that are required to reproduce published results in the scientific literature.

In this thesis, we have used the born open data approach (Rouder, 2015), wherein data was continuously uploaded to the OSF data repository as they were collected. This method is advantageous over uploading all data after the study is completed because the data are safely stored in a public database that is timestamped. In addition, these data allow for more transparency because any excluded data should be justified if exclusion criteria were not set *a priori*. This highlights the significance of preregistration because all inclusion and exclusion criteria are pre-specified.

Not all journals require authors to make data available upon submission; however, some have signed the Transparency and Openness Promotion guidelines (Nosek et al., 2015). This aims to foster transparency in the scientific landscape. Authors are obligated to provide available data when they publish in journals that are a signatory to the Transparency and Openness Promotion agreement if their data are not already available publicly.

One major hindrance to the reproducibility of scientific findings is the inaccessibility of a pipeline containing the full analysis scripts used to produce the results of published findings. Even if the methods are described in great sufficient detail, there is some level of freedom in the analysis process that might influence the result. It might even be that different versions of the same software might influence the result. To avoid all these, the best way to encourage a more reproducible science is to make the complete analysis pipeline available to make it feasible to be reproduced independently by other scientists. We did this for our papers.

A recent study sought to analyze open data practices among authors of randomized controlled trials (Gabelica, Cavar, & Puljak, 2019); however, the authors found a very low response rate (4%) to request of original data. This finding highlights challenges faced to ensure scientific rigor with easy accessibility to research data and materials. From a personal experience, we sought to obtain the data from Axelrod et al. (2015) and Axelrod et al. (2018)

); however, this was not possible, as discussed in our commentary (Csifcsák et al., 2019). Additionally, the open availability of analytical scripts ensures a faster adoption of new methods. We have recently argued for the adoption of the ordinal probit regression model for the analysis of MW thought-probe responses. We shared of our scripts to ensure their ease of use by others, as evident by a recent preregistered study (Filmer et al., 2019).

5.6 Conclusion

Admittedly, our main analysis in **Paper III** was exploratory, and we have marked it as such because it did not follow our preregistered protocol. Though based on a single study, we think that there might be some room for tDCS in MW research and that it might be effective in modulating MW. We reported a failed replication in **Paper I**; however, we found an effect when using our novel FT-RSG task. Our sample size of 30 per group in **Paper III** is not substantial when compared with the sample size of 96 per group in **Paper I**. Therefore, we need to conduct a high-powered preregistered replication study with more participants. We are cautiously optimistic about the prospect of tDCS in MW research; however, we recognize that this study should be replicated independently or via self-replication. To date, we are now pursuing a large-scale self-replication of our study. Stimulating the left DLPFC may influence MW; however, our results were conflicting compared with previous studies (Axelrod et al., 2015; Axelrod et al., 2018). We found reduced MW as a result of anodal 4×1 left DLPFC stimulation, which suggested that tDCS protocols may be effective for MW-associated psychopathologies, such as depression. More work is required to elucidate the underlying neural mechanisms.

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REGISTERED REPORT STAGE 2

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Increasing propensity to mind-wander by transcranial direct current stimulation? A registered report

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Abstract

Transcranial direct current stimulation (tDCS) has been proposed to be able to modulate different cognitive functions. However, recent meta-analyses conclude that its efficacy is still in question. Recently, an increase in subjects' propensity to mind-wander has been reported as a consequence of anodal stimulation of the left dorsolateral prefrontal cortex (Axelrod et al., Proceedings of the National Academy of Sciences of the United States of America, **112**, 2015). In addition, an independent group found a decrease in mind wandering after cathodal stimulation of the same region. These findings seem to indicate that high-level cognitive processes such as mind wandering can reliably be influenced by non-invasive brain stimulation. However, these previous studies used low sample sizes and are as such subject to concerns regarding the replicability of their findings. In this registered report, we implement a high-powered replication of Axelrod et al. (2015) finding that mind-wandering propensity can be increased by anodal tDCS. We used Bayesian statistics and a preregistered sequential-sampling design resulting in a total sample size of $N = 192$ participants collected across three different laboratories. Our findings show

Abbreviations: ANOVA, analysis of variance; BF, Bayes Factor; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; EEG, electroencephalography; EF, electric field; FPN, frontoparietal control network; HDI, highest density interval; JZS, Jeffreys–Zellner–Siow; LOOIC, leave-one-out cross-validation information criterion; MAAS, Mindful Attention and Awareness Scale; MPFC, medial prefrontal cortex; NHST, null hypothesis significance testing; OSF, Open Science Framework; PANAS, Positive and Negative Affect Schedule; rIPL, right inferior parietal lobule; RTCV, Reaction time coefficient of variation; RT, reaction time; SART, Sustained Attention to Response Task; tDCS, transcranial direct-current stimulation; UiT, University of Tromsø; UniGö, University of Göttingen; UvA, University of Amsterdam; WAIC, Watanabes information criterion.

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support against a stimulation effect on self-reported mind-wandering scores. The effect was small, in the opposite direction as predicted and not reliably different from zero. Using a Bayes Factor specifically designed to test for replication success, we found strong evidence against a successful replication of the original study. Finally, even when combining data from both the original and replication studies, we could not find evidence for an effect of anodal stimulation. Our results underline the importance of designing studies with sufficient power to detect evidence for or against behavioural effects of non-invasive brain stimulation techniques, preferentially using robust Bayesian statistics in preregistered reports.

KEYWORDS

DLPFC, mind wandering, non-invasive brain stimulation, tDCS

1 | INTRODUCTION

Mind wandering can be tentatively defined as a shifting of the attentional focus from external task demands to internal thoughts (Smallwood & Schooler, 2006). Episodes of mind wandering are very common during activities of daily life (Killingsworth & Gilbert, 2010) and during experimental tasks. Depending on various factors such as task difficulty (Feng, D'Mello, & Graesser, 2013) and mood (Smallwood, Fitzgerald, Miles, & Phillips, 2009), the percentage of time we spend mind wandering is estimated to be between 30% and 50%. In recent years, much interest has focused on the neural basis of mind wandering (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mason et al., 2007; Mittner et al., 2014). One consistent finding is that mind wandering involves the default-mode network (DMN; Raichle et al., 2001), a network of brain areas that are activated during internal mentation (Andrews-Hanna, 2012; Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 2008). The finding that activity in these areas is increased has been replicated in several independent studies employing different tasks and methodologies (Christoff et al., 2009; Mittner et al., 2014; Weissman, Roberts, Visscher, & Woldorff, 2006).

Less well understood is the role of the frontoparietal control network (FPN; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010) which also seems to be involved in the initiation and sustenance of mind wandering (Smallwood, Brown, Baird, & Schooler, 2012). Several studies have linked perceptual awareness to the propagation of stimulus-induced neural activity to the FPN, representing a "global workspace" that provides conscious access to cognitive representations (for reviews, see: Baars, Franklin, & Ramsoy, 2013; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Dehaene & Changeux, 2011). During mind wandering, Smallwood et al. (2012) argue that the FPN might determine the contents of consciousness and serve as a common workspace for both internally focused trains of thoughts (associated with the DMN) and externally guided cognition (operated by the dorsal attention network; DAN). In this view, the FPN is a flexible network that contributes to switches between different modes of the brain: An internally directed, decoupled mode (DMN) and an externally focused mode during which activity in the DAN are increased. The dorsolateral prefrontal cortex (DLPFC) is a key region of the FPN and has been hypothesized to be essential in initiating and sustaining internal trains of thoughts, consequently leading to attenuated processing of external stimuli (perceptual decoupling; Smallwood et al., 2012). Based on this theory, it can be hypothesized that modulating the excitability of the DLPFC could affect the frequency and/or length of mind-wandering episodes. However, because the FPN is supposedly crucial both for the maintenance of an externally focused and an internally focused state, it is theoretically unclear whether mind wandering would be facilitated or inhibited using neuromodulation.

Recently, three interesting studies (Axelrod, Rees, Lavidor, & Bar, 2015; Kajimura, Kochiyama, Nakai, Abe, & Nomura, 2016; Kajimura & Nomura, 2015) investigated this question empirically using transcranial direct current stimulation (tDCS). This non-invasive brain stimulation technique is thought to be capable of inducing robust excitability changes in the stimulated neural tissue (Stagg & Nitsche, 2011) by modulating synaptic efficacy and inducing synaptic plasticity. Intriguingly, Axelrod et al. (2015) could show an increase in the propensity to mind wander (as measured by self-reports) during a sustained attention task when anodal tDCS was applied above the DLPFC relative to two control conditions, a sham (inactive) stimulation and stimulation of the occipital

cortex. This finding would seem to support the theory reviewed above. Higher excitability of the DLPFC (induced by anodal tDCS) in this framework could lead to a better ability of the FPN to suppress distracting perceptual stimuli and/or to maintain the ongoing train of internal thoughts. Furthermore, Kajimura and Nomura (2015) and Kajimura et al. (2016) investigated similar questions in a different experimental setup and found a pattern of results that is complementary in the sense that they observed reduced frequency of task-unrelated thoughts after applying cathodal tDCS above the left DLPFC relative to anodal stimulation. Together, these findings appear to provide evidence for Smallwood et al. (2012)'s theory and can be seen as a major advance in the understanding of the neural correlates of mind-wandering episodes.

The result that mind-wandering propensity can be influenced by tDCS has important implications both for basic neuroscience and in more applied settings. In the scientific literature, the finding has attracted the attention of several leading researchers (Broadway, Zedelius, Mooneyham, Mrazek, & Schooler, 2015; Fox & Christoff, 2015), with 51 independent citations so far. In their commentary on Axelrod et al. (2015), Fox and Christoff (2015) argue that changes in meta-awareness induced by the stimulation of DLPFC might be responsible for the observed changes. Similarly, Broadway et al. (2015) are enthusiastic about Axelrod et al. (2015)'s finding and argue that it "[…] marks a new era for research into mind wandering and previews some of the insights that continued methodological advances will likely make possible". We believe that such strong endorsements from leading researchers in the field are likely to result in a surge of research activity building on Axelrod et al. (2015)'s result. From a more applied perspective, mind wandering has been, for example, associated with accidents in car driving (He, Becic, Lee, & McCarley, 2011; Yanko & Spalek, 2014) and aviation (Wiegmann et al., 2005), and a technique that consistently and reliably allows to manipulate the propensity to mind-wander has thus great potential to avoid many of these human errors. Furthermore, ruminations, which may be seen as a special case of mind wandering, are core features of clinical conditions such as major depression or obsessive-compulsive disorder. Therefore, a technique to reliably influence such processes could open up exciting avenues towards better treatment alternatives.

However, all of these considerations rest on the validity and most importantly the replicability of the observed effects. Although the findings summarized above have great potential influence, the evidence so far is inconclusive because it is based on clearly underpowered studies. Concretely, the studies used a low sample size (about $N = 10–20$ per group) such that the results could very well be the result of random fluctuations. In addition, even though Axelrod et al. (2015) replicated their main result in a second experiment, Kajimura and Nomura (2015) and Kajimura et al. (2016) failed to replicate Axelrod et al. (2015)'s findings when using anodal stimulation of the DLPFC relative to a sham condition (though the effect was in the expected direction and the replication was not a direct one). Based on these arguments, we believe that a conclusive, high-powered replication of Axelrod et al. (2015)'s finding is essential for establishing a sound basis on which future researchers can advance the understanding and application of tDCS in the setting of mind wandering (or avoid spending unnecessary resources should the effect prove to be unstable).

Preregistered replications are considered to be the best way to establish a firm basis for the existence of an effect and they provide a rigorous way to avoid the problems underlying the low replicability rate in psychology (Chambers, Feredoes, Muthukumaraswamy, & Etchells, 2014; Nosek & Lakens, 2014; Simons, Holcombe, & Spellman, 2014). The need for rigorous replication may be further motivated by the recent meta-analytical findings in the field of tDCS. After an enthusiastic explosion of studies applying tDCS to affect many cognitive functions and psychiatric diseases, recent meta-analytic studies draw much more cautious conclusions (Horvath, Forte, & Carter, 2015a,b; Tremblay et al., 2014). In fact, Horvath et al. (2015a,b) question the very existence of any effect of tDCS on cognition. However, stimulation parameters and tasks are diverse and strong conclusions cannot be made at this point in time and Horvath et al. (2015a,b) conclude with an urgent call for more direct replications in the field of tDCS. Finally, a review focusing exclusively on stimulation of the DLPFC (the target region of Axelrod et al. (2015) found very variable effects and "[..] sometimes apparently conflicting results" (Tremblay et al., 2014). Clearly, direct, preregistered replications are necessary to be able to identify findings that are reliable in this important field.

Our project aimed to replicate the finding reported by Axelrod et al. (2015). For this purpose, we conducted a multicentre study (measuring in Tromsø Amsterdam, and Göttingen) using identical experimental setups following a preregistered protocol in order to pool an appropriately large sample size. We used Bayesian methods to estimate the effect size of anodal stimulation and to establish success or failure of the replication attempt (Verhagen & Wagenmakers, 2014).

2 | METHODS

All materials, simulations and analyses are available in a public repository hosted by the Open Science Framework (OSF) at https://osf.io/dct2r/. The repository was registered (frozen) before data collection such that none of the materials can be covertly changed after data have been collected. The link to the registered version of the project is https://osf.io/bv32d/.

2.1 | Participants

Participants were collected from the respective subject-recruitment facilities of three universities, the University of Tromsø (UiT), the University of Amsterdam (UvA) and the University of Göttingen (UniGö). Ethical approval for the study was granted at all three universities. Based on our design analysis (see below), we applied a sequential data collection protocol (Schönbrodt & Wagenmakers, 2018; Schönbrodt, Wagenmakers, Zehetleitner, & Perugini, 2017) and set out to collect between at least 120 and maximum 192 participants (a minimum of 20 and maximum of 32 participants per stimulation condition and study site). Subjects who failed to provide a complete dataset for technical (e.g., failure of the equipment) or other reasons (e.g., experiment not completed) were excluded from the analysis and replaced by new subjects. Specifically, in order to be included in the experiment, all of the following conditions needed to be satisfied for a participant:

- the participant did not have any neurological/psychiatric diseases (based on self-report)
- participants did not have previous experience with tDCS (to increase the efficacy of blinding)
- the participant was between 18 and 40 years old
- the participant completed the experimental session
- the stimulation equipment was functional across the complete session
- the data collected by the experimental computer was complete
- the participant complied with the instructions

After recruitment, participants were randomly allocated to either a sham or an anodal DLPFC stimulation condition according to a randomization list.

2.2 | Apparatus

As the experiment was conducted across three separate locations, we enforced similar conditions in the three laboratories by fixing specifications for the apparatus and environment (see https://osf.io/2xqz6/). These were set up in collaboration with the authors of the original study to be as close to the original experiment as possible. First, we required a quiet room free from distracting elements. No one besides experimenter and participant was allowed to enter the room during the study. In addition, optimal lighting conditions were ensured (avoid, e.g., frontal lighting that may be disturbing). Standard 19" flat-screen monitors were used in the study and the size of the stimuli was adjusted by the experimental program to ensure that the stimuli were presented in equal size on the retina. The experimental computer ran identical versions of PsychoPy (release 1.83.04; Peirce, 2007) and the experimental software and experimenters were encouraged to make sure that the computer did not run any unnecessary background processes. Finally, all participants wore earplugs to minimize the influence of environmental noise, which they inserted once they read the instructions and possibly asked questions.

We also provided comprehensive, standardized instructions for the experimenters (see https://osf.io/k3jt4/) for running the experiments. All experimenters were required to read the instructions and practice testing on at least two pilot subjects before acquiring real data. Experimenter interaction was kept at a minimum and instructions were delivered electronically to ensure a standardized procedure. There were, however, opportunities for the participant to receive clarification and ask questions (prompted by the experimental computer). A list of possible questions and standardized answers that were given by the experimenters is available at https://osf.io/fxgvh/.

The study used the Sustained Attention to Response Task (SART) which is a variant of the Go/Nogo task that is very commonly used in mind-wandering research (Smallwood & Schooler, 2006). In this task, numbers between 0 and 9 were presented in the centre of the screen in quick succession. The participant was required to respond to each stimulus by pressing a button (Go-trials) except when the target number "3" was displayed. In this case, the response was to be withheld completely (Nogo-trials). No feedback about the correctness of a response was given and the stimuli stayed on screen for a fixed period, irrespective of the users' response. In the context of mind-wandering studies, brief self-reports ("thought probes") were presented occasionally during the experiment. These probes consisted of a single question, "To what extent have you experienced task-unrelated thoughts prior to the thought probe?" and were answered on a scale from "1" (minimal) to "4" (maximal).

In accordance with Axelrod et al. (2015), stimuli were presented in black (RGB: [0,0,0]) on a grey background (RGB: [104,104,104]). The stimuli were presented in the centre of the screen and covered 3° of visual angle. The subject's distance to the monitor was fixed at 60 cm and the maximum length of the stimuli was readily determined to be 3.14 cm so as not to exceed 3°. Stimulus duration was set to 1 s and an inter-stimulus interval of 1.2 s was used. We provided scripts that tested the size of stimuli (https://osf.io/ax8qr/) and required the experimenters in each laboratory to run these scripts before data acquisition to ensure comparability.

Participants were required to put both hands on the space-key and respond to the stimuli by pressing it (using whatever hand they preferred). They were asked to balance their performance between response speed (Go-trials) and accuracy (omissions in Go- and false alarms in Nogo-trials). At regular intervals during the experiment, thought probes consisting of a question and a visual scale from 1 to 4 (see

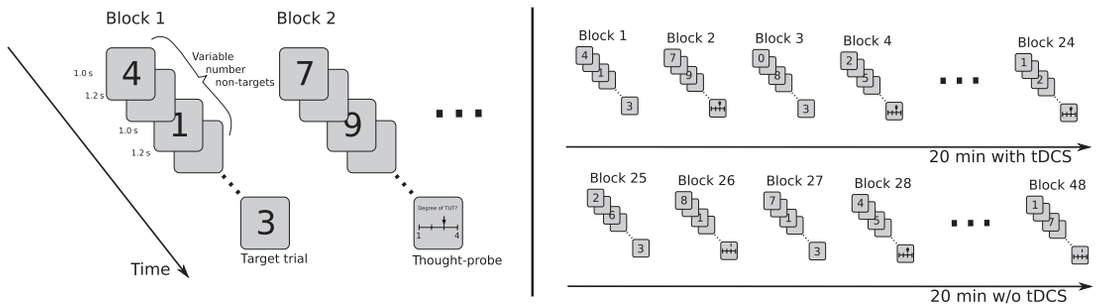

FIGURE 1 Sustained Attention to Response Task used in this study. The experiment consisted of two halves where tDCS stimulation was online in the first half and turned off in the second. Each half consisted of 24 blocks of trials ending in either a target or a thought probe. The number of non-target trials was variable in each block. For details, see text

Figure 1) were presented. When a thought probe appeared, participants were asked to press a number between 1 and 4 (on the keyboard) to indicate their level of task-unrelated thoughts. Self-report questions were presented for 6 s during which subjects could adjust their response (by pressing one of the keys corresponding to numbers 1–4). After each key press, an arrow appeared above the pressed number to indicate the currently chosen response. After 6 s, the screen was cleared if there was a response and the experiment continues. If no key was pressed for 6 s, the thought probe remained on screen until a key was pressed.

The total duration of the experiment was around 40 min. During the first 20 min, participants received tDCS; the second half of the experiment was without stimulation. The original study (Axelrod et al., 2015) used a marked underrepresentation of target stimuli. In their experiment, they presented a total of 24 targets while approximately 1,000 non-targets were presented. We used the same procedure and to ensure that both halves contain an equal number of trials of each type, the following trial randomization procedure was employed:

- the number of thought probes was fixed at 24, 12 per 20 min period
- the number of target trials (Nogo-trials) was fixed at 24, 12 per 20 min period
- given these constraints and a total duration of 40 min, 1,000 non-target trials were presented: 24 thought-probes × 6 s + 24 targets × (1.0 + 1.2 s) + 1,000 non-targets × (1.0 + 1.2 s) = 39 min, 57 s
- trial presentation was divided into 48 blocks (not known to the participants) of unequal length
  - each block consisted of a variable number of non-target trials (mean 20, *SD* 5.69, min 12, max 29)
  - non-target stimuli were independently drawn from the set {0, 1, 2, 4, 5, 6, 7, 8, 9} with equal probability
  - each block ended either in a target trial (stimulus "3") or a thought probe
  - target blocks and thought probe blocks were presented in a pseudorandom manner so that three blocks with target stimuli and three blocks with thought probes were appearing randomly in a set of six blocks ensuring that thought probes were not presented exclusively at the beginning/end of the experiment, typically associated with reduced/increased frequency of mind wandering respectively
- the number of non-targets across blocks was in addition constrained such that a total of 500 non-target trials were used across 24 blocks (such that the durations of the two halves of the experiment were identical)
  - this was achieved by repeatedly drawing 24 samples from a truncated normal distribution (truncated to lie between 12 and 29) until the sum of their rounded values equalled 500
  - this procedure was repeated for each half of the experiment

Before the start of the experiment proper, there was a short training session of four blocks containing two targets and two probes (84 trials in total).

A Python-script using the PsychoPy library (Peirce, 2007) implementing this procedure is available at https://osf.io/ctfjk/. Instructions were translated into Dutch, German and Norwegian by native speakers (complete instructions and the English template used to derive the local instructions can be found in https://osf.io/hrxg8/).

2.3 | Additional measures

After completing the experimental procedure, participants were required to complete three questionnaires: one measuring the mood of the participants, a state-mindfulness questionnaire and an own questionnaire referring to the content

of the mind-wandering episodes that the participants experienced. The analyses (e.g. correlations between questionnaire scores and thought probes responses or parameters of task performance) carried out on these additional measures were not preregistered and are reported as exploratory.

Similar to the study by Kajimura and Nomura (2015), the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was used for measuring the mood of our subjects. We used this scale, because of the link between prefrontal activity, task-unrelated thoughts and emotion regulation. First, there seems to be a bidirectional causal link between mind wandering and negative mood states (Killingsworth & Gilbert, 2010; Smallwood et al., 2009). Second, there is converging evidence that the DLPFC plays a critical role in the top–down control of emotion (Okon-Singer, Hendler, Pessoa, & Shackman, 2015), which is in accordance with the fact that symptom severity in major depression was quite consistently reduced by anodal tDCS applied over the left DLPFC (for reviews and controversies, see: Brunoni, Ferrucci, Fregni, Boggio, & Priori, 2012; Berlim, Van den Eynde, & Daskalakis, 2013; Shiozawa et al., 2014). Finally, two recent study results showed that tDCS applied over the DLPFC can influence the frequency of ruminative thoughts of negative emotional content in healthy volunteers (Kelley, Hortensius, & Harmon-Jones, 2013; Van-derhasselt, Brunoni, Loeys, Boggio, & De Raedt, 2013). In this regard, monitoring mood changes in studies investigating the effects of non-invasive brain stimulation on mind-wandering propensity seems to be inevitable.

The PANAS scale consists of 20 items (10–10 describing positive or negative emotional states), which are to be rated from 1 (very slightly or not at all) to 5 (extremely). Positive and negative mood scores are calculated separately, and these values are used to assess the current or past mood states of the participants. We hypothesized that increasing intensity of negative feelings during the experiment would be associated with an increase in mind-wandering propensity in the anodal tDCS condition. Therefore, we asked our subjects to complete the PANAS twice: first for measuring their current (post-SART) mood ("how do you feel right now") and second to retrospectively measure their baseline (pre-SART) mood ("how did you feel at the beginning of the experiment"). Given that the completion of the PANAS in itself might induce subtle mood changes, we decided not to use it before the main experiment in order to avoid interference with the replication attempt. The PANAS scale is available in the Dutch (Engelen, De Peuter, Victoir, Van Diest, & Van den Bergh, 2006), German (Janke & Glöckner-Rist, 2014) and Norwegian (Gullhaugen & Nøttestad, 2012) languages and the translated versions were used at each of the three locations.

We also asked the participants to complete the Mindful Attention and Awareness Scale (MAAS; Brown & Ryan, 2003), which is a 15-item scale designed to measure an individual's disposition to attend to the present experience and overcome disrupting stimuli or internal states. It has previously been shown that MAAS scores negatively correlate with both the frequency of self-reported mind-wandering and behavioural measures (e.g. response time variability, SART errors) of mind wandering (Mrazek, Smallwood, & Schooler, 2012). As low MAAS scores are considered to be indicative of an increased mind-wandering trait that is stable over time (Brown & Ryan, 2003), MAAS scores are expected to correlate with mind-wandering frequency in the sham tDCS condition only. Moreover, the absence of correlations between the MAAS and self-reported mind-wandering propensity in the anodal tDCS condition would indicate that the effect of tDCS is independent of trait-like inter-individual differences. The MAAS is available in Dutch (Schroevers, Nykliček, & Topman, 2008), German (Michalak, Heidenreich, Ströhle, & Nachtigall, 2008) and Norwegian (Verplanken, Friborg, Wang, Trafimow, & Woolf, 2007).

Finally, because periods of mind wandering are not uniform in nature and distraction from the task can be induced by disturbing external stimuli (Stawarczyk, Majerus, Maj, Van der Linden, & D'Argembeau, 2011) such as tDCS electrodes placed on the forehead, we also asked the participants to freely report the content of their mind wandering during the task. We also used four additional questions with 7-item Likert scales (1: not at all, 4: to a medium degree, 7: extremely) to estimate the degree to which participants were (a) thinking about task context (e.g., task difficulty, reflections on task performance, etc.), (b) distracted by tDCS (e.g., skin itching, tingling, skin wetness, etc.), (c) distracted by other stimuli (e.g., noises, visual stimuli, body sensations such as thirst or back pain) and (d) thinking about personal issues (e.g., past memories, future plans, etc.). Also, we asked the participants to guess whether they received real or sham stimulation using a 7-item Likert scale (1: sham, 4: don't know, 7: real). With these questions, we aimed to exclude the possibility that the effect of tDCS on mind-wandering propensity was in fact related to the unpleasant sensations caused by the stimulation or by the participants' expectations about stimulation-related effects (Turi et al., 2014). This questionnaire and a translation into the three local languages can be found at https://osf.io/d3mys/.

2.4 | Stimulation protocol

The stimulation protocol adhered to the one reported in Axelrod et al. (2015), with only minor modifications. All three laboratories used an identical model of the NeuroConn DC stimulator (https://osf.io/n4pbd/). To deliver the current, we used rubber electrodes (cathode: 7×5 cm; anode: 4×4 cm) with conductive paste (Ten20; Weaver and Company, USA). One of the electrodes was placed above position F3 (according to the

International 10–20 system used in electroencephalography, EEG), the other above the right supraorbital area. The position of the stimulation electrode positioned at F3 was measured by applying the adequately sized EEG cap (circumference 56, 58 or 60 cm) on the participant's head. The EEG cap was chosen based on measuring the circumference of each participant's head. After marking the F3 position, the EEG cap was removed and the centre of the stimulating electrode corresponded to the F3 position. In addition, the edges of both electrodes were precisely measured and marked which served as the landmark points for preparing the electrode–skin interface. The skin in the predefined surface regions was gently cleaned using alcohol and cotton swab without over-abrading the skin. A small amount of conductive paste was homogeneously distributed over the previously cleaned skin surface and the rubber electrode surface to ensure good contact between them. The electrodes were pressed firmly with medium pressure to the head in order to adhere the electrodes to the skin. To ensure that the conductive paste was distributed only over the predetermined regions, the extra conductive paste was wiped-off. Connector position was from anterior to posterior direction for the F3 electrode and from right supraorbital to right temporal lobe direction for the return electrode. Impedance values were kept below 10 kΩ; subjects exceeding this threshold were not included in the study.

In the anodal stimulation condition, participants received 20-min long continuous stimulation at 1.0 mA intensity with 30 s fade-in and 30 s fade-out periods, whereas the sham protocol applied the fade-in and fade-out periods and the minimum possible stimulation duration of 15 s. As the study uses double-blind design, the stimulators ran in study-mode where each stimulation protocol was arbitrarily linked to a letter and secured with a 5-digit code. The Neuroconn DC stimulator has certain hardware limitations that did not allow standard blinding using the 5-digit codes if the exact stimulation parameters described by Axelrod et al. (2015) were to be used. More specifically, the pseudostimulation mode accessible by the 5-digit codes produces a sham protocol with a stimulation duration of 40 s in addition to the fade-in and fade-out periods, which was not desirable. Therefore, part of the stimulator's display was covered with non-transparent tape to avoid the experimenter getting feedback about which condition was currently been run. Details about preparing and using the stimulator are available at https://osf.io/2xqz6/and https://osf.io/k3jt4/. The mapping between stimulator code and stimulation mode were only accessible to a single researcher from each laboratory that was also responsible for programming the device but not involved in data acquisition.

2.5 | Statistical methods

We used exclusively Bayesian statistics because of their many advantages compared to the more commonly used null hypothesis significance testing (NHST) approach (see e.g., Gelman et al., 2013; Kruschke, 2014). In addition, we report standard frequentist statistics for comparability with the original study.

All preregistered analyses discussed in the following were implemented as scripts in the R programming language (R Core Team, 2015) using the BayesFactor package (Morey & Rouder, 2015) and Stan (Carpenter et al., 2017) as the modelling backend and R-packages `rstan` (Stan Development Team, 2016) and `brms` (Bürkner, 2017) for interfacing Stan from R. The replication and meta-analytic Bayes factors were calculated using code provided by Verhagen and Wagenmakers (2014) on their webpage (http://www.josineverhagen.com/?page_id=76). A listing of the exact version of R and all packages used are provided in the file https://osf.io/ytjnh/as generated by script https://osf.io/3t36k/. The analysis scripts were developed using data generated by pilot subjects using the final experimental software. After the data were collected, these scripts were supposed to be executed without changes (only the pilot data files exchanged with the real ones) and the results reported. However, several minor adjustments to the analysis scripts were necessary because of coding errors and changes in the analysis packages used. All such changes are summarized in the Appendix and details are available in the form of difference files in our OSF repository. Both the raw data and all output of the analysis scripts were stored and uploaded to OSF and the quantities described in the following sections reported in the results section of this paper.

2.5.1 | Effect of anodal stimulation on self-reported mind wandering

The main result of this study concerns the comparison of the groups receiving sham and anodal stimulation of the left prefrontal cortex in terms of their mean self-reported thought probe scores. The original study (Axelrod et al., 2015) found that propensity to mind-wander (as measured by the mean of a subjects' responses to all thought probes presented during the experiment) was increased for subjects receiving anodal stimulation. We tested this prediction using a directed Jeffreys–Zellner–Siow (JZS) Bayes Factor (Rouder, Speckman, Sun, Morey, & Iverson, 2009) that tests the hypotheses that (a) the effect is in the expected (positive) direction against the hypothesis that (b) the effect is either zero or in the unexpected (negative) direction. We supplemented the analysis with BFs quantifying the evidence in support of the hypothesis that the effect is positive or negative compared to exactly zero and an interval estimate for the effect size.

In particular, we first calculated a directional Bayes Factor, BF_{+-}, testing the hypothesis that the result of subtracting the mean thought probe responses of the anodal group from that of the sham group is larger than zero against the hypothesis that it is less or equal to zero (Morey

& Rouder, 2015). We used a prior with an *r*-scale parameter of $\sqrt{2}/2 = 0.707$ that assumes that effect sizes are distributed according to a Cauchy distribution with scale 0.707. This choice of prior was motivated by the fact that observed effect sizes in tDCS studies are mostly small or medium (e.g., the absolute value of effect sizes for cognitive effects of DLPFC stimulation reported by Horvath et al. (2015a,b) were on average 0.4). In case this BF is larger than 1, we found evidence for a positive effect of anodal stimulation. Values smaller than 1 quantify evidence for a negative effect. In case the real underlying effect size is zero, the BF_{+-} is likely to be inconclusive because there is similar amount of evidence for a positive or a negative effect respectively.

Therefore, to better evaluate evidence for zero effect of stimulation, we calculated two BFs testing the hypotheses that the effect is zero, against the existence of a positive (BF_{0+}) or negative effect (BF_{0-}). We used the same prior distribution as before. BFs larger than one quantify evidence for the hypothesis that the effect is zero while a BF lower than one indicates evidence for a positive (BF_{0+}) or negative effect (BF_{0-}). Thus, while the previous BF_{+-} directly tests the hypothesis predicted by the original study, this BF tests for the absence of any effect.

In addition, we used a final, undirected model (comparing any effect against a null-effect) to extract an estimate for the posterior distribution of effect sizes which we quantified by its mean and highest density interval (HDI). This estimate produced a range of values that contains the real effect size with 95% probability given that the model is correct and assigns probabilities to each of those values. Therefore, we can exclude values falling outside of the 95% HDI with high probability.

The four measures described so far are quantifying slightly different aspects of the data but are, of course, not independent. If the directional BF_{+-} is large, we expect the posterior HDI to be mostly or completely positive, the BF_{0+} to be well below one and BF_{0-} to be inconclusive. Conversely, in case of high BFs in favour of the null hypothesis, we expect a lower BF in favour of a positive effect and a posterior distribution (HDI) that includes zero.

In addition to these analysis, we calculated the replication Bayes Factor developed in Verhagen and Wagenmakers (2014). This Bayes Factor, $BF_{replication}$, pitches two competing theories against one another: a theory that a proponent of the original study might hold (i.e., that the replication effect size will be in line with the distribution of effect sizes implied by the original study) and a skeptic's null hypothesis that the effect size does only deviate randomly from zero. The advantage of this BF is that it directly tests the question whether or not the results of the original study have been replicated or are more likely the result of random fluctuations. However, the test is likely to be inconclusive when the effect size observed in the replication is much lower than that from the original study (which is often likely, given the "significance filter" ensuring that published effect sizes that are based on low sample size are large; Gelman & Carlin, 2014). This is in line with the finding that underpowered studies might be unfalsifiable per se (Morey and Lakens, 2016). For this reason, we calculated this $BF_{replication}$ only as a secondary measure of replication success as it was likely to be inconclusive. Only when the difference between the original effect size and the obtained one is large enough compared to that between zero and the replication effect size, the replication BF favours the null hypothesis instead of the presence of an effect.

Finally, we were interested in the total amount of evidence for the presence of an effect when pooling both the original study and the replication attempt (because the two studies are very similar, data can be assumed to be exchangeable). For this purpose, the fixed-effect meta-analytic Bayes factor BF_{meta} (Rouder & Morey, 2012) has been developed which merges the original and the new data. The original study showed strong support for the presence of an effect, possibly because of the significance filter that ensures large effect sizes of significant findings (Gelman & Carlin, 2014). Therefore, we expected the BF_{meta} to be biased in favour of a positive effect (Nuijten, van Assen, Veldkamp, & Wicherts, 2015) and the results from the BF_{meta} received less weight when drawing conclusions from our analyses.

The script for the analyses described here is available at https://osf.io/r75ze/.

2.5.2 | Design analysis

The previous section described our main analyses that determine success or failure of this replication attempt. Based on these primary analyses, we conducted a design analysis based on simulations to find a sampling plan that would allow to find conclusive evidence for these measures.

In order to determine an appropriate sample size that allows to find an effect with high probability, we are required to specify a realistic effect size estimate. It is a well-known fact that published effect sizes that are based on small sample sizes and the criterion of statistical significance are inflated because of the "significance filter" (Gelman & Carlin, 2014): For an effect to become significant at low sample sizes, the effect must be large. We therefore thought it likely that the very strong effect of $d = 1.59$ reported by Axelrod et al. (2015) was an overestimate and that the real effect size would be much lower. We note here, that the effect size reported in Axelrod et al. (2015) used a non-standard estimate of the pooled variance that accounts for differences in means and therefore results in the lower (though still huge) estimate of $d = 1.24$ that was reported in their study. In the field of tDCS, observed effect sizes are usually of small or medium size. The absolute value of effect sizes for cognitive effects of

DLPFC stimulation reported by Horvath et al. (2015b) were on average 0.4 ($SD = 0.59$; median = 0.29, meta-analytic mean = 0.31, $SD = 0.41$) and a recent preregistered tDCS study (which does not suffer from the significance filter) found an effect size of $d = 0.45$ (Minarik et al., 2016).

We therefore designed our study to be able to detect effects in this range with appropriate probability and report a design analysis for a wide range of effect sizes. It has recently been proposed that underpowered studies are unfalsifiable (Morey & Lakens, 2016). These authors convincingly argue that even large discrepancies between an original, underpowered study and a (direct) replication study cannot be detected with high probability even if the replication study has infinite sample size. Accordingly, we choose to base our power calculations not on the goal to replicate (or not-replicate) the original study but rather focus on estimating the real effect and of excluding the possibility of a zero effect while also analysing the expected distributions of the BFs.

Following Kruschke (2014), we ran a Bayesian power analysis where our primary goal was to exclude the null hypothesis of an effect size of $d = 0$ from the posterior 95% highest-density interval in the positive direction. Practical reasons did not allow us to exceed a sample size of $N = 192$, such that each laboratory committed to collecting a maximum of $N = 64$ subjects (32 per condition). In addition, we did not want to collect more data than necessary for ethical reasons. Therefore, we chose to apply a sequential design with a specified maximum sample size of $N = 192$ (Schönbrodt & Wagenmakers, 2018; Schönbrodt et al., 2017). In order to avoid spurious rejections of the existence of an effect, we chose to first collect a minimum sample size of $N = 120$ (20 per lab and condition). If the 95% posterior highest density interval (HDI) did not exclude zero at this point, we continued sampling until a maximum of $N = 192$ had been reached. Once the initial 120 subjects were collected, we stopped after each batch of 18 subjects (3 per lab and condition) and evaluated whether the lower bound of the 95% HDI was larger than zero. If that would have been the case, we would have stopped data collection; otherwise we would continue until the designated maximum (this was the case in our study, see Results). Note that this was a directional stopping rule: We would only stop collecting data in case the HDI was fully positive. If it would have been fully negative, we would have continued sampling up to the full sample-size. The reason for

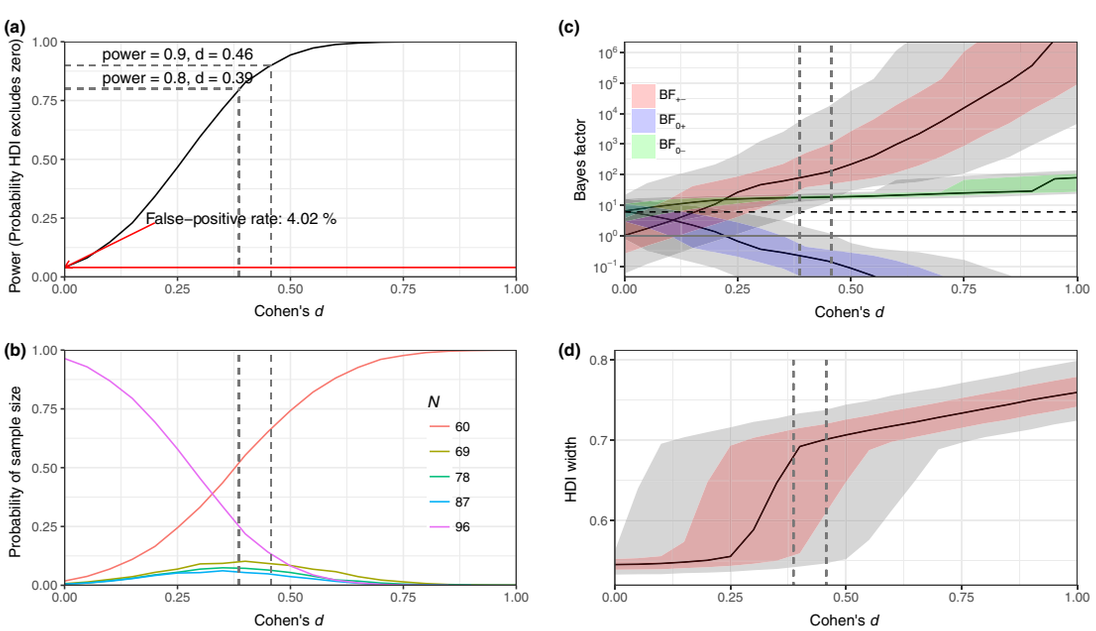

FIGURE 2 Design analysis for a sequential design with a maximum N of 192, an initial N of 120 and optional stopping after batches of 18 subjects in case the 95% HDI excluded zero. (a) Probability that the HDI excludes zero as a function of the real underlying effect size. Dashed lines show the effect size for which our sampling plan has 80% and 90% power respectively. (b) Probability to collect samples of different sizes as a function of real effect size. In case of a low real effect size, collection of the full sample of $N = 96$ per group is highly likely while only the minimal $N = 60$ per group will likely be collected if the effect size is large. (c) Distribution of BFs (both BF_{+-} and BF_{01}) we are likely to find given the underlying effect size. Horizontal dashed line indicates BF = 6. (d) The expected width of the posterior HDI given the underlying effect size. As needed sample size decreases with increasing effect size, the width of the HDI increases as well. Coloured and grey ribbons show 80% and 95% HDI for the respective parameter.

this asymmetry was that a negative effect would have been surprising (given that we expected a positive effect) and we would have wanted to collect as much evidence for that as possible. The final posterior HDI was not biased in either direction, though.

In Figure 2, we provide a simulation-based analysis of this design. The simulation underlying this analysis proceeded as follows:

1. Pick an effect size estimate d (we ran this simulation for effect sizes ranging between 0 and 1 in steps of 0.05)
2. For each d, run $n_{rep} = 10,000$ simulations as follows:
   - generate a random data set with an effect size of d
   - following the sampling plan described above, calculate
     (a) the posterior HDI from the (undirected) Bayesian t-test described by Rouder et al. (2009) and implemented in Morey and Rouder (2015)
     (b) the Bayes Factors discussed above, BF_{+-}, BF_{0+} and BF_{0-} and return the first N for which the lower bound of the HDI is above zero (or N_{max} if this did not happen), the associated BFs, the associated width of the HDI and whether or not the HDI excluded zero
3. Summarize/visualize the results for each effect size estimate

The code for running this analysis and to produce Figure 2 is available at https://osf.io/srwe6/.

Given this sampling plan, the probability of obtaining a false positive, concluding that the HDI excludes zero even if $d = 0$, is 4.02%. The probability to find a conclusive HDI that excludes zero (power) is a function of the underlying real effect size (Figure 2a). For realistic estimates of the effect size around $d = 0.4$, we have a power between 0.8 ($d = 0.39$) and 0.9 ($d = 0.46$). We could also determine the expected size of our sample (Figure 2b): With a real effect size of 0.4, we had a probability to stop after the initial sample of $N = 60$ per group of 0.54 and the probability to go to the maximum was 0.18. This illustrates the efficiency of this sampling plan as we had a good chance of being able to stop data collection at an earlier stage. Figures 2 c and d show the distribution of the expected BF_{+-}, BF_{0+}, BF_{0-} and the expected width of the posterior HDI. At $d = 0.4$, the expected directional BF is around 86 and the expected width of the HDI around 0.7 (see Table 1). In case of a zero underlying effect size, the design is less efficient: the BFs in favour of the null hypothesis were only expected to be of moderate size (around 6).

The analyses described so far used a Cauchy distribution with scale parameter $r = \sqrt{2}/2$ as the prior distribution on the effect size. The expected results for both the HDI and the BFs are not sensitive to the choice of this prior parameter. We reran the simulation described above for two other common choices of the scale-parameter, $r = 1$ and $r = \sqrt{2}$ and the effect on the outcome variables was minimal. This is due to the rather large sample even with the lowest possible sample size allowed by our sampling plan because the likelihood eventually overwhelms any reasonable choice of prior.

2.5.3 | Hierarchical ordered probit model

In addition to the aforementioned analysis, we analysed the data using a novel analysis method that has not been used previously to analyse thought probe data. We used a hierarchical Bayesian model developed for analysing rank-ordered data. In the previous analyses and in most if not all of the literature, mind-wandering thought probes are first averaged within-subject before this average is submitted to the final between-subject analysis. This kind of analysis is problematic

TABLE 1 Summary of the sampling plan in case of two hypothetical scenarios: The null hypothesis is true ($d = 0$, left) and the real effect has an effect size of $d = 0.4$ (right). If the null hypothesis is correct, the directional BF, BF_{+-}, will be inconclusive as there is about the same amount of evidence for the effect being negative or positive, while both BF_{0+} and BF_{0-} are likely to be of moderate size. In the case of a small-to-medium effect size of $d = 0.4$, the BF_{+-} results in compelling evidence while the BF_{0+} is less compelling (median $1/BF_{0+}$ only moderately in support of positive effect). The BF_{0-} shows compelling evidence for the null and is not easy to interpret when the real underlying effect is positive as it only compares evidence for negative and zero effect sizes. The expected width of the HDI is about 0.55 in case of $d = 0$ but only 0.69 for the case of $d = 0.4$. This effect exists because sample size is maximal when $d = 0$

	$d = 0$			$d = 0.4$		
	Median	***P*(BF > 6)**	**Quantiles**	**Median**	***P*(BF > 6)**	**Quantiles**
BF_{+-}	1.02	0.13	[0.06, 21.4]	86.2	0.96	[6.97, 7473.6]
BF_{0+}	6.3	0.52	[0.78, 16.11]	0.20	0.003	[0.003, 1.88]
$1/BF_{0+}$	0.16	0.01	[0.06, 1.28]	4.89	0.44	[0.53, 310.5]
BF_{0-}	6.45	0.53	[0.93, 16.0]	17.9	0.99	[13.11, 24.1]
$1/BF_{0-}$	0.16	0.006	[0.06, 1.07]	0.06	0	[0.04, 0.08]
HDI width	0.55		[0.53, 0.56]	0.69		[0.54, 0.73]
P(HDI > 0)	0.043			0.81		

TABLE 2 Model selection criteria for models of increasing complexity. The hierarchical ordered probit-model including a time-on-task covariate is the most appropriate of the models. weights = posterior probability that each model has the best expected out-of-sample predictive accuracy; LOOIC = leave-one-out cross-validation criterion. The model with the lowest LOOIC is preferred

Model	Description	LOOIC (SE)	Weight
1	Metric	1116.8 (17.7)	0.0
2	Ordered probit	1048.6 (6.3)	0.0
3	Hierarchical metric	992.8 (22.6)	0.0
4	Hierarchical ordered probit	929.1 (18.3)	0.0
5	Hierarchical ordered probit + time-on-task	904.2 (20.2)	1.0

in at least three ways: first, it constitutes a "waste" of data because information about within-subject variability in responses to thought probes is lost. Second, treating thought probe responses as a metric variable is problematic because assumptions underlying the employed methods are likely not to be met. Finally, interesting and known effects on responding are ignored. Most prominently, an effect that is visible in all mind-wandering studies we have seen so far, is the time-on-task effect that is well-known to affect how likely subjects are to respond positively to mind-wandering probes (Thomson, Seli, Besner, & Smilek, 2014).

These points can be improved upon by using an appropriate model. The first point, modelling within- and between-subject variability, can be accounted for by a hierarchical modelling approach where subject-level parameters are separately estimated while constraining these estimates by a group-level distribution. The second point (treating ordered variables as metric) can be improved upon by using an ordered probit model. A Bayesian implementation of such a model is described in Kruschke (2014; Ch. 23). Basically, the assumption of an underlying metric (normal) variable is made which is thresholded by the participant into discrete response bins. In this setting, both the threshold and the parameters of the underlying distribution are estimated separately. Finally, covariates (e.g., time-on-task) can be easily integrated using this method.

To justify the need for these advanced analysis methods, we compared models of different complexity on a thought probe data set. As we did not have access to Axelrod et al. (2015)'s original data, we used data from an unpublished study collected in our laboratory. In this study, we also used the SART paradigm (though using slightly different parameters, such as number of trials and targets). We also employed the same 4-point scale as used in the current study and 20 thought probes spread out across the experiment were collected from each of 19 participants. A detailed description of this study can be found in https://osf.io/mf6ts/. We believe that this data, while not identical to the current study, could give an indication of the magnitude of within- or between-subject variation in responding to thought probes.

In the preparation of the analysis, we analysed these data using a range of models of increasing complexity (code for fitting and diagnosing these models is available at https://osf.io/3zga2/). We compare the models based on their predictive performance using leave-one-out cross-validation (LOOIC) and Watanabes information criterion (WAIC) implemented in the `loo` package (Vehtari, Gelman, & Gabry, 2015) which are the state-of-the-art model-selection criteria for hierarchical Bayesian models (Gelman, Hwang, & Vehtari, 2014). These criteria are reported on the deviance scale and differences in about 10 units are considered strong (Spiegelhalter, Best, Carlin, & Van Der Linde, 2002). In general, LOOIC is the preferred criterion, while WAIC can be a viable and computationally easier approximation to LOOIC (Gelman et al., 2014) when calculation of the LOOIC is not possible. For all reported models, LOOIC and WAIC produced identical results and we therefore only report the former.

The first model uses a basic analysis strategy as a baseline, treating MW probes as metric and interchangeable across trials and subjects. Next, we implemented an ordered-probit model where individual responses were treated independently. The comparison of these two models determined whether treating the data as metric was justified. The third and fourth models implement a hierarchical version of the first two models, where subject-level means are constrained by a group-level distribution. Comparing these two models to the first two can help to determine whether the explicit modelling of within- and between-subject variation is necessary. Finally, we added time-on-task as a covariate to the hierarchical ordered probit model. Table 2 lists the LOOIC criterion (standard error in parentheses) for each of the models. It is clear that the ordered probit model more appropriately models the data than a model treating the data as metric both in the basic ($\triangle$LOOIC = 34.1, SE = 6.0) and the hierarchical case ($\triangle$LOOIC = 31.9, SE = 5.9). Finally, adding the covariate time-on-task strongly improves predictive accuracy, $\triangle$LOOIC = 12.5, SE = 5.0.

Based on these considerations, we chose the hierarchical ordered probit model that included a time-on-task covariate as the final analysis model. The model is mathematically fully specified in Appendix 1, including choice of the prior distribution, and implemented in the R-script https://osf.io/r3w32/. We report and interpret all coefficients in terms of posterior mean and HDI.

2.5.4 | Effect of location (lab)

Despite the uniform study design applied at all locations (UiT, UvA, UniGö), unknown contextual factors might cause

TABLE 3 Demographics across the three laboratories

Lab	Proportion male	Mean/*SD* Age	Min/Max Age
AMS	10/64	20.66 (2.35)	[18, 31]
GOE	28/64	23.30 (2.66)	[18, 34]
TRM	20/64	22.75 (3.77)	[19, 35]
All	58/192	22.2 (3.19)	[18, 35]

substantial variability in effect sizes between the three laboratories. Therefore, we compared the tDCS effects resulting from the data from all three laboratories independently by calculating independent estimates per laboratory for the full hierarchical ordered probit model presented in the previous section. These estimates in terms of posterior mean and HDI are presented side by side for comparing the variability in the different variables across laboratories. We also augmented the model with covariates for study location (UiT, UvA, UniGö). Comparing the posterior means for the location coefficients and their HDI as well as a model comparison analysis of the augmented versus the non-augmented model enabled us to rule out or quantify location-specific effects. For details see Appendix 1. The script implementing these analyses is available at https://osf.io/xkkdk/.

2.5.5 | Frequentist analyses

For comparability with the previous literature, we also conducted standard two-sample *t*-tests on mean thought probe responses for sham versus anodal stimulation (both directed and undirected). We also report standardized effect sizes (Cohen's *d*) for these effects. These analyses are only conducted because they correspond directly to the analytical strategy chosen by the authors of the original study (Axelrod et al., 2015). Unfortunately, our sequential sampling scheme prevents us from calculating these statistics for the final sample as the stopping rule invalidates the *p*-values. We, therefore, use only the guaranteed initial sample size of $N = 60$ per group for this analysis. The script implementing these analyses is available at https://osf.io/v6fka/.

2.5.6 | Exploratory analyses

To further assess whether mind wandering or other task-related measures were influenced by tDCS, we conducted five Bayesian repeated-measures analyses of variance (ANOVA) tests along with their frequentist equivalents with time (two levels: first vs. second parts of the task, associated with online vs. offline effects, respectively) as within-subject and stimulation (two levels: anodal vs. sham tDCS) as between-subject factors. This analysis design is identical to that used by the original study (Axelrod et al., 2015), which focused on three measures of interest, each entered as the dependent variable in separate ANOVAs: thought probe ratings, mean reaction times for Go stimuli (GoRT) and mean error rates for Nogo stimuli (commission errors). We extended this analysis with two additional parameters: reaction time coefficients of variation (RTCV) and error rates for Go stimuli (omission errors). RTCV was quantified as dividing the standard deviation by mean RT scores, calculated for both parts of the task and for each participant separately. Both RTCV and omission errors were proposed to index lapses of attention during the SART, and therefore, are regarded as behavioural indices of mind wandering (Cheyne, Solman, Carriere, & Smilek, 2009). All analyses within this section were done using JASP 0.9 (JASP Team, 2018). Bayesian tests were run with default prior scales of JASP (r scale fixed effects: 0.5). Interaction terms were assessed by comparing models including the effect to equivalent models without the effect ($BF_{inclusion}$). Based on the recommendation by Jeffreys (1961), we report results with BF values providing moderate evidence for either the alternative ($BF > 3$) or null hypothesis ($BF < 0.33$). Depending on the type of variable (continuous vs. ordinal), correlations between behavioural measures were assessed by calculating either Pearson's or Kendall's correlation coefficients. To demonstrate effect size for frequentist ANOVAs, we report partial η^2 values. Given the exploratory nature of correlation analyses performed herein, the reported *p*-values are not corrected for multiple comparisons and findings should be treated with caution.

3 | RESULTS

3.1 | Demographics

Our sample consisted predominantly of females (70%, 134/192) who were young adults ($M = 22.2$ years, $SD = 3.19$ years, range 18–35 years). There were no strong differences in these characteristics between laboratories, see Table 3. During data acquisition, three subjects in Tromsø had to be excluded due to missing electrode contact after the first half of the experiment (two subjects) and a technical malfunction of the electrode cables (one subject). In Amsterdam, two subjects had to be excluded, one because of an interruption of the experimental session and one that turned out not to fulfil the inclusion criteria after the session. No subjects were excluded in Göttingen.

3.2 | Preregistered analyses

In agreement with our sequential-sampling plan, we tested several times during data acquisition whether our stopping criterion was fulfilled. This criterion was that the 95% HDI of the posterior effect size estimate would exclude zero in the positive direction. This did not turn out to be the case, and therefore, the maximum sample size was collected resulting

in $N = 64$ subjects per laboratory and a total of 192 participants. In summary, the mean posterior effect size was consistently estimated to be slightly negative and the HDIs all included zero, see Table 4 and Figure 3.

3.2.1 | Effect of anodal stimulation on self-reported mind wandering

With our final sample size, the effect size estimated according to our preregistered analysis plan was $d = -0.11$, HDI = [−0.38,0.17]. Negative effect sizes indicate that subjects in the anodal stimulation condition were less likely to respond off-task on the thought probes than subjects in the sham stimulation condition. Accordingly, the directional Bayes Factor, BF_{+-}, which compared the hypotheses that the effect was positive to the hypothesis that it was zero or negative was in support of negative effect sizes ($BF_{+-} = 0.29$) but only slightly so. According to this test, it is about 3.4 times as likely that the effect size was zero or negative when compared to a strictly positive effect. We also prespecified several BFs that would test the null hypothesis of a zero effect against several alternatives (against a positive, BF_{0+}, a negative, BF_{0-}, or any effect, BF_{01} respectively). All of these Bayes Factors

TABLE 4 Results at the preregistered stopping points. The criterion for stopping the data collection was that the 95% HDI around the effect size would exclude zero in the positive direction. The effect size was consistently negative and all HDIs included zero, and therefore, the complete sample was collected

N	Cohen's *d*	BF_{0+}	BF_{0-}	BF_{01}	BF_{+-}	$BF_{replication}$	BF_{meta}
120	−0.09 [−0.44, 0.24]	7.46	3.21	4.48	0.43	0.002	0.34
138	−0.06 [−0.38, 0.25]	7.27	3.91	5.08	0.54	0.003	0.28
156	−0.05 [−0.35, 0.25]	7.30	4.44	5.52	0.61	0.003	0.25
174	−0.07 [−0.36, 0.22]	8.65	3.93	5.41	0.45	0.003	0.32
192	−0.11 [−0.38, 0.17]	10.65	3.09	4.79	0.29	0.002	0.48

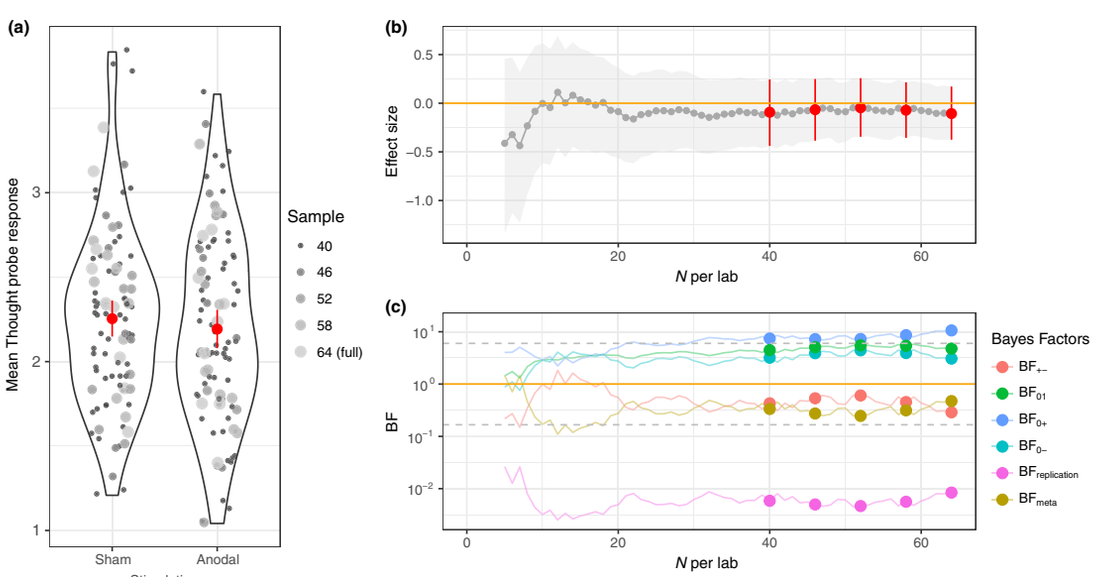

FIGURE 3 Results of the sequential sampling plan. Target statistics for increasing sample size (per lab) are plotted. Dots represent the preregistered time points at which data collection could have been stopped in case that the HDI would have excluded zero in the positive direction. (a) Scatter plot of individual subjects' mean thought probe responses together with a density estimate and mean and confidence interval (red). (b) Effect size and 95% HDI for the effect of anodal stimulation on mean thought probes. All HDIs included zero at all times. The final mean effect size was in the opposite direction than hypothesized. (c) Bayes factors quantifying evidence in support of various hypotheses (see text for details)

were in support of the null hypothesis with varying degrees of strength. When comparing the null hypothesis to the a priori hypothesized positive effect, the null hypothesis was about 10.65 times more likely to be true, $BF_{0+} = 10.65$. When comparing the null hypothesis to any non-zero effect size, the null hypothesis was less strongly supported, $BF_{01} = 4.79$ and even when comparing the null against a negative effect size (that was unlikely a priori but seems more plausible given the observed negative effect size), the null was slightly favoured, $BF_{0-} = 3.09$.

Finally, we also calculated the replication Bayes Factors, $BF_{replication}$, and the meta-analytic BF, BF_{meta} (Verhagen & Wagenmakers, 2014). The replication BF tests the hypothesis that the observed data from our replication study is consistent with the originally reported effect size against the alternative that it is not. We found strong support for the alternative ($BF_{replication} = 0.002$) indicating that it is about 500 times as likely that the effect was not consistent with the originally reported effect size, that is, that the effect did not replicate. The meta-analytic BF was calculated to judge overall support for the presence of any effect of anodal stimulation on thought probes when pooling both the original and the replication study. Also, this BF supported the null hypothesis but only weakly so ($BF_{meta} = 0.48$) which was expected given that the original study reported a huge, and most likely overestimated, effect size ($d_{original} = 1.24$) which would bias the result of the meta-analytic BF in favour of a positive effect.

3.2.2 | Hierarchical ordered probit model

The preregistered hierarchical ordered probit model was fit to the final data set. The posterior mean and HDIs are reported in Table 5. We ran 12 parallel chains for 2,000 iterations each, treating the first 1,000 samples as warmup resulting in a final of 12,000 independent samples from the posterior distribution. We used that many samples in order to properly estimate the tails of the distribution which were needed for accurately reporting the 95% HDI. The Gelman–Rubin diagnostic (Gelman & Rubin, 1992) was calculated to ensure that all reported results had an $\hat{R} \leq 1.05$. We also visually inspected the traceplots for all variables and no anomalies were spotted.

TABLE 5 Results of fitting the hierarchical ordered probit model. As expected, there is a positive effect of trial number (time on task). However, contrary to our hypothesis, the coefficient coding for the effect of anodal stimulation is negative (with the HDI including zero)

Variable	Coefficient (Mean and 95% HDI)
Intercept (μ_g)	2.25 [2.14, 2.35]
Trial (β_1)	0.20 [0.18, 0.23]
Stimulation (β_{anodal})	−0.09 [−0.24, 0.07]
Threshold (θ_2)	2.53 [2.51, 2.56]
Probe-level variance (σ)	0.78 [0.76, 0.80]
Group-level variance (σ_g)	0.62 [0.57, 0.68]

In order to show the appropriateness of the model, we conducted posterior predictive checks (Gelman, Meng, & Stern, 1996). We generated $n_{rep} = 100$ complete data sets by drawing coefficients randomly from the posterior distribution and simulating data sets according to the model specification. The distribution of summary statistics from these posterior simulations can be compared to the actually observed data to evaluate model fit. Figure 4 shows the result of these checks. Model fit is excellent on the group-level, but not all individual differences are picked up by this model.

The results of this analysis show a clear positive effect of time-on-task as previously reported, $\beta_1 = 0.20[0.18,0.23]$, indicating that subjects were more likely to report being off-task

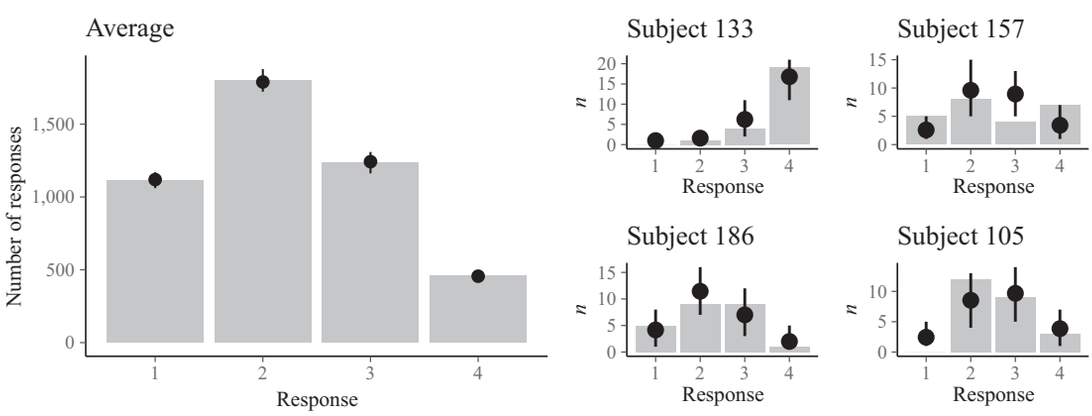

FIGURE 4 Posterior predictive distribution of average responses to thought probes (left) and for four randomly selected subjects (right). Grey bars represent data, black dots and error bars represent mean and 95% HDI for simulated data

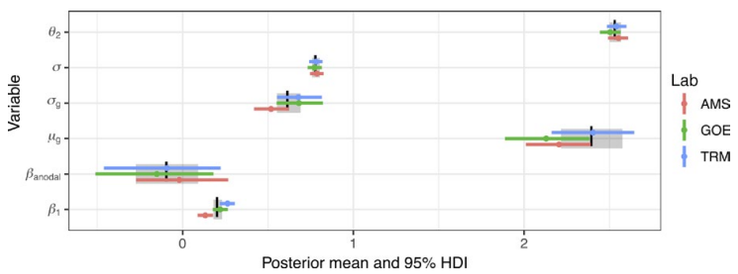

FIGURE 5 Coefficient estimates independently for each laboratory and from a combined model. Coloured lines are estimates from individual laboratory data and the black line and grey area correspond to posterior mean and 95% HDI from the combined model

later in the experiment (about 0.67 units on the 4-point Likert scale comparing the end to the beginning of the experiment). The results also show that anodal stimulation did not appear to increase the likelihood to answer off-task on the thought probes, $\beta_{\text{anodal}} = -0.09[-0.24, 0.07]$. While the mean coefficient estimate is negative, its 95% HDI includes zero and therefore does not provide evidence against the null hypothesis.

3.2.3 | Effect of location (lab)

In order to test whether the laboratory in which each of the three subsets of data was collected would have an impact on the estimation of the effects, we preregistered to fit the model from the previous section separately to the data from the three locations. In addition, we estimated a preregistered extended model where laboratory was entered as a covariate (see Appendix for details). The same model-fitting and -checking procedure as detailed above was used to ensure that the model-fits were reliable.

Results for these analyses are presented in Figure 5. The estimates of the relevant coefficients are in good agreement between laboratories. Coefficients are estimated to be of a similar magnitude and the HDIs of the separately estimated coefficients overlap in almost all cases. The combined model, treating laboratory as a fixed-effect covariate seems to provide a good compromise between the independent estimates. The only exception is the coefficient for the time-on-task effect, β_1. The HDIs estimated for the Amsterdam sample $\beta_1 = 0.13[0.088, 0.18]$ does not overlap with those from the Tromsø $\beta_1 = 0.26[0.22, 0.31]$ or the Göttingen $\beta_1 = 0.22$, [0.18, 0.27] samples. This finding indicates that participants in the AMS laboratory showed a lesser time-on-task effect on thought probes than those in GOE or TRM.

We hesitate to provide an interpretation of this finding as it is quite possibly a spurious result: Analysing the result from Figure 5 involves 18 comparisons. Therefore, using 95% HDIs and decision by non-overlap of these intervals, we would already expect to see one or two positive results due to chance alone (given that the models were fit on independent datasets).

We also preregistered a model comparison between the ordinal probit-regression model with and without the laboratory covariate based on the LOOIC and the WAIC. This analysis can provide evidence for or against the suitability of including laboratory as a covariate in the model, that is, whether a considerable amount of the variation in the data is being explained by this factor or not. The model that does not have any information about which laboratory the data were collected in resulted in a LOOIC of 10,093.2 ($SE = 83.1$) and a WAIC of 10,091.8 ($SE = 83.0$) while the extended model had a LOOIC of 10,092.7 ($SE = 83.1$) and a WAIC of 10,091.6 ($SE = 83.0$). These are virtually identical ($\triangle$LOOIC $= -0.3$, $SE = 0.8$; $\triangle$WAIC $= -0.1$, $SE = 0.8$), and therefore, these criteria do not prefer any of the two models.

Even though the extended model did not provide a better model fit, we can check the regression coefficients corresponding to the different laboratories. Analysing the extended model further, these coefficients were estimated as $\beta_{\text{AMS}} = -0.17$, $[-0.35, 0.02]$ and $\beta_{\text{GOE}} = -0.29$, $[-0.47, -0.10]$. According to this model, participants at the University of Göttingen were therefore less likely to respond to be off-task when compared to participants in Tromsø. As before when investigating the data from the laboratories separately, participants from Amsterdam were slightly less likely to respond with off-task than participants from Tromsø but slightly more likely to response off-task than subjects from Göttingen (though these HDIs did overlap).

We did not expect a priori to find any differences between the estimates from the three different laboratories. Since there were some indications of possible differences in the data, we chose to run several exploratory analyses to investigate possible reasons for this finding (see Section 3).

3.2.4 | Frequentist analyses

In accordance with our preregistered analysis plan, we performed independent *t*-tests on individually calculated mean

thought probe scores. Note that only the initial sample of $N = 120$ is used in these tests as the stopping rule would invalidate p-values calculated for the complete sample since these would have to be corrected for the intermediate looks at the data. The two-tailed *t*-test exploring whether anodal tDCS resulted in altered (i.e. either increased or decreased) mind-wandering propensity relative to sham stimulation was not significant ($t(117.68) = -1.01$, $p = 0.312$, Cohen's $d = -0.102$). Also, the one-tailed *t*-test assessing directional effects indicated that anodal tDCS was not associated with increased propensity of mind wandering ($t(117.68) = -1.01$, $p = 0.843$).

3.3 | Exploratory analyses

3.3.1 | Sensitivity of the preregistered analyses on choice of prior

In order to judge the extent to which our results depend on the choice of the prior distribution, we repeated the key analyses reported in the previous sections using different choices of the *r*-scale parameter. In addition to the *r*-scale value of $\sqrt{2}/2 = 0.707$ used in the preregistration, we included parameter settings across a range of values. First, we included an analysis with $r = 0.4$, resulting in a rather restrictive prior distribution informed by the magnitude of previously reported effect sizes in this literature. We also included larger values of $r = 1$ and $r = \sqrt{2} = 1.414$ that are commonly used values for this parameter and that are more congruent with the original result of the effect of tDCS on mind wandering. The results of these analyses are reported in Table 6. The size of the Bayes Factors depends quite strongly on the choice of the prior: Evidence for the null hypothesis is reduced with lower *r*-scale values since the null hypothesis is more likely a priori. The estimated size of the effect (and its uncertainty quantified by the HDI) was largely unaffected by the choice of the prior, indicating that the sample size was large enough such that the posterior is dominated by the likelihood for reasonable choices of the prior distribution.

3.3.2 | Influence of brain stimulation on other task measures

In accordance with the well-known time-on-task effect on mind wandering (i.e. more attentional lapses in later parts of the task) that we already reported in our preregistered analyses, we found compelling evidence for the effect of time ($BF_{10} = 7.03 \times 10^8$; $F_{1,190} = 52.421$; $p < 0.001$; $\eta^2 = 0.216$), although this effect was numerically rather small (first part: $M = 2.12$; $SD = 0.52$; second part: $M = 2.33$; $SD = 0.62$). Summary statistics for these analyses are presented in Table 7. In addition, participants became faster ($BF_{10} = 106.46$; GoRT: $F_{1,190} = 14.714$; $p < 0.001$; $\eta^2 = 0.072$) and made more key presses on Nogo trials (commission errors: $BF_{10} = 1{,}958.5$; $F_{1,190} = 21.409$; $p < 0.001$; $\eta^2 = 0.101$) in the second part of the experiment. This finding indicates a change in the speed-accuracy trade-off with task progress (Pearson's correlation between GoRT and commission errors for the whole task: $BF_{10} = 4.07$; $r(190) = -0.199$; $p = 0.006$), and might be related to more mind wandering during the second part of the task (Kendall's correlation between thought probe ratings and GoRT for the whole task: $BF_{10} = 3.55$; $\tau(190) = 0.131$; $p = 0.008$; between thought probe ratings and commission errors: $BF_{10} = 554.09$; $\tau(190) = 0.203$; $p < 0.001$). Finally, response times were more variable in the second part of the SART (RTCV: $BF_{10} = 5.83$; $F_{1,190} = 8.352$; $p = 0.004$; $\eta^2 = 0.042$), an effect that can also be attributed to increasing mind-wandering propensity with time spent on the task (Kendall's correlation between thought probe ratings and RTCV: $BF_{10} = 3{,}639.73$; $\tau(190) = 0.224$; $p < 0.001$; Pearson's correlation between GoRT and RTCV: $BF_{10} = 1{,}411.99$; $r(190) = 0.312$; $p < 0.001$; between commission errors and RTCV: $BF_{10} = 1.08 \times 10^8$; $r(190) = 0.446$; $p < 0.001$). Although omission errors on Go trials were not affected by time-on-task ($BF_{10} = 0.11$), they correlated positively both with mind wandering ($BF_{10} = 10.99$; $\tau(190) = 0.150$; $p = 0.004$) and with other task measures (GoRT: $BF_{10} = 101.1$; $r(190) = 0.268$; $p < 0.001$; RTCV: $BF_{10} = 5.42 \times 10^{27}$; $r(190) = 0.711$; $p < 0.001$).

With respect to the effect of tDCS on mind wandering or task performance, neither the main effect of stimulation (BF_{10} between 0.23 and 0.53; $F < 1.59$, $p > 0.208$) nor its interaction with time ($BF_{inclusion}$ between 0.15 and 0.28; $F < 1.241$, $p > 0.265$) was significant for either of the five measures of interest.

TABLE 6 Sensitivity of the preregistered results. The strength of the evidence quantified by the Bayes Factors depends on the choice of the prior (preregistered $r_{scale} = \sqrt{2}/2$): Larger priors result in stronger evidence for the null hypothesis. The estimate of the effect size (and its precision in terms of the HDI) is largely unaffected by choice of prior

Prior r_{scale}[a]	Cohen's d[b]	BF_{0+}	BF_{0-}	BF_{+-}	BF_{01}
0.4	−0.10 [−0.36, 0.16]	6.33	1.91	0.30	2.94
$\sqrt{2}/2$	−0.11 [−0.38, 0.17]	10.65	3.09	0.29	4.79
1	−0.11 [−0.38, 0.17]	15.06	4.13	0.27	6.49
$\sqrt{2}$	−0.11 [−0.40, 0.17]	21.19	5.74	0.27	9.03

[a]Parameter defining the prior distribution of the used models. [b]Posterior mean and 95% highest-density interval (HDI).

TABLE 7 Summary statistics of different outcome variables split by stimulation and online (part 1) and offline (part 2). Mean ± standard deviations are reported

	1st part Anodal	1st part Sham	2nd part Anodal	2nd part Sham
Thought probes	2.08 ± 0.56	2.15 ± 0.49	2.30 ± 0.62	2.36 ± 0.63
RT (ms)	393.4 ± 71.6	381.5 ± 61.8	380.6 ± 87.2	368.5 ± 55.6
RTCV	0.29 ± 0.13	0.28 ± 0.08	0.30 ± 0.12	0.29 ± 0.11
Commission errors (%)	35.7 ± 19.8	38.4 ± 18.8	43.1 ± 23.6	42.9 ± 20.6

3.3.3 | Exploratory analysis of location effects

In order to further investigate the effects of laboratory in which each of the three data sets was collected on thought probe responses reported earlier, we extended the hierarchical probit regression model described in Appendix 1 by introducing interaction effects for lab × stimulation and lab × trial treating Tromsø as the baseline. The resulting model produced a better fit in terms of model-selection criteria (LOOIC = 10077.2, $SE = 83.4$) than the model with only laboratory as a main effect ($\triangle$LOOIC = 7.3, $SE = 4.3$). Using this model, the HDIs for the main effect of laboratory no longer exclude zero, $\beta_{AMS} = -0.19$, [−0.45, 0.07], $\beta_{GOE} = -0.24$, [−0.50, 0.02] even though they are still indicating reduced off-task reports in both Amsterdam and Göttingen when compared to Tromsø. There is no evidence that the brain stimulation affected the thought probe reports differentially in the three laboratories, $\beta_{GOE\times stimulation} = -0.09$, [−0.45, 0.27], $\beta_{AMS\times stimulation} = -0.06$, [−0.29, 0.42]. Finally, the time-on-task effect seems to be reduced in subjects from Amsterdam as compared to Tromsø, $\beta_{AMS\times trial} = -0.13$, [−0.18, −0.08] but not in Göttingen, $\beta_{GOE\times trial} = -0.04$, [−0.09, 0.01]. This finding agrees with the results from the preregistered analysis which found that the time-on-task effect was reduced in Amsterdam in independent analyses for each laboratory.

Furthermore, we were interested in whether the apparent effect of laboratory might not actually be due to a gender effect. Previous research has reported gender differences in mind-wandering propensity (Bertossi, Peccenini, Solmi, Avenanti, & Ciaramelli, 2017) and given that we sampled a slightly higher proportion of females in Amsterdam than in the other laboratories (see Table 3), the observed laboratory effect might actually be due to differences in mind-wandering in males and females. We investigated this possibility by augmenting the probit-regression model that includes laboratory as covariate with an additional covariate coding for the gender of the participant. Assuming that any differences between the laboratories were due to gender effects, we would therefore expect the laboratory coefficients to be estimated near zero and the coefficient coding for gender to show an effect. This augmentation of the model did not improve the model-fit (LOOIC = 10,091.8, $SE = 83.1$; $\triangle$LOOIC = −0.4, $SE = 0.2$). The coefficients for the laboratory variables were similar to the ones estimated from the model not including gender as a covariate, $\beta_{AMS} = -0.16$, [−0.35, 0.01] and $\beta_{GOE} = -0.27$, [−0.45, −0.08] and the coefficient for gender was spread wide around zero, $\beta_{male} = -0.06$, [−0.22, 0.11] indicating that gender was not likely to be responsible for the aforementioned laboratory effect.

3.3.4 | Questionnaires

When analysing changes in self-reported mood states during the task, both Bayesian and frequentist repeated-measures ANOVA revealed a main effect of time for positive, but not negative mood scores (PANAS-positive: $BF_{10} = 8.37 \times 10^{14}$; $F_{1,190} = 92.480$; $p < 0.001$; $\eta^2 = 0.327$; PANAS-negative: $BF_{10} = 0.32$; $F_{1,190} = 2.236$; $p = 0.136$; $\eta^2 = 0.012$), indicating a significant reduction in positive mood by the end of the task (pre-task rating: $M = 29.35$; $SD = 6.26$; post-task rating: $M = 25.09$; $SD = 7.22$). Neither the main effect of stimulation nor its interaction with time was significant for the PANAS scores. Furthermore, since mind wandering has been associated with negative mood states (Killingsworth & Gilbert, 2010; Smallwood et al., 2009), we hypothesized a correlation between mind-wandering propensity (subjective thought probe reports) and changes in mood scores measured by the PANAS. Despite our expectations, thought probe responses did not correlate with pre- versus post-SART difference scores for PANAS-negative (anodal tDCS group: $BF_{10} = 0.36$; $\tau(94) = 0.099$; $p = 0.179$; sham tDCS group: $BF_{10} = 0.13$; $\tau(94) = 0.009$; $p = 0.908$) or PANAS-positive items (anodal tDCS group: $BF_{10} = 0.36$; $\tau(94) = 0.98$; $p = 0.052$; sham tDCS group: $BF_{10} = 0.15$; $\tau(94) = 0.035$; $p = 0.622$).

Using the MAAS questionnaire, we have also collected self-reported scores on the individual's inherent ability to attend to the present experience and remain undistracted. Higher MAAS scores indicate higher level of concentration, and therefore, we anticipated that MAAS scores would negatively correlate with thought probe scores. However, in contrast to our hypothesis, neither group showed a relationship between MAAS scores and mind wandering, albeit the correlations were in the expected direction (anodal tDCS group: $BF_{10} = 0.36$; $\tau(94) = -0.098$; $p = 0.166$; sham tDCS group: $BF_{10} = 0.29$; $\tau(94) = -0.088$; $p = 0.214$).

4 | DISCUSSION

The aim of the study was to replicate the findings reported by Axelrod et al. (2015) about the potential effect of anodal tDCS on mind-wandering propensity. Mind-wandering propensity was assessed by self-reports (thought probes) while participants were engaged in a sustained attention task. Building upon the findings of the original publication, we tested the hypothesis that anodal tDCS over the left DLPFC would increase mind-wandering propensity relative to an inactive (sham) stimulation. The present replication study was performed as a fully preregistered, multicentre study utilizing a sequential sampling plan with equal sample size across laboratories.

Contrary to our hypothesis and the findings from Axelrod et al. (2015), we found that the participants receiving anodal stimulation were numerically less likely to respond being off-task when compared to the group receiving sham stimulation over the left DLPFC. Overall, however, our findings show support in favour of a null-effect of stimulation on self-reported thought probe scores as shown by an analysis based on Bayes Factors. When comparing a null-effect to an effect in the positive direction as hypothesized a priori, there was strong evidence for a null effect ($BF_{0+} = 10.65$). Also, when testing the hypothesis of the effect being zero against the full range of possible non-zero effects, there was moderate evidence for a null effect ($BF_{01} = 4.79$) and even when comparing against a purely negative effect, the null was somewhat favoured ($BF_{0-} = 3.09$). In addition, there was extreme evidence ($BF_{replication} = 0.002$) that the original study was not replicated using a special Bayes Factor designed to indicate replication success (Verhagen & Wagenmakers, 2014). When pooling data from both the original and replication study, there was strong evidence ($BF_{meta} = 0.059$) for the absence of an effect of anodal stimulation. We conclude from these results that there is no support for the supposition that bipolar anodal tDCS in the form used in our and the original study (Axelrod et al., 2015) can influence the propensity to mind-wander. On the contrary, we found substantive evidence against the existence of such an effect.

Our failure to replicate the original study is perhaps not particular surprising when viewed in the context of previous replication failures in the field of psychology (e.g. Klein et al., 2014; Open Science Collaboration, 2015; Wagenmakers et al., 2016) in general and brain stimulation in particular (Horvath, Carter, & Forte, 2016; Learmonth et al., 2017; Vannorsdall et al., 2016). Typically, a result obtained in an initial, often low-powered study fails to be reproduced in large-sample replication attempts (Boekel et al., 2015). Replications are the cornerstone of empirical research and crucial for scientific progress. Even though this is a well-known fact, replication attempts are still rare (Makel, Plucker, & Hegarty, 2012). Several reasons for this problematic state of affairs have been pointed out by many authors (Chambers, 2017; Simmons, Nelson, & Simonsohn, 2011) which comprise factors on many different levels. We conclude that the original result by Axelrod et al. (2015) was most likely a false-positive finding caused by strong variability and low sample size. We believe that it is crucial that future studies aiming to establish a specific experimental effect should be required to (a) employ sample sizes that are adequate to find effects of a reasonable magnitude and (b) to either preregister their study from the outset or provide a preregistered replication of their own result. Such requirements would go a long way to protect the literature from the omnipresent false positives, even though replication by independent, if possible multiple, laboratories is the ultimate goal (Simons, 2014).

It is important to point out, however, that our failed replication of the study by Axelrod et al. (2015) does not imply that tDCS is an ineffective tool for modulating mind-wandering propensity. On the contrary, we are aware of four other studies that reported evidence for active stimulation either increasing or reducing the mind-wandering propensity during various tasks. In three studies, Kajimura and colleagues showed that anodal stimulation of the right inferior parietal lobule (rIPL) reduces mind-wandering propensity (Kajimura, Kochiyama, Abe, & Nomura, 2018; Kajimura & Nomura, 2015; Kajimura et al., 2016). In their first two reports (Kajimura & Nomura, 2015; Kajimura et al., 2016), the cathode was placed above the left DLPFC, rendering the contribution of left DLPFC versus rIPL to the observed effect impossible to distinguish. However, in their most recent study, the authors used an extracephalic return electrode, providing evidence for rIPL stimulation being primarily responsible for the mind-wandering reducing effect (Kajimura et al., 2018). Interestingly, analysis of effective connectivity patterns revealed that the behavioural effect of anodal tDCS on decreased mind-wandering propensity was mediated by weaker afferent connections from the medial prefrontal cortex (MPFC) to the posterior cingulate cortex, highlighting the MPFC node within the DMN as a key mediator for inducing and/or maintaining task-unrelated thoughts (Kajimura et al., 2016). The role of the MPFC in influencing mind wandering is also supported by another study showing that cathodal tDCS targeting the left MPFC reduces attentional lapses during a choice reaction time task in males (Bertossi et al., 2017). Given the negative results of the current study, however, it is important to replicate any of these positive effects before accepting them as facts.

As detailed in the introduction, several neuroimaging studies and theoretical accounts attribute an important role to the FPN (and, more specifically, to the DLPFC) in regulating mind-wandering episodes under various circumstances (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016; Christoff et al., 2009; Dumontheil, Gilbert, Frith, & Burgess, 2010; Smallwood et al., 2012). In this regard, the positive

finding by Axelrod et al. (2015) fits well in this framework, seemingly providing direct evidence for the causal (rather than correlational) involvement of the left DLPFC to regulating mind-wandering propensity. However, the poor spatial focality of bipolar tDCS montages is well known (Csifcsák, Boayue, Puonti, Thielscher, & Mittner, 2018; Laakso et al., 2016; Opitz, Paulus, Will, Antunes, & Thielscher, 2015, with stimulation-induced electric fields (EFs) spreading well beyond the area of scalp electrodes, most probably influencing neural excitability in a wide range of cortical areas (Keeser et al., 2011). Using high-resolution realistic head models of healthy adults, we have recently demonstrated that tDCS protocols targeting the left DLPFC show substantial inter-individual variability in the spatial distribution of tDCS-induced EFs (Boayue, Csifcsák, Puonti, Thielscher, & Mittner, 2018). Using our previously described and publicly available pipeline (Boayue et al., 2018), we now present new modelling results to gain insight into the potential underlying neural effects that were induced by our tDCS protocol. We focused on the normal component of the EF, that is, on the component perpendicular to the cortical surface, either entering (positive values) or leaving the cortex (negative values). Previous work identified these currents as being excitatory or inhibitory in nature (Rahman et al., 2013), enabling us to assess the direction of the expected effect. In Figure 6 (left panel), we show that despite targeting the left DLPFC, this montage induces EFs in both the medial and lateral aspects of the two hemispheres. Moreover, the right and left MPFC receives excitatory and inhibitory stimulation, respectively, which is particularly interesting as both the enhancement and reduction in MPFC activity by tDCS was associated with changes in mind-wandering propensity (Bertossi et al., 2017; Kajimura et al., 2016). Based on these, we argue that stimulation of the MPFC could just as well be responsible for the effect reported by Axelrod et al. (2015) than that of the left DLPFC. In addition, the variability maps shown in Figure 6 (right panel) clearly indicate that the magnitude of EFs in the bilateral DLPFC is highly variable between participants.

The tDCS protocol employed in our and the original study even though standard in the field has some drawbacks: First, the protocol used a weak stimulation intensity (1 mA) resulting in electric field magnitudes of about 0.1–0.2 V/m in the target area (see Figure 6). These estimates are based on computational models that have also been validated by intracranial measurements (Opitz et al., 2016). It is unclear whether the electric field induced by transcranial electric stimulation is robust and strong enough to cause any physiological effect (Huang et al., 2017), let alone manifest at the behavioural level. Therefore, it is possible that the stimulation intensity of 1 mA with the present bipolar montage is just not potent enough for the tDCS-induced electric field to have an effect on neural excitability (Vöröslakos et al., 2018). Second, the bipolar tDCS protocol produces diffuse electric fields resulting in a lack of specificity and the unintended stimulation of other regions (Csifcsák et al., 2018). The result is a diffuse stimulation of the target region. A better approach might be the use of recently developed high definition brain stimulation protocols, for example, 4×1 ring protocols, which

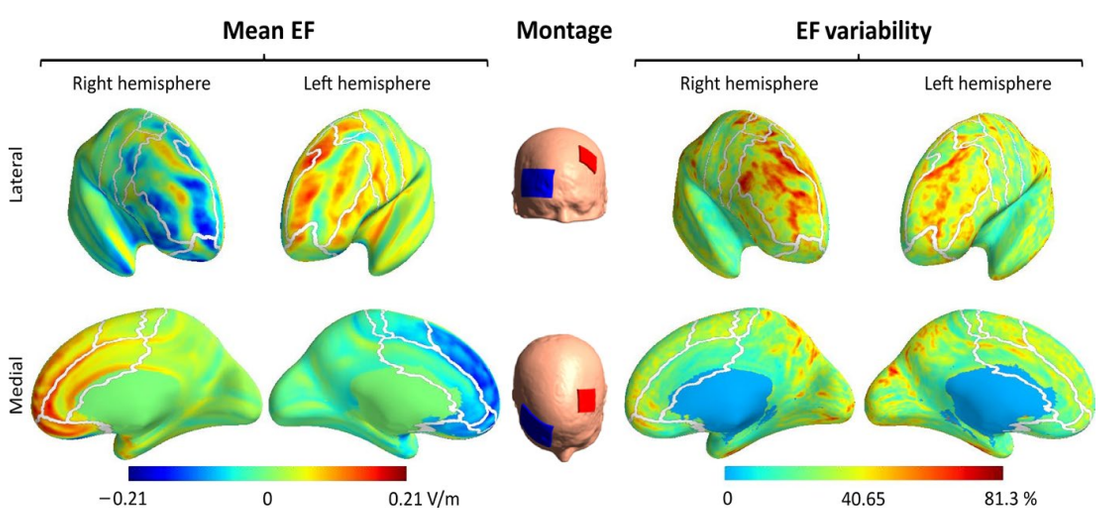

FIGURE 6 Simulation of transcranial direct current stimulation-induced electric fields (EFs) in the cortex of 18 head models for the montage used in our study and by Axelrod et al. (2015). Group-averaged mean values are presented on the left side, whereas the variability in effects across individuals is presented on the right side. For these simulations, we focused on the normal component of the EF, manifesting in positive (anode-like) and negative (cathode-like) values in the mean maps. Across-subject variability was quantified as the EF coefficient of variation ($\frac{standard\ deviation}{mean} \times 100$). Simulation parameters and methods were as described in Csifcsák et al. (2018)

allows for more targeted stimulation (Datta et al., 2009). These protocols allow a much more precise targeting of a region of interest while minimizing the electric field in other parts of the brain. However, this increased focality comes at the price of possibly influencing different regions in different subjects because of substantial differences in brain anatomy (Opitz et al., 2015). It is therefore desirable to use individualized montages based on head models from high resolution magnetic resonance (MR) images to guide optimal electrode placement to result in comparable electric field distributions in individual brains. Taken together, routine usage of this approach could in the future help to increase focality of stimulation and to reduce between-subject variance of the results.

As part of our exploratory analysis, we found that anodal tDCS was not associated with either online or offline effects on task performance. Still, we found robust time-on-task effects regarding thought probes, accuracy and reaction time measures, which are in line with previous findings (Bastian & Sackur, 2013; Cheyne et al., 2009; McVay & Kane, 2012; Smallwood & Schooler, 2006). Interestingly, although the negative correlation between response times and commission error rates is indicative of a speed-accuracy trade-off, these parameters were inversely influenced by mind-wandering propensity on a between-subject level. Participants reporting more mind wandering were characterized not only by higher error rates but also by longer (rather than shorter) reaction times. Response time slowing has been associated with task-unrelated thoughts previously, and it was also found to be predictive of omission errors, as in our study (McVay & Kane, 2012; Smallwood & Schooler, 2006). Nevertheless, these data strengthen views that there is a complex relationship between self-reported mind-wandering intensity and performance patterns on the SART (McVay & Kane, 2012), since the latter can be influenced by factors other than mind-wandering per se (e.g. impulsivity or response strategy; Helton, Weil, Middlemiss, & Sawers, 2010). Finally, it is worth mentioning that RT variability (RTCV) showed the strongest correlation with thought probes, highlighting this measure as the most promising objectively quantifiable SART performance index for estimating the prevalence of off-task periods (Bastian & Sackur, 2013).

Rather surprisingly, we did not find a relationship between mind-wandering propensity and the participants' mood scores. Despite the often described link between negative mood and task-unrelated thoughts (Killingsworth & Gilbert, 2010; Smallwood et al., 2009), the causal relationship between these phenomena might be too subtle to be detected by our relatively simple questionnaires and thought probe. Moreover, to avoid inducing mood changes prior to tDCS, we asked our participants to rate their pretask mood retrospectively, which most probably restricted the reliability of our mood data. The individual's predisposition to mindfully attend to the present has been regarded as a personality attribute that is opposed to the propensity to mind wander (Mrazek et al., 2012). However, in our data set, we did not observe a negative correlation between thought probe responses and MAAS scores. Interestingly, recent work pointed out that rather than merely being in contrast, these phenomena can interact in a very complex and at times synergistic way (Agnoli, Vanucci, Pelagatti, & Corazza, 2018; Seli, Carriere, & Smilek, 2015). For example, it was suggested that the deliberate versus spontaneous nature of mind wandering is differently related to certain factors of mindfulness (Seli et al., 2015). Thus, the fact that our thought probes were not enquiring about this aspect of mind wandering might have rendered our analysis insensitive to unveiling the relationship between these phenomena.

We also found indications for differences in mind-wandering propensity between the laboratories. Even though the results were not very strong (0.2–0.3 units on the 4-point Likert scale) and did not increase the model fit in terms of the model-selection criteria, participants from the University of Amsterdam were generally less likely to respond off-task to the thought probes than participants from Tromsø. This finding may have several possible explanations. For example, subtle differences in how the thought probes are being expressed in the three languages (German, Dutch and Norwegian) may have caused participants to give slightly different interpretations to the meaning of the scale. This is a common issue when comparing scales across languages and it is often recommended to disregard any cross-language main effects, assuming that the scales still have metric equivalence but may have a shifted origin (van de Vijver & Leung, 2011). Another possibility is national differences in acceptability of deviations from task-conform behaviour. Recently, researchers have begun to look more closely into boundary conditions of the thought probe technique (Weinstein, 2017; Weinstein, De Lima, & van der Zee, 2018). This finding is a first indication that it may be important to consider language- or nationality-specific effects as well.

In summary, in a high-powered, preregistered multicentre study, we were not only unable to detect an effect of anodal transcranial direct current stimulation on mind-wandering propensity, but we actually found evidence for the absence of such an effect. Our findings further emphasize the significance of direct replications for the further advancement of the field of cognitive neuroscience in general and brain-stimulation in particular.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

NB designed study, collected data and drafted paper; GC designed study and drafted paper; PA gave technical advice and commented on paper; TZ gave technical advice on tDCS, collected data and drafted paper; AA gave technical advice on tDCS, collected data and commented on paper; JG collected data and commented on paper; GH gave technical advice on data analysis and commented on paper; BF designed study and commented on paper; AO gave technical advice on computational modelling, commented on paper; AT gave technical advice on computational modelling and commented on paper; MM designed study, coordinated activity, analysed data and drafted paper.

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APPENDIX 1

Hierarchical ordered probit model

The model is fully specified as follows: Each response to a thought probe (one of the set {1,…,*K*}) given by subject *j* in trial *t*, is modelled as a categorical variable with probability *K*-simplex *p* (a *K*-simplex is a set of *K* positive numbers that sum to one).

$$\text{probe}_{j,t} \sim \text{Categorical}(p).$$

The probabilities for each of the responses are calculated by assuming an underlying, continuous, normally-distributed "mind-wandering" variable *y* with parameters $\mu_{j,t}$ and σ that is thresholded into the discrete responses at thresholds $\theta_1, \ldots, \theta_{K-1}$. The probabilities to give each of the responses is the area under the normal curve of *y* that falls into the *K* response-bins $[-\infty, \theta_1], \ldots, [\theta_{K-1}, \infty]$. Therefore, the probabilities are calculated as

$$p_k = \Phi\left(\frac{\theta_k - \mu_{j,t}}{\sigma}\right) - \Phi\left(\frac{\theta_{k-1} - \mu_{j,t}}{\sigma}\right)$$

where Φ is the cumulative standard normal distribution (see Kruschke, 2014, for a comprehensive presentation of this model).

The underlying distribution is modelled with a hierarchical linear model

$$\mu_{j,t} = \beta_{0,j} + \beta_1 z(t) + \beta_{\text{anodal}}\text{anodal}_j \quad (1)$$

where $z(t)$ is the *z*-transformed trial number and anodal_j is an indicator variable specifying whether a subject was in the control group (0) or in the anodal stimulation group (1). The subject-level intercepts are constrained by a group-level distribution

$$\beta_{0,j} \sim \text{Normal}(\mu_g, \sigma_g).$$

Priors are set to be vague as recommended in Kruschke (2014):

$$\mu_g \sim \text{Normal}\left(\frac{1+K}{2}, K\right),$$

$$\sigma_g \sim \text{Uniform}\,(K/1000, 10K),$$

$$\sigma \sim \text{Uniform}\,(K/1000, 10K)$$

and

$$\beta_1 \sim \text{Normal}(0, K).$$

The test of the hypothesis that anodal stimulation can increase mind-wandering is whether the distribution for the β_{anodal} coefficient will be larger than zero.

For analyzing the effect of laboratory where the data for a specific subject was collected, we run three instances of this model with the datasets from the three universities and present the resulting posterior distribution side-by-side. In addition, we augment this model with a covariate for laboratory, modifying Equation 1 to read

$$\mu_{j,t} = \beta_{0,j} + \beta_1 z(t) + \beta_{\text{anodal}}\text{anodal}_j + \beta_{\text{labAMS}}\text{AMS}_j + \beta_{\text{labGOE}}\text{GOE}_j$$

where AMS and GOE are indicator variables coding for whether a subject was recorded in Amsterdam or Göttingen, respectively (with Tromsø serving as the baseline). This augmented model will be compared to the model without these covariates using the LOOIC and WAIC indicators to evaluate whether the inclusion of this information would improve the fit of the model.

Changes to the original protocol

The changes detailed here are part of our OSF protocol and can also be found under https://osf.io/37kfj/.

Changes made after pre-registering with EJN but before any data was collected

The changes documented here have been made before the first dataset was collected. It is part of a registration at OSF that has been made on November, 2nd 2017, https://osf.io/bv32d/.

Additional instructions for experimenter

- added three more questions (the last three) to the Q&A sheet with standardized answers to questions that the data-collectors from the three laboratories are using in case there are questions from the participants; those were added purely for preventive reasons because of experiences during piloting

Adapted translated instructions

- adapted the German instructions to reflect the English template; this was because of an oversight in which only the English template was adjusted during preparation of the study while the translations were forgotten. This oversight was spotted by our German collaborators and we fixed this before any data-collection

Expanded instructions to avoid accidental unblinding

- during the course of the pilots at our partnering institutions, we became aware of the fact that our previously detailed protocol could result in accidental unblinding of the experimenter. This is due to the fact that the impedance

measurement on the stimulator reflects the ramp-down period which is earlier in the sham as compared to the real stimulation condition. We account for this by requiring the experimenters to cover the stimulation device after recording the initial impedance measurement and to turn it off without lifting the cover before turning it on again for the final post-stimulation measurement of impedance. This is reflected in updated portions of the experimenter instructions.

- we added a note to the datasheet where the experimenter should input the number of times the impedance measurement had to be repeated to come below the required 10 kOhm.

Screen size

We became aware of an error in our pre-registration where we specified that we would be using 12'' flat screen monitors. The actual screen size in the three laboratories was 19''. This difference in screen sizes had no impact on the size of the displayed stimuli as those were adjusted to cover 3° of visual angle independently for each laboratory.

Changes made after starting the data collection but before any analysis was conducted

None.

Changes made after finished data-collection

It was necessary to adapt several of the pre-registered analysis scripts. There were two reasons for these changes:

1. There were updates to some of the used analyses packages which required changes to the code in order to run as intended
2. There were errors in the original analysis-script that were only spotted when confronted with real data.

At our OSF-repository https://osf.io/dct2r/, we store a copy of the updated analysis files and we also keep the output of the `diff` utility that stores any changes made to the original scripts in an easily readable format. These files are called `<scriptname>.diff` where `<scriptname>` is replaced with each of the changed script files. The original script files can be retrieved from the pre-registration at https://osf.io/bv32d/.

Paper II

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Research paper

Effects of transcranial direct current stimulation for treating depression: A modeling study

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) above the left dorsolateral prefrontal cortex (lDLPFC) has been widely used to improve symptoms of major depressive disorder (MDD). However, the effects of different stimulation protocols in the entire frontal lobe have not been investigated in a large sample including patient data.

Methods: We used 38 head models created from structural magnetic resonance imaging data of 19 healthy adults and 19 MDD patients and applied computational modeling to simulate the spatial distribution of tDCS-induced electric fields (EFs) in 20 frontal regions. We evaluated effects of seven bipolar and two multi-electrode 4 × 1 tDCS protocols.

Results: For bipolar montages, EFs were of comparable strength in the lDLPFC and in the medial prefrontal cortex (MPFC). Depending on stimulation parameters, EF cortical maps varied to a considerable degree, but were found to be similar in controls and patients. 4 × 1 montages produced more localized, albeit weaker effects.

Limitations: White matter anisotropy was not modeled. The relationship between EF strength and clinical response to tDCS could not be evaluated.

Conclusions: In addition to lDLPFC stimulation, excitability changes in the MPFC should also be considered as a potential mechanism underlying clinical efficacy of bipolar montages. MDD-associated anatomical variations are not likely to substantially influence current flow. Individual modeling of tDCS protocols can substantially improve cortical targeting. We make recommendations for future research to explicitly test the contribution of lDLPFC vs. MPFC stimulation to therapeutic outcomes of tDCS in this disorder.

1. Background

Transcranial direct current stimulation (tDCS) is one of the most widespread non-invasive brain stimulation (NIBS) methods that have been used for alleviating symptoms of major depressive disorder (MDD). During conventional bipolar tDCS, two electrodes, an anode and a cathode, are placed on the head, and the stimulator is set to deliver weak (typically 1 or 2 mA) currents to the brain for 8–20 min (Filmer et al., 2014; Miniussi et al., 2013; Antal et al., 2017). Early animal studies provided evidence that polarizing currents applied to the cortical surface shift the resting membrane potential of pyramidal neurons in a polarity-dependent manner, which in turn can facilitate or inhibit their spontaneous and stimulus-evoked activity under the anode and cathode, respectively (Bindman et al., 1964; Purpura and McMurtry, 1965). In line with these findings, human studies have shown that tDCS induces polarity-specific effects in the motor or sensory cortex, although results are less consistent for prefrontal cortex (PFC) stimulation (Antal et al., 2003; Nitsche and Paulus, 2000; Tremblay et al., 2014).

TDCS is primarily applied above the left dorsolateral prefrontal cortex (lDLPFC) in MDD, a region that was shown to be hypoactive in this disorder (Fales et al., 2008; Grimm et al., 2008; Siegle et al., 2007). In healthy volunteers, anodal tDCS suppressed the evaluation of emotionally negative stimuli (Boggio et al., 2009; Maeoka et al., 2012; Peña-Gómez et al., 2011) and improved frustration tolerance in a demanding cognitive task (Plewnia et al., 2015a). Thus, it is reasonable to

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assume that by increasing excitability in the left DLPFC, dysfunctional control over negative thoughts and attentional bias towards negative stimuli can be restored in MDD patients, leading to significant improvement in symptomatology (Disner et al., 2011; Plewnia et al., 2015b; Rive et al., 2013). In support of this, successful pharmacotherapy, cognitive therapy or invasive brain stimulation have all been associated with normalization (i.e., enhancement) of lDLPFC activity (Bench et al., 1995; DeRubeis et al., 2008; Mayberg et al., 2005).

Since the first report on the clinical efficacy of anodal tDCS over the lDLPFC in MDD (Fregni et al., 2006a), nine double-blind, sham-controlled studies were conducted involving more than 300 patients (Bennabi et al., 2015; Blumberger et al., 2012; Boggio et al., 2008; Brunoni et al., 2013, 2017; Loo et al., 2010, 2012, 2018; Palm et al., 2012). Still, only five studies reported significant improvements in symptoms severity when compared to sham stimulation (Boggio et al., 2008; Brunoni et al., 2013, 2017; Fregni et al., 2006a; Loo et al., 2012), which might be related to different sample sizes, dissimilarities between stimulation protocols, between-patient variations in brain anatomy and/or patient selection criteria. However, a recent meta-analysis that included individual patient data of six randomized, sham-controlled, double-blind trials provided clear evidence for the superiority of active tDCS versus sham stimulation (Brunoni et al., 2016a).

Studies reviewed so far offer a relatively straightforward model for understanding the clinical effects of tDCS in MDD: (1) in the healthy, the lDLPFC is involved in suppressing the influence of negative emotional stimuli on behavior, (2) the lDLPFC is hypoactive in depression, (3) processes linked to lDLPFC are implicated in the psychopathology of MDD, and (4) successful treatment normalizes lDLPFC activity in MDD. Due to the fact that several studies have successfully used tDCS to influence neurophysiological and/or behavioral outcomes by placing the electrodes above the region of interest (Antal et al., 2003; Meinzer et al., 2012; Nitsche et al., 2007; Nitsche and Paulus, 2000), it is usually assumed that the primary effects of tDCS are manifested under the electrode pads. However, the spatial resolution of tDCS is rather poor: Given that the current flows from the anode towards the cathode, substantial effects should also be expected in brain areas situated between the two electrodes. This assertion was confirmed by modeling and neuroimaging studies, with stimulation-induced electric fields (EFs) and hemodynamic responses being very strong in regions between the electrodes (Antal et al., 2011; Bai et al., 2014; Baudewig et al., 2001; Bikson et al., 2010a; Datta et al., 2009; Datta, 2012; Laakso et al., 2016; Lang et al., 2005; Miranda et al., 2013; Seibt et al., 2015). These results raise the possibility that tDCS-associated behavioral effects might also be linked to the stimulation of regions that are not intentionally targeted.

In this study, we used computational modeling to analyze the spatial distribution of EFs in realistic head models created from structural magnetic resonance imaging (MRI) scans of 19 healthy adults and 19 MDD patients. Simulations were performed on a relatively large cohort of participants because inter-individual differences in head and brain anatomy were shown to significantly influence current flow (Datta, 2012; Laakso et al., 2016; Opitz et al., 2015; Seibt et al., 2015). Given the evidence for systematic anatomical alterations in MDD (Bora et al., 2012; Kempton et al., 2011; Price and Drevets, 2010; Schmaal et al., 2017), we also included head models created from patient data to assess whether and to what extent healthy individuals and MDD patients differ in terms of the spatial distribution of tDCS-induced EFs in the brain. We compared the effects of five montages used in the six studies included in a recent meta-analysis because, when merged together in the individual patient data approach, these were shown to be significantly superior to sham stimulation in MDD (Brunoni et al., 2016a). In addition, we simulated the protocols of the two most recent double-blind randomized studies involving the largest patient groups so far (Brunoni et al., 2017; Loo et al., 2018). Based on earlier studies that implicated stronger EFs in regions between electrode pads, we expected to find robust stimulation-related effects outside the DLPFC (Bikson et al., 2010a; Datta et al., 2009; Miranda et al., 2013; Seibt et al., 2015). Finally, we simulated the effects of two 4×1 tDCS montages to make recommendations for an improved protocol with more selective targeting of MDD-associated areas (Datta et al., 2008, 2009).

2. Methods and materials

2.1. Participants

High-resolution head models were created from T1-weighted anatomical images that were collected in a separate functional MRI study (Lepping et al., 2016). The data was obtained from the OpenfMRI database (https://openfmri.org/; accession number: ds000171). Structural scans of 19 healthy adult participants with no history of depression or other psychiatric disorders (11 females; mean ± SD age: 28.79 ± 10.86) and 19 unmedicated patients formerly diagnosed with MDD and experiencing a depressive episode at the time of the scanning (11 females; mean ± SD age: 33.52 ± 13.35) were used.[2] For full details regarding demographic data, we refer to the original paper (Lepping et al., 2016).

2.2. Creation of head models

The workflow for data extraction is shown in Fig. 1. Except for four manual steps (see Supplementary methods), all procedures were done in a fully automated manner, using a pipeline developed in Nipype (http://nipype.readthedocs.io/en/latest/) (Gorgolewski et al., 2011). Automated tissue segmentation was performed in SPM12 (Friston et al., 1994) for skin, skull, eyeballs and CSF, and in FreeSurfer (Fischl et al., 1999) for gray and white matter. We used an extended version of SimNIBS 2.0 (Thielscher et al., 2015), a freely available software package for simulating the effects of NIBS techniques (www.simnibs.org/) for creating the final head models. Head meshes consisted of approximately 3,200,000 tetrahedral elements, assigned to six tissue types (Supplementary Fig. 1).

2.3. TDCS simulations and data extraction

TDCS electrodes for the seven bipolar montages were sized and positioned as described in the original papers (Table 1). Electrode parameters and orientations are presented in Supplementary methods. Head models for all participants and the consistency of electrode placement for one montage are shown in Supplementary Fig. 2. For 4×1 montages, four surrounding cathodes were positioned around the central anode to form a circle with a radius of approximately 7 cm (Villamar et al., 2013). The central electrode was placed above the target region, which was either the lDLPFC (electrode F3) or the medial prefrontal cortex (MPFC; electrode Fz). The MPFC was chosen because our analysis for the bipolar montages indicated especially strong tDCS fields in this region.

After setting the current intensities for all montages[3] (Table 1), we ran field calculations based on the Finite Element Method (FEM) (Saturnino et al., 2015). Tissue conductivities are shown in Supplementary Table 1. The resulting spatial maps of tDCS-induced EF distributions for each participant and montage were saved as two-dimensional maps corresponding to the middle of the cortical sheets of individual head models, registered to the average surface ('fsaverage') of FreeSurfer. These reconstructed cortical surfaces were used for atlas-based automated parcellation of the frontal lobe into 20 regions (10 labels per hemisphere: primary motor cortex, lateral premotor cortex,

[2] Data of one control participant ("sub-control20") was excluded due to technical problems with head model creation.

[3] In the montage used by Palm et al. (2012), the stronger stimulation intensity of 2 mA was applied because this was associated with slightly better clinical outcome.

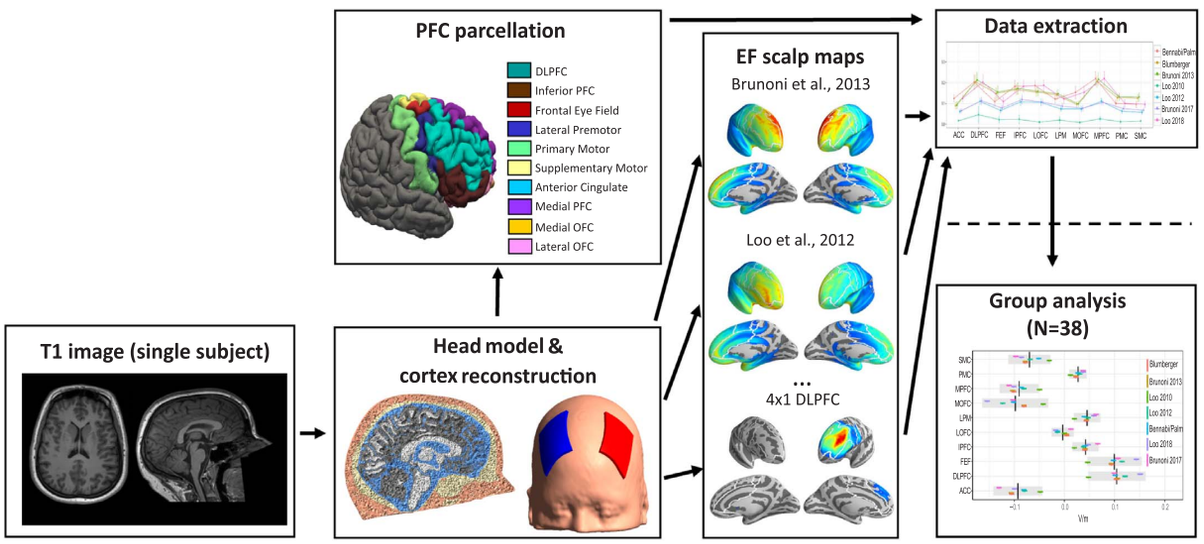

Fig. 1. Workflow for data extraction. Abbreviations: DLPFC: dorsolateral prefrontal cortex; EF: electric field; PFC: prefrontal cortex.

Table 1
Main tDCS parameters used for simulation.

Parameter	Montage								
	Bennabi et al. (2015)/Palm et al. (2012)	Brunoni et al. (2013)	Blumberger et al. (2012)	Loo et al. (2010)	Loo et al. (2012)	Brunoni et al. (2017)	Loo et al. (2018)	**4 × 1 DLPFC**	**4 × 1 MPFC**
Anode position	F3	F3	F3	F3	F3	OLE system (left hemisphere)	F3	F3	Fz
Cathode position	RSO	F4	F4	RSO	F8	OLE system (right hemisphere)	F8	C3, FT7, Fp1, Fz	Fpz, Cz, F3, F4
Electrode size	5 × 7 cm	5 × 5 cm	5 × 7 cm	5 × 7 cm	5 × 7 cm	5 × 5 cm	5 × 7	Diameter: 1.2 cm	Diameter: 1.2 cm
Current intensity	2 mA	2 mA	2 mA	1 mA	2 mA	2 mA	2.5 mA	Anode: 2 mA Cathodes: 0.5 mA	Anode: 2 mA Cathodes: 0.5 mA

OLE: Omni-Lateral Electrode; RSO: right supraorbital.

supplementary motor cortex (SMC), frontal eye field (FEF), medial and lateral orbitofrontal cortex (MOFC, LOFC), inferior PFC, DLPFC, MPFC and anterior cingulate cortex (ACC)) (Ranta et al., 2009, 2014).

In order to compare the spatial distribution of EFs in different montages, EF cortical maps were normalized to individual maxima measured in the whole cortex. For analyzing inter-individual variability in the spatial distribution of EF "hotspots" (small regions with peak EFs), we created flattened cortical surfaces using Pycortex (https://github.com/gallantlab/pycortex) (Gao et al., 2015) to visualize the degree of hotspot overlap across individuals in the control and MDD groups separately. Hotspots were defined as nodes with peak 1% and 5% EF magnitude in the whole cortex. Montage-, label- and hemisphere-specific EF magnitude data were extracted for each participant for group analysis.

We quantified electric field strength in two ways: the absolute strength (vector norm) of the EF ($EF_{intensity}$) at each node is informative of the EF strength at that location, while the intensity of the EF component normal to the cortical surface (EF_{normal}) reflects currents either entering or leaving the cortex (i.e., with an orientation perpendicular to the cortical surface), being associated with polarity-specific (anodal- or cathodal-like) effects (Rahman et al., 2013). For both measures, label- and hemisphere-specific mean and peak values were obtained. Finally, we calculated a focality-index by quantifying the proportion on positive (inward-flowing) or negative (outward-flowing) peak 1% hotspots ($EF_{normal+}$ and $EF_{normal-}$, respectively) in certain regions (lDLPFC or bilateral MPFC) relative to the whole cortex. This index allowed montage comparison in terms of spatial selectivity (results reported in Supplementary Results).

2.4. Data analysis

We used Bayesian estimation methods for all reported analyses. These methods have many advantages over traditional null-hypothesis testing framework especially in an exploratory context with many variables such as ours, where the focus must necessarily lie on effect estimation rather than hypothesis testing (Gelman et al., 2014; Kruschke, 2010). In addition, Bayesian methods allow the quantification of both estimation and irreducible uncertainty at all levels (i.e., region, subject and group-levels), which is important to explore structure in the data. Also, computation of the full Bayesian posterior allows employing the most sophisticated model-selection criteria available to date (Vehtari et al., 2015). Full details of data analysis are described in Supplementary methods. We report our results in terms of posterior means and 95% highest-density intervals (HDIs), which reflect the range in which the estimated parameter is located with 95% probability.

Changes in EF strengths were analyzed by submitting mean $EF_{intensity}$ or EF_{normal} values to Bayesian hierarchical regression analysis (for details see Supplementary methods). For the bipolar montages, we estimated all models that included all possible combinations of group (N = 2), montage (N = 7), label (N = 10) and hemisphere (N = 2) as well as all possible interactions between those variables as predictors (all dummy-coded), and let the intercept vary by subject. The intercepts were constrained by a group-level normal distribution with mean μ_a and standard deviation σ_a.

Non-informative (uniform) priors were placed on all variables. We used a model-selection strategy using the leave-one-out cross-validation information criterion (LOOIC), which resolves several of the difficulties of the deviance information criterion (Gelman et al., 2014; Vehtari et al., 2015; Watanabe, 2013). Differences in LOOIC larger than 10 can be considered strong (Pratte and Rouder, 2012). We followed the same strategy for the 4 × 1 tDCS montages, where we estimated all models that included a combination of group (N = 2), montage (N = 2, MPFC vs. lDLPFC), label (N = 10) and hemisphere (N = 2).

The EF strength was modeled as a function of montage, label, hemisphere and group (for bipolar and 4 × 1 montages separately), because we anticipated stimulation effects to vary across these dimensions, with the intercept accounting for between-subject variation regardless of group membership.

3. Results

3.1. Bipolar montages

Model selection for the hierarchical Bayesian regression analysis revealed that the model incorporating hemisphere, label and montage as predictors accounted best for the mean $EF_{intensity}$ and EF_{normal} distributions (Supplementary Tables 2 and 3).

The effect of label and hemisphere is not surprising, as cortical maps corresponding to $EF_{intensity}$ distributions indicated that tDCS-induced EFs were not restricted to the target lDLPFC region (see Fig. 2 for three representative bipolar montages and Supplementary Fig. 3 for the other four protocols). As expected, the overall effect of tDCS was also robust in non-targeted areas, primarily in bilateral MPFC, but also in the right DLPFC (rDLPFC) and the right LOFC (Supplementary Fig. 4). For the EF_{normal}, a marked hemispheric effect was present: inward-flowing ($EF_{normal+}$) current magnitudes were comparable in the lateral surface of the left hemisphere and medial surface of the right hemisphere, and conversely, outward-flowing ($EF_{normal-}$) currents were of similar intensity in the medial surface of the left hemisphere and lateral surface of the right hemisphere. In line with this, mean EF_{normal} values were positive for the lDLPFC and left FEF, but also for the right MPFC, ACC, MOFC and SMC, indicating that on average, these regions received anodal-like stimulation, while cathodal-like effects ($EF_{normal} < 0$) were dominant in the rDLPFC/right FEF, and the left MPFC, ACC, MOFC and SMC. This specific spatial distribution of normal currents can be expected when considering the direction of current flow in these montages: positive currents enter the lateral aspect of the left hemisphere near the anode, leave the cortex at the medial surface of the same hemisphere, re-enter the cortex at the right medial surface, and leave the brain near the cathode, at the lateral aspect of the right hemisphere.[4]

With respect to the effect of montage, substantial differences were found between the seven bipolar montages. These were mainly due to the distinct effects of the Loo et al. (2010), Loo et al. (2012) and Loo et al. (2018) protocols: given the weaker stimulation intensity (1 mA), EF strength was much lower in all regions for the Loo et al. (2010) montage, and the strongest stimulation intensity of 2.5 mA yielded opposite effects for the Loo et al. (2018) protocol. With respect to the montage by Loo et al. (2012, 2018), stronger excitatory ($EF_{normal+}$) effects were induced in the lateral and medial aspects of the right hemisphere in many cortical labels, including the ACC, MOFC and MPFC (Supplementary Fig. 4). As for the lDLPFC, excitatory effects were equally strong in four montages (results regarding the focality-index are reported in Supplementary Results and shown in Supplementary Fig. 5) (Bennabi et al., 2015; Blumberger et al., 2012; Brunoni et al., 2013, 2017; Palm et al., 2012).

Finally, an important finding was that group as predictor was never included into the winning model (Supplementary Tables 2 and 3), with the second-best model incorporating group as predictor differing from the winning model by at least > 60 LOOIC units, suggesting that anatomical variations due to MDD diagnosis did not substantially contribute to the observed effects across regions. It is, however, possible that anatomical differences are manifest within cortical regions which cannot be picked up by our global analysis. In our more detailed analysis of the spatial distribution of EF_{normal} currents in labels receiving the strongest stimulation (i.e., the DLPFC and the MPFC) we found subtle group differences in the location of nodes with particularly high activities, being most prominent along the superior frontal sulcus (Fig. 3). Analysis of hotspot distributions yielded very similar results with respect to group differences for peak 1% and 5% hotspots (Fig. 3 and Supplementary Fig. 6).

3.2. 4 × 1 montages

As anticipated, the 4 × 1 DLPFC protocol proved well-suited for a highly selective excitatory stimulation of the left hemisphere, peaking in the lDLPFC, and conversely, excitatory effects of the 4 × 1 MPFC montage were rather restricted to the MPFC (Fig. 4 and Supplementary Fig. 5). However, EF magnitudes were also smaller by around 25% for these montages (Fig. 4). It is worth noting that the 4 × 1 DLPFC protocol also produced relatively strong $EF_{normal+}$ and $EF_{normal-}$ currents in the superior-lateral and medial surface of the left MPFC, respectively. Moreover, the 4 × 1 MPFC montage yielded high $EF_{normal+}$ values in the bilateral DLPFC and ACC.

For these two protocols, model selection indicated that label, hemisphere and montage were the best predictors of $EF_{intensity}$ and EF_{normal} parameters, but again, group was not included in the winning model (Supplementary Tables 4 and 5). Second-best models incorporating group as predictor were inferior to winning models by at least 30 LOOIC units, indicating substantially weaker model fit.

4. Discussion

We used realistic head models built from structural MRI scans to analyze the spatial selectivity of tDCS protocols that are most promising for alleviating the symptoms of MDD (Brunoni et al., 2016a). EF strength was quantified in 20 regions of the frontal lobe to look for latent effects in areas distant from the electrodes. Importantly, by including a relatively large number of head models derived from patient data, our study also enabled assessing how MDD-related neuropathology influenced current flow in the brain.

4.1. Stimulation of lDLPFC might not be related to clinical efficacy

Our results conform with previous computational modeling studies in that bipolar protocols are suitable for the stimulation of the lDLPFC (Bai et al., 2014; Ho et al., 2014; Laakso et al., 2016; Seibt et al., 2015). In addition to the lDLPFC, our simulations showed that traditional bipolar montages have also induced strong EF_{normal} currents in the bilateral FEF. FEF stimulation might also be related to improved cognitive control, since this region is part of the dorsal frontoparietal network, implicated in top-down control of attentional selection of

[4] We also note that cortical "stripes" with opposite sign of the EF_{normal} resembled the folding pattern of the cortex, which again was indicative of the direction of current flow being restricted by cortical anatomy (by the spatial distribution of gyri and sulci).

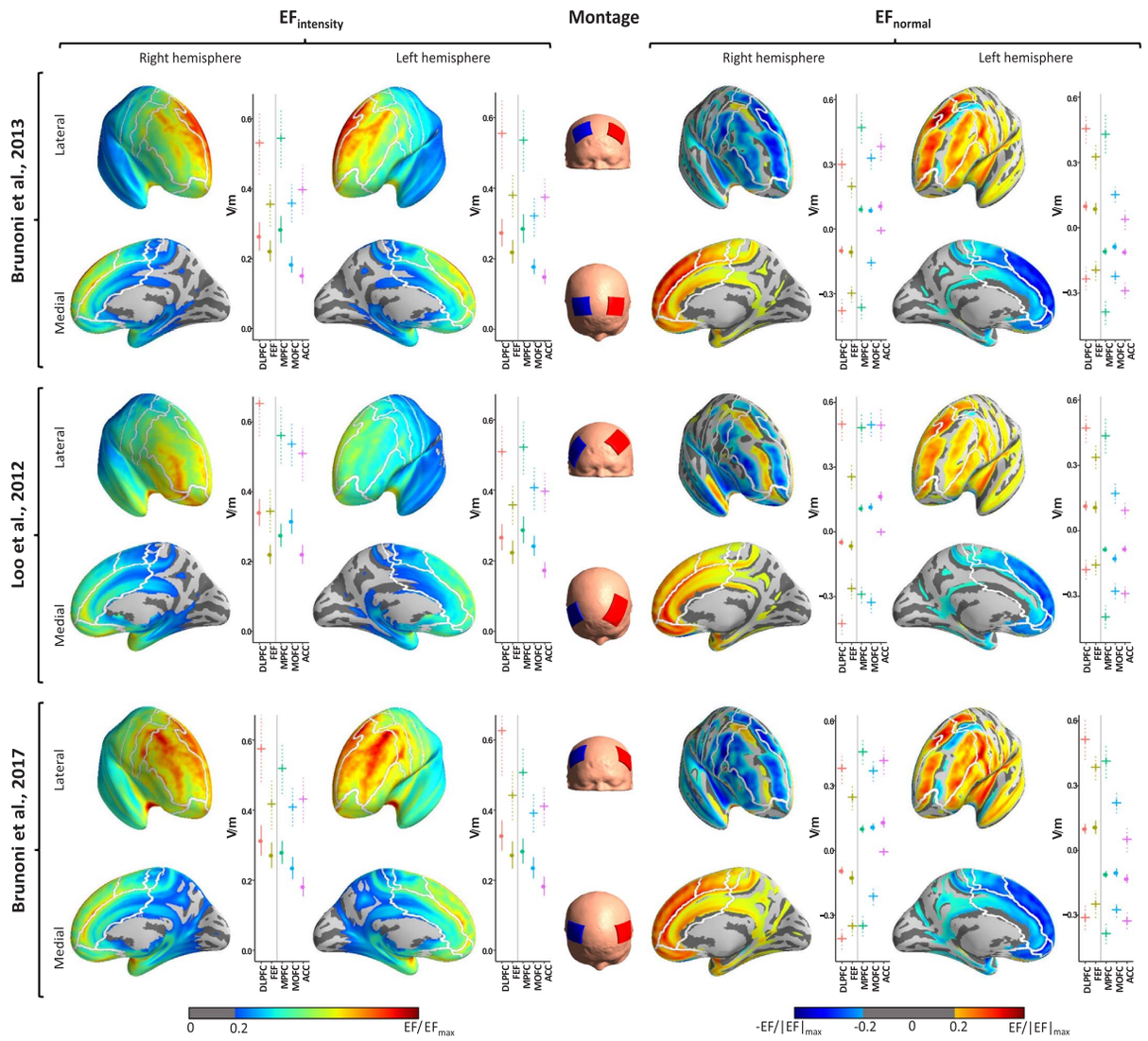

Fig. 2. Electric field distributions for the montages by Brunoni et al. (2013), Loo et al. (2012) and Brunoni et al. (2017), shown separately for total electric field strength ($EF_{intensity}$, left) and the electric field component normal to the cortical surface (EF_{normal}, right). Please note that dark blue represents low activity for $EF_{intensity}$, but strong outward-flowing currents for EF_{normal}. Dots and solid lines represent global means and standard deviations (across subjects), whereas plus signs and dotted bars correspond to mean and standard deviations for individual peaks ($EF_{intensity}$: maxima; EF_{normal}: maxima and minima), calculated separately for the five labels of interest (DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye field; MPFC: medial prefrontal cortex; MOFC: medial orbitofrontal cortex; ACC: anterior cingulate cortex). Scales were normalized to the highest absolute EF value ($|EF|_{max}$) in the entire cortex. Values below 0.2 ($EF_{intensity}$) or between − 0.2 and 0.2 (EF_{normal}) are not visualized.

environmental stimuli (Corbetta et al., 2008). Nevertheless, we argue that stimulation of lDLPFC/FEF might not be causally associated with symptom improvement in MDD. Firstly, although recent meta-analyses showed that anodal tDCS above the lDLPFC improves performance on tests of executive functioning and working memory in healthy adults and MDD patients (Brunoni et al., 2016b; Hill et al., 2016; Mancuso et al., 2016), the degree of cognitive improvement in MDD seems to be independent of the magnitude of clinical response, pointing towards independent mechanisms (Boggio et al., 2007; Brunoni et al., 2016b; Fregni et al., 2006b). The association between lDLPFC stimulation, cognitive enhancement and symptom alleviation is stronger for a more focal NIBS technique, repetitive transcranial magnetic stimulation (rTMS), since initial improvement in visuospatial working memory performance was pointed out as a significant predictor of subsequent clinical response (Hoy et al., 2012). Secondly, strongest EFs in the lDLPFC were detected in the montage by Loo et al. (2018) (Supplementary Fig. 4), despite the fact that to date this is the largest study with a negative outcome (i.e., comparable clinical effects for real vs. sham tDCS). Also, the focality-index for the lDLPFC in the montage by Brunoni et al. (2017) was relatively low, indicating that selective stimulation of this region is not absolutely necessary for symptom improvement. Finally, there is converging literature highlighting the MPFC, a region characterized by strong tDCS-induced EFs in our study, as one of the most promising novel targets for non-invasive stimulation in MDD (Downar and Daskalakis, 2013).

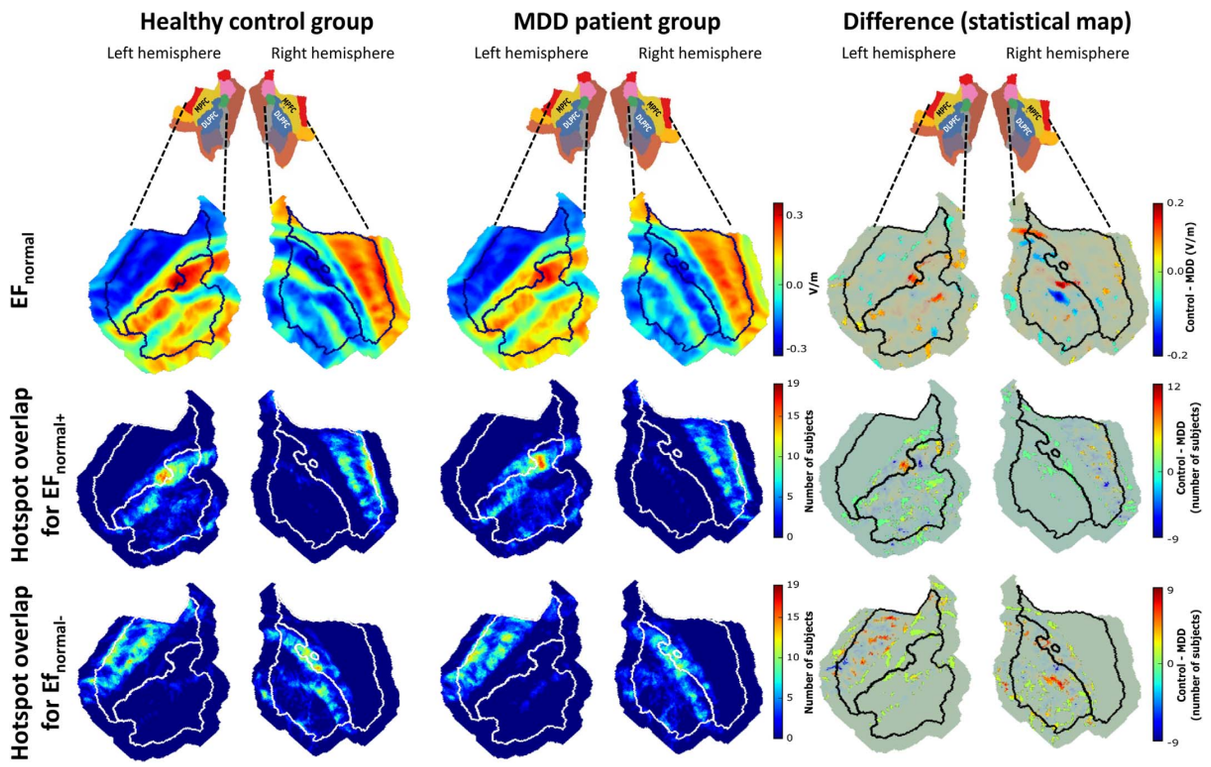

Fig. 3. Spatial distribution of currents normal to the cortical surface (EF_{normal}) for the montage by Brunoni et al. (2013) in the flattened bilateral dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (MPFC), plotted separately for healthy participants and MDD patients. Upper row: group mean EF_{normal} values calculated for each node separately. Statistical map shows nodes with control vs. patient EF_{normal} difference values belonging to the top 5% interval with respect to a nonparametric permutation test (with random assignment of participants to 2 groups repeated 1000 times). Middle and lower rows: spatial overlap of hotspots with EF values in the top 1% (for $EF_{normal+}$) or bottom 1% (for $EF_{normal-}$) range. Statistical maps show nodes with control vs. patient differences that fall within the top or bottom 2.5% intervals with respect to a nonparametric permutation test (1000 random assignments of participants to 2 groups). Red values indicate nodes with larger degree of hotspot overlap in the control group, whereas blue values depict nodes with substantially more hotspots within patients.

4.2. MPFC stimulation as a possible mechanism for clinical efficacy

Our most important finding concerns the strong stimulation of regions in the medial surface of the PFC (bilateral MPFC, ACC, MOFC) in every bipolar montage. At first glance, this result is not very surprising given the well-established poor spatial resolution of tDCS (Bikson et al., 2010b; Datta et al., 2009; Miranda et al., 2013; Saturnino et al., 2015), and similar effects were also noted by previous modeling and neuroimaging studies (Bai et al., 2014; Ho et al., 2014; Keeser et al., 2011; Laakso et al., 2016; Peña-Gómez et al., 2012; Seibt et al., 2015). Still, while neuroimaging studies have attributed distant effects to the stimulation of the lDLPFC and to the consequential perturbation of the intrinsic organization of complex brain networks (Deco et al., 2011), we show that even direct stimulation of the MPFC, ACC and MOFC is around the same magnitude as that of the lDLPFC. This raises the possibility that excitability changes in these regions contributed to the observed clinical effects of "DLPFC-targeting" bipolar tDCS protocols.

The MPFC has been implicated in downregulation of emotional reactions especially when participants used reappraisal strategies, a key element of cognitive therapy (Buhle et al., 2014; Disner et al., 2011; Etkin et al., 2015; Goldin et al., 2008; Kim and Hamann, 2007; Ochsner et al., 2004). Abnormal hemodynamic responses in MPFC have been consistently shown in MDD patients, associated with failures in both automatic and voluntary emotion regulation (Kaiser et al., 2015; Rive et al., 2013; Taylor et al., 2008). Crucially, the dorsal part of the MPFC (DMPFC, the area receiving strongest stimulation in our bipolar montages) has been highlighted as a unique region characterized by increased connectivity with three large-scaled networks (cognitive control network, default mode network, affective network) in MDD, and linked to symptoms such as impaired executive functioning, rumination, increased self-focus and emotional dysregulation (Sheline et al., 2010).

From another perspective, MDD is characterized by altered sensitivity to reward and punishment, which might underlie impaired value-based decision-making in patients, typically observed in reinforcement learning (RL) paradigms (Chase et al., 2010; Chen et al., 2015; Eshel and Roiser, 2010; Huys et al., 2013; Pizzagalli et al., 2005). The MPFC/ACC/MOFC play key roles in RL (Cavanagh and Frank, 2014; Silvetti et al., 2014), and interestingly, the DMPFC shows enhanced activity during probabilistic reversal learning after serotonin (5-HT) depletion in healthy volunteers, a phenomenon associated with elevated punishment sensitivity in these individuals (Evers et al., 2005). This is particularly relevant to the context of impaired RL in MDD, because serotoninergic dysfunction in patients has also been linked to maladaptive choices in the face of future losses (Dayan and Huys, 2008; Huys et al., 2016).

Taken together, medial PFC regions have been linked to MDD though several psychological phenomena (emotion regulation, value-based decision-making and RL) and neural substrates (brain networks, serotoninergic neurotransmission). It is therefore no wonder that by targeting the DMPFC with rTMS, recent studies achieved significant symptom reduction in MDD (Downar et al., 2014; Salomons et al., 2014; Schulze et al., 2016). Based on our simulations, we therefore argue that conventional bipolar tDCS protocols have inadvertently

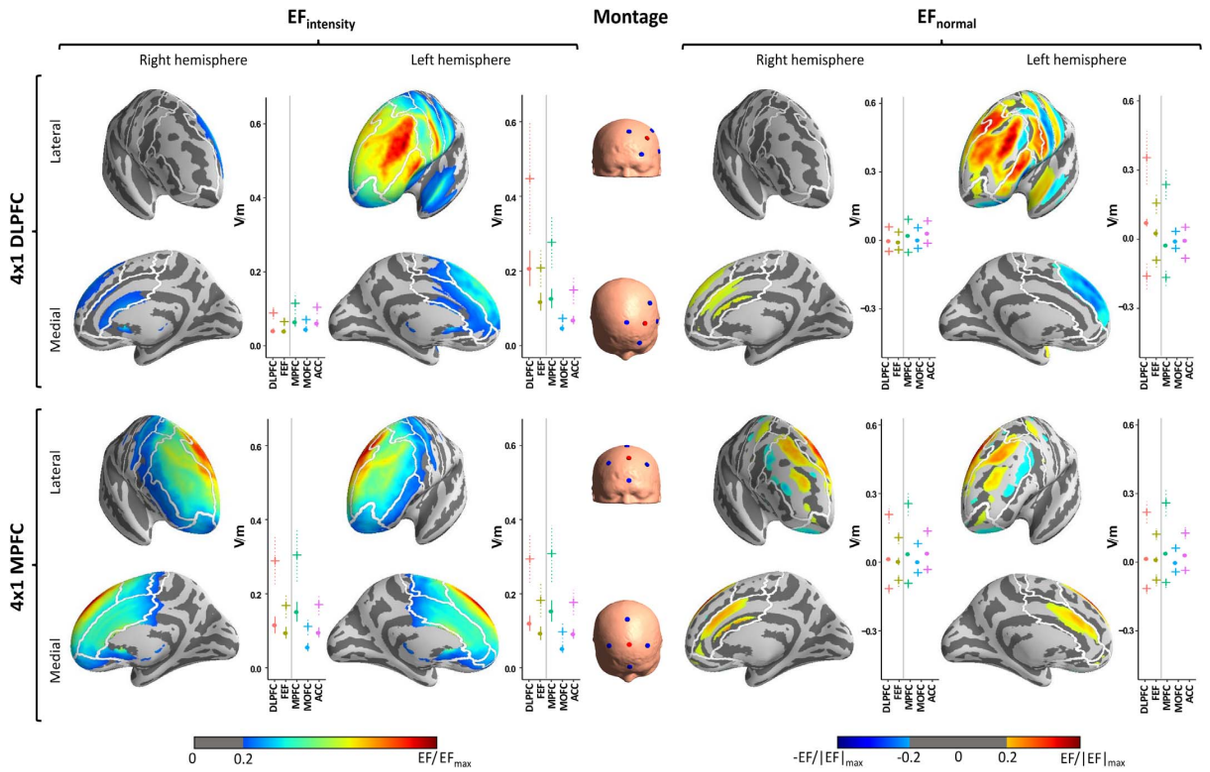

Fig. 4. Electric field distributions for the 4 × 1 montages, shown separately for total electric field strength ($EF_{intensity}$, left) and the electric field component normal to the cortical surface (EF_{normal}, right). Please note that dark blue represents low activity for $EF_{intensity}$, but strong outward-flowing currents for EF_{normal}. Dots and solid lines represent global means and standard deviations (across subjects), whereas plus signs and dotted bars correspond to mean and standard deviations for individual peaks ($EF_{intensity}$: maxima; EF_{normal}: maxima and minima), calculated separately for the five labels of interest (DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye field; MPFC: medial prefrontal cortex; MOFC: medial orbitofrontal cortex; ACC: anterior cingulate cortex). Scales were normalized to the highest absolute EF value ($|EF|_{max}$) in the entire cortex. Values below 0.2 ($EF_{intensity}$) or between − 0.2 and 0.2 (EF_{normal}) are not visualized.

stimulated medial PFC structures as well and modulated cognitive processes associated with this area.

Our simulations also indicated a strong hemispheric lateralization for the bipolar electrode arrangements both in lateral and medial regions. Regarding the DLPFC/FEF, the dominance of inward (positive) and outward (negative) currents in the left and right hemisphere respectively, fits well to the DLPFC left-lateralized hypoactivity/right-lateralized hyperactivity model of MDD (Grimm et al., 2008). In the case of MPFC/ACC/MOFC, however, the preponderance of negative (putatively inhibitory) currents in the left relative to positive (putatively excitatory) currents in the right hemisphere is more difficult to interpret. As noted earlier, connectivity patterns of the DMPFC implicated this region in disrupted coordination between three resting-state functional networks in MDD, albeit without any hemispheric lateralization (Sheline et al., 2010). In theory, increased functional coupling between the DMPFC and functional networks could be normalized by reducing neural excitability in this region, an effect that we observed in the left hemisphere only. Perhaps, left-lateralized inhibitory ($EF_{normal-}$) currents are more relevant for symptom improvement, as only the left (but not right) DMPFC was reported to show reduced resting-state metabolism in MDD patients responding to either pharmacotherapy or cognitive behavior therapy (Kennedy et al., 2007). The fact that activity in the subgenual ACC is increased in MDD, but normalized after successful invasive stimulation (Lozano et al., 2008; Mayberg et al., 2005) also highlights the left-lateralized inhibitory effect as a strong candidate for the clinically relevant outcome.

4.3. Bipolar montages induce different EF patterns in the frontal lobe

Montage was a strong predictor of the calculated EF distributions in the winning statistical models, implying that stimulation parameters influence current flow substantially even though the position of the anode is fixed. With respect to normalized cortical maps (Fig. 2 and Supplementary Fig. 3), the protocols by Loo et al. (2012, 2018) produced highly different EF patterns in both hemispheres, with less focal effects in DLPFC or MPFC (Supplementary Fig. 5). We believe that the more widespread and right-lateralized effect was caused by the inferior-lateral scalp position of the cathode (placed at position F8), allowing currents to flow through a large cortical area in this hemisphere. Interestingly, out of the seven tDCS protocols, only three were associated with significant real vs. sham clinical effects (Brunoni et al., 2013, 2017; Loo et al., 2012), meaning that protocols with almost indistinguishable EF patterns (e.g., Brunoni et al. (2013) vs. Blumberger et al. (2012)) do not necessarily yield similar clinical outcomes, and conversely, protocols that seem to differ in their neural mechanisms can still lead to symptom improvement, i.e., Brunoni et al. (2013, 2017) vs. Loo et al. (2012). This can be explained by the large variety of brain abnormalities associated with this disorder (Kempton et al., 2011; Price and Drevets, 2010; Schmaal et al., 2017), but perhaps even more importantly, with the different patient selection criteria in these studies. For example, while Blumberger et al. (2012) recruited patients with severe depression, including those resistant to electroconvulsive therapy, the studies by Brunoni et al. (2013, 2017) included patients with relatively low degree of refractoriness. Therefore, in addition to

careful stimulation parameter selection, other factors such as concomitant pharmacotherapy, symptom severity or treatment resistance can all contribute to the clinical efficacy of tDCS in MDD (Brunoni et al., 2016b).

4.4. TDCS effects are very similar in healthy individuals and MDD patients

With respect to between-group differences, we found largely similar EF maps for healthy individuals and MDD patients. This indicates that the cortical flow of currents is not substantially influenced by anatomical alterations associated with this disorder. Nevertheless, it is possible that more nuanced, systematic differences in the distribution of the EFs exist within the segmented cortical regions as our statistical model resolves only differences between regions. When looking at the spatial distribution of hotspots within the four regions of interest (bilateral DLPFC and MPFC), we identified subtle differences between the two groups, since some cortical nodes were more likely to receive strong stimulation in the control group, whereas others were more affected by tDCS in patients. At this point, it is not clear if this phenomenon would be related to any behavioral tDCS-related effect, because such detailed delineation of the functional properties of subregions within the human DLPFC or MPFC is not available. Yet, this observation implies that spatial characteristics of tDCS within target areas should be considered when assessing differences in stimulation effects between different groups of participants.

4.5. Implications for future studies

So far, we argued that studies using conventional bipolar tDCS protocols aimed at targeting the lDLPFC should take the potential effects of MPFC stimulation into account. However, due to strong EFs in the lDLPFC, it seems to be rather difficult to disentangle the degree to which DLPFC and MPFC stimulation contributes to clinical efficacy. We acknowledge that the arguments favoring the MPFC in terms of antidepressive effects are speculative at this point, but they also offer testable predictions for future research. We therefore propose comparing the effects of lDLPFC- and MPFC-targeting 4 × 1 protocols by assessing changes in behavioral performance with cognitive tasks associated with the activity of these regions (i.e., cognitive control tasks for DLPFC vs. RL paradigms for MPFC) (Chase et al., 2010; Pizzagalli et al., 2005; Salehinejad et al., 2017; Wolkenstein and Plewnia, 2013).

4.6. Limitations

The main limitation of our study is that it is purely based on computational simulations of head anatomy and current flow, and therefore, provides only a rough approximation of the neural effects that can be expected in a real clinical setting. Perhaps most importantly, our head models consisted of tissues with isotropic conductivities, which might be especially problematic for the white matter. Still, a recent study found that modeling white matter anisotropy primarily influenced current density in deeper structures, while leaving superficial gray matter targets relatively unaffected (Wagner et al., 2014).

Our models of EF distribution in the cortex are static as they do not account for the temporal dynamics of stimulation effects. TDCS-associated currents were shown to influence the cerebral vasculature in a polarity-dependent manner (Giorli et al., 2015), that can also impact neural excitability and change tissue impedance during tDCS sessions. However, to the best of our knowledge, such effects have not yet been incorporated into any computational model of brain stimulation thus far.

Another limitation is that our dataset did not enable assessing the relationship between EF strength in target regions (i.e., in the lDLPFC and in bilateral MPFC) and the magnitude of clinical response to tDCS in patients. Since standard deviations for both mean and peak EF values were rather large in these cortical labels (Figs. 2, 4 and Supplementary Fig. 3), we can assume that between-patient variability in the degree of tDCS-related symptom improvement is at least partially related to stimulation strength in target regions (in addition to other factors such as refractoriness to previous therapeutic interventions). We think that this issue can be directly assessed in the future by simultaneously performing patient stimulation and EF modeling in the same cohort of participants.

5. Conclusions

TDCS is a promising tool for alleviating symptoms of several neurological and psychiatric brain disorders (Antal et al., 2017; Filmer et al., 2014; Hill et al., 2016). However, its mechanism of action is not well understood, and the considerably large number of negative studies might be related to non-optimal stimulation protocols (Tremblay et al., 2014). Our results underline the utility of computational modeling for elucidating the neural underpinnings of tDCS and uncovering potentially hidden effects (Datta et al., 2009; Miniussi et al., 2013; Miranda et al., 2013; Opitz et al., 2015). By using structural scans of patients, it is now possible to simulate the effects of NIBS on individual head models. This approach might enable the development of personalized interventional protocols, leading to more precise cortical targeting and an increased potential for achieving clinical efficacy.

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Data availability statement

All analysis scripts, individual and group-averaged anatomical cortical surfaces with PFC labels and montage-specific $EF_{intensity}$ and EF_{normal} cortical maps are available for download at https://osf.io/u5brq/.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2018.02.077.

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Effects of transcranial direct current stimulation for treating depression: A modeling study

Supplementary Material

Supplementary Methods

Manual procedures

Our data analytic workflow consisted of four manual procedures.

1) As the very first step, we inspected scans of all participants, and manually removed signals corresponding to the MRI marker placed on the forehead of each subject using FreeSurfer.
2) We inspected and manually corrected results of the automated tissue segmentation with FreeSurfer (done by G.Cs., verified by O.P.). Manual corrections were primarily restricted to the skull-CSF boundary, but in some cases also involved the skin-skull interface. The resulting adjusted masks were used for the creation of head models.
3) Following automated PFC parcellation, ACC labels did not consistently encompass the subgenual region (sgACC), an area implicated in MDD (Mayberg et al., 2005). Therefore, we manually adjusted ACC labels for each individual and hemisphere using FreeSurfer to make sure they include the sgACC.
4) In order to define the scalp location of tDCS electrodes individually, we manually defined coordinates corresponding to four reference locations (nasion, inion, left and right pre-auricular points), and run a modified version of a published script (Huang et al., 2013) to obtain the center coordinates of electrodes.

TDCS electrode parameters

For the montage used by Brunoni and colleagues (Brunoni et al., 2013), medial margins of both electrodes were oriented parallel to the midsagittal plane. Orientations of 5 x 7 cm electrodes were adjusted after personal communication with the authors (Bennabi et al., 2015; Blumberger et al., 2012; Loo et al., 2010, 2012; Palm et al., 2012). For the montages used by Bennabi et al. (2015) and Palm et al. (2012), longer edges of both electrodes were oriented perpendicular to the midsagittal plane. For the montage by Blumberger et al. (2012), longer edges of both electrodes were oriented parallel to the midsagittal plane. In the study by Brunoni et al. (2017), electrodes were placed according to the Omni-Lateral Electrode (OLE) System (Brunoni et al., 2017; Seibt et al., 2015). In this protocol, we determined the midpoint between electrodes T7 and T8, and placed a vector at that position, pointing at the inion. Next, we rotated this vector anteriorly by 165° along the midsagittal plane (defined by the nasion-Cz-inion scalp locations) and determined its scalp projection (‘frontal midsagittal position’; FMP), which was used for calculating the centers of the tDCS electrodes on the scalp surface. This was done by rotating the vector pointing at FMP along the T7-FMP-T8 plane laterally to the extent that the electrode centers would be positioned 7.5 cm laterally from the FMP along the scalp (assuming that the head has a spherical shape). This way, the distance between the superior margins of both tDCS electrodes was 10 cm (with electrode size of 5x5 cm), as described by the OLE protocol. Electrodes were oriented so that superior electrode margins were perpendicular to the T7-FMP-T8 plane. For the montages used by Loo and colleagues (Loo et al., 2010, 2012, 2018), the longer edge of the anode was oriented towards the nose (with an angle of approximately 45° to the midsagittal plane), whereas the longer edge of the cathode was oriented perpendicular to the line corresponding to the right eyebrow.

For bipolar montages, electrode thickness was always set to 1 mm; sponge pocket thickness was 2.5 mm. We positioned circular connectors (diameter: 0.5 cm) at the middle of the electrode pads. For the 4x1 montages, electrodes with a diameter of 1.2 cm and thickness of 1 mm were used, with the addition of a gel layer (thickness: 2.5 mm) between the electrode-skin surface.

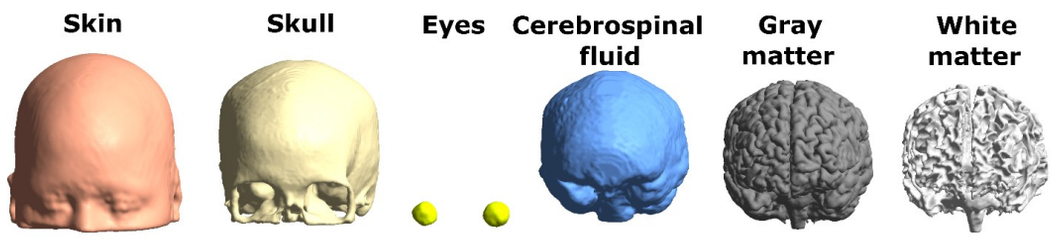
Data analytic strategy

All reported models were fitted using Hamiltonian Monte-Carlo (HMC) techniques. We sampled from the joint posterior distribution of the parameters given the model using the HMC algorithms implemented in the Stan software (Carpenter et al., 2017; Hoffman and Gelman, 2014). All fits used eight parallel chains, each with a warm-up period of 1,000 samples. Chains were initialized at random values and we sampled 1,000 samples from each of the converged chains. We used no thinning as this was not deemed necessary by visual inspection of the chains and autocorrelation statistics. Resulting samples for each individual variable were visually inspected for convergence to ensure good mixing behaviour. We also applied the Gelman-Rubin diagnostic (Gelman and Rubin, 1992) and ensured that all reported results had $\hat{R} \leq 1.05$.

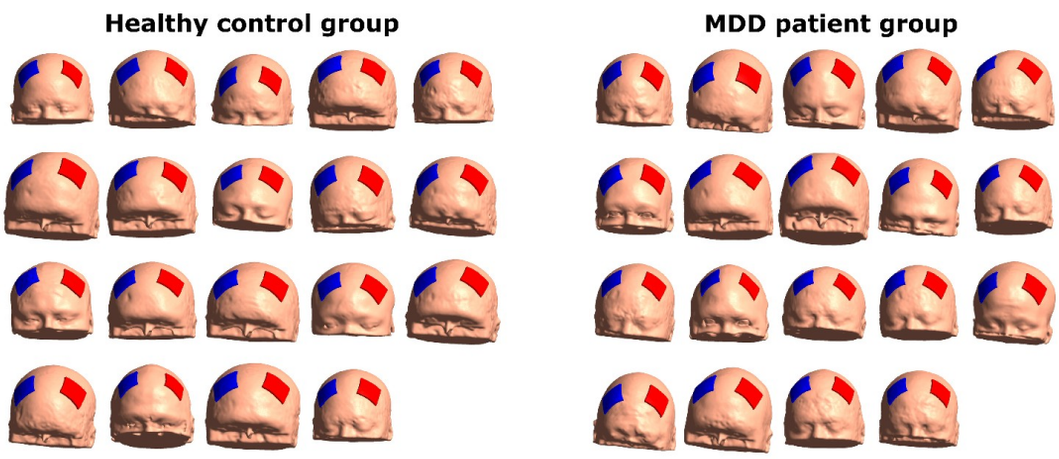
Supplementary Results

Comparison of spatial focality

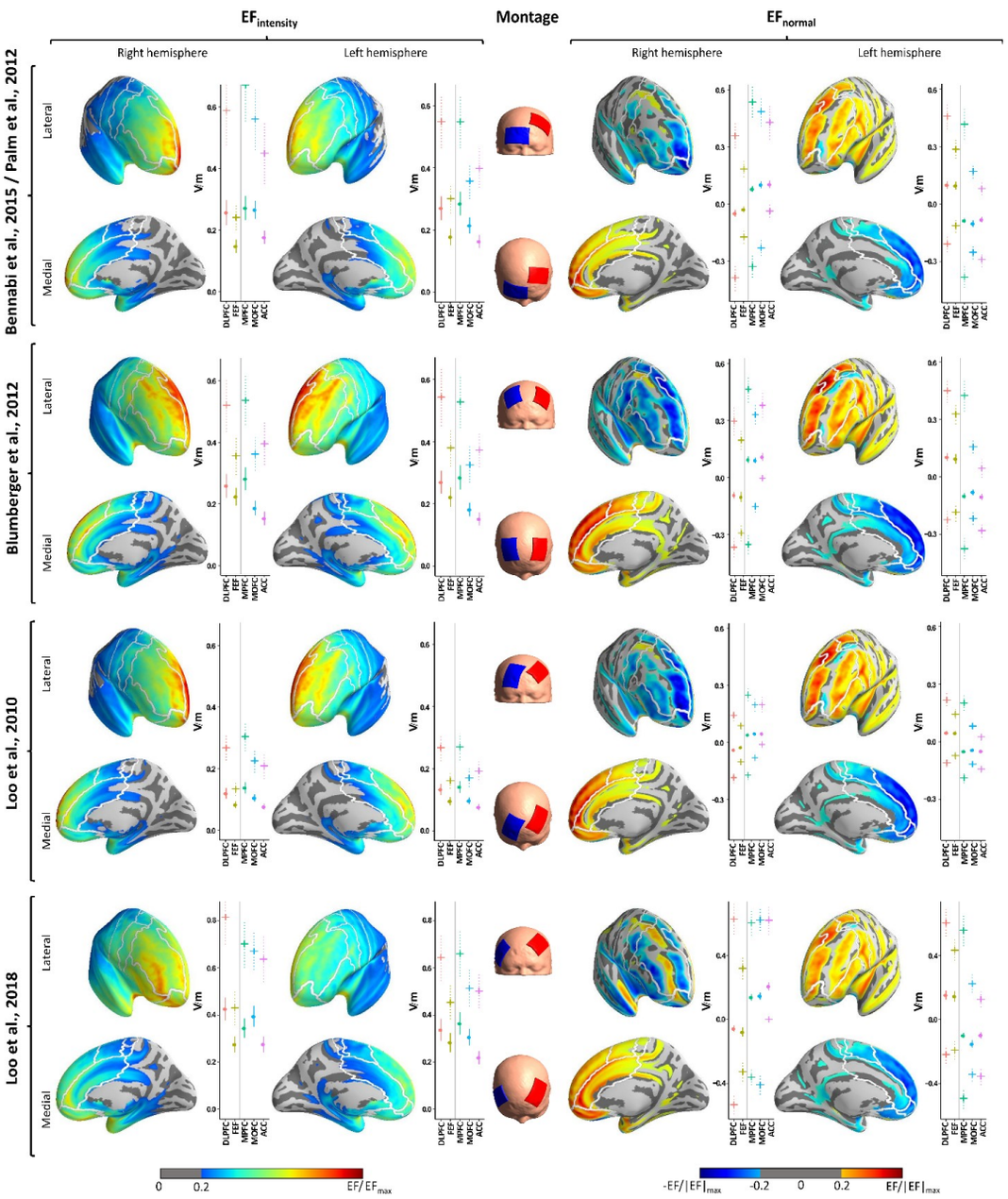
As our last analysis, we compared focality-indices (FI) calculated for each bipolar and 4x1 montage separately (Supplementary Figure 5). Given that bipolar montages induced strong EFs in the bilateral MPFC, we compared montages for their ability to selectively induce inward ($EF_{normal+}$) or outward ($EF_{normal-}$) directed fields in either the lDLPFC or the MPFC (FI_{lDLPFC}, FI_{MPFC}, respectively). All bipolar montages exerted similarly selective excitatory effects in the lDLPFC, except for the Loo et al. (2012, 2018) and Brunoni et al. (2018) protocols, yielding lower FI_{lDLPFC} values, probably due to the relatively large number of hotspots in the lateral aspect of the right hemisphere and inferior regions of the left hemisphere. Additionally, $EF_{normal-}$ values for FI_{lDLPFC} were very close to zero, suggesting the predominance of inward-flowing currents in this region. In accordance with our previous analyses, the FI_{MPFC} was very high in bilateral MPFC, both for anode-like and cathode-like effects, but again, the Loo et al. (2012, 2018) and Brunoni et al. (2018) montages were characterized by lower values.



Supplementary Figure 1. The six tissue compartments of the head models.

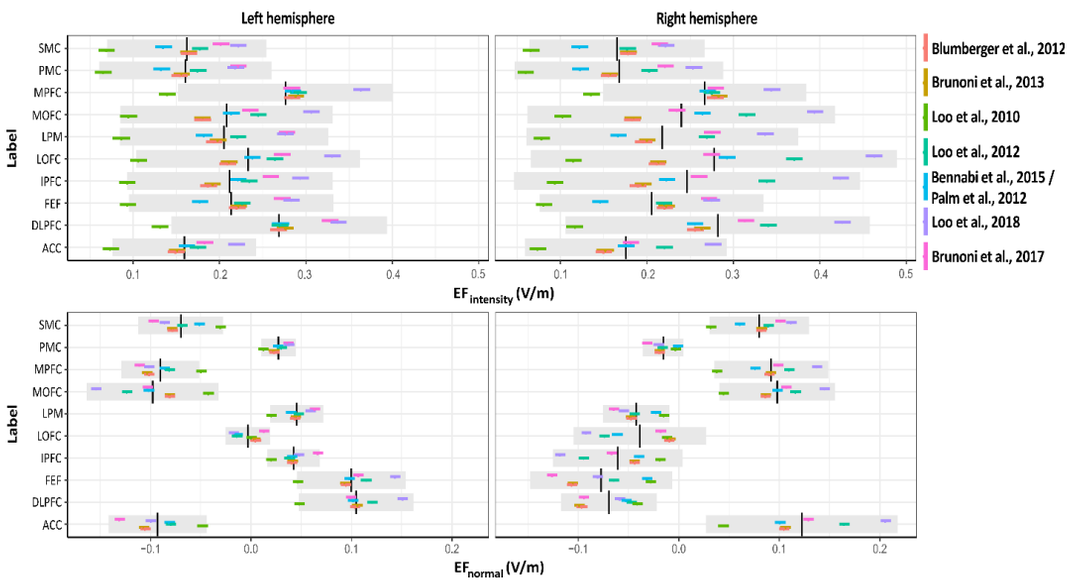


Supplementary Figure 2. The 38 head models with electrodes placed according to the protocol by Brunoni et al. (2013).

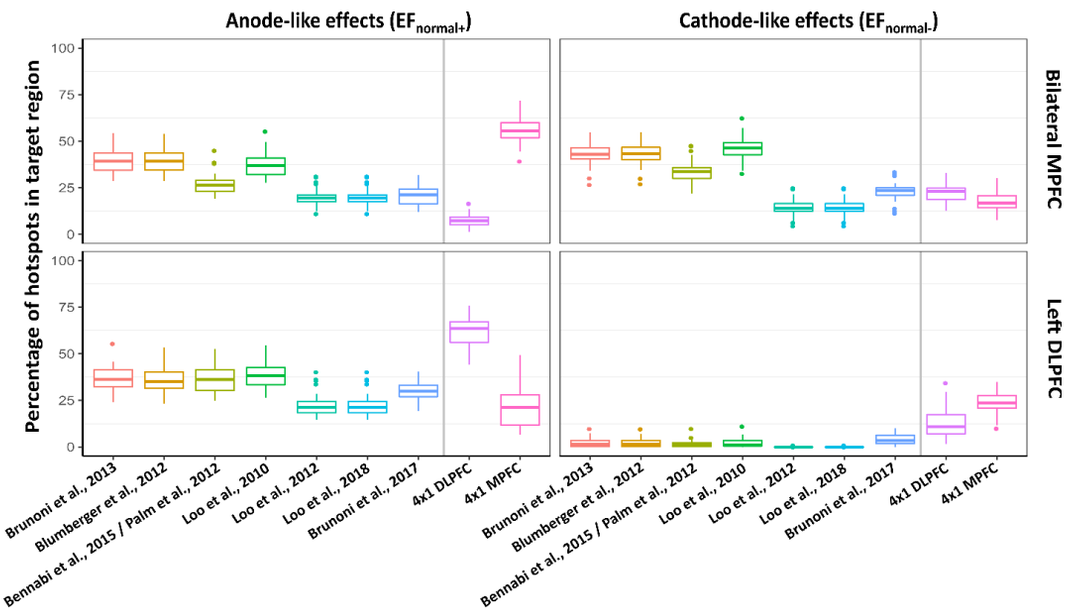


Supplementary Figure 3. Electric field distributions for the Bennabi et al. (2015)/Palm et al. (2012), Blumberger et al. (2012), Loo et al. (2010) and Loo et al. (2018) montages, shown separately for total electric field strength ($EF_{intensity}$, left) and the electric field component normal

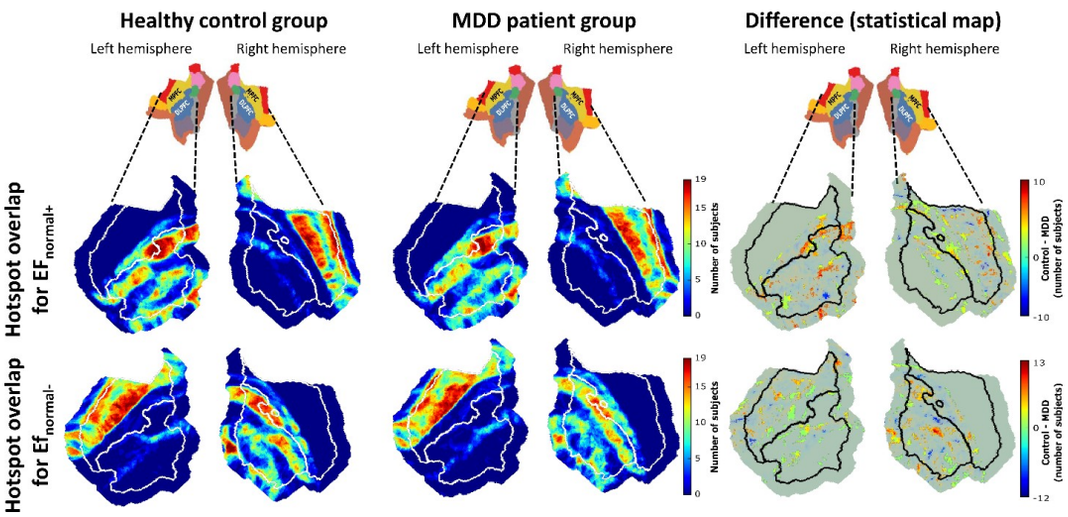
to the cortical surface (EF_{normal}, right). Please note that dark blue represents low activity for $EF_{intensity}$, but strong outward-flowing currents for EF_{normal}. Dots and solid lines represent global means and standard deviations (across subjects), whereas plus signs and dotted bars correspond to mean and standard deviations for individual peaks ($EF_{intensity}$: maxima; EF_{normal}: maxima and minima), calculated separately for the five labels of interest (DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye field; MPFC: medial prefrontal cortex; MOFC: medial orbitofrontal cortex; ACC: anterior cingulate cortex). Scales were normalized to the highest absolute EF value ($|EF|_{max}$) in the entire cortex. Values below 0.2 ($EF_{intensity}$) or between -0.2 and 0.2 (EF_{normal}) are not visualized.



Supplementary Figure 4. Distribution of total electric field strength ($EF_{intensity}$) and currents normal to the cortical surface (EF_{normal}) across the seven bipolar montages, 10 cortical labels (SMC: supplementary motor cortex; PMC: primary motor cortex; MPFC: medial prefrontal cortex; MOFC: medial orbitofrontal cortex; LPM: lateral premotor cortex; LOFC: lateral orbitofrontal cortex; IPFC: inferior prefrontal cortex; FEF: frontal eye field; DLPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortex) and two hemispheres. Dots and solid bars represent estimated posterior means and 95% highest-density intervals. Vertical black bars represent means of all montages, gray stripes correspond to 2 * standard deviation.



Supplementary Figure 5. Focality-indices (percentage of top 1% nodes in target region) for the bilateral medial prefrontal cortex (MPFC) and left dorsolateral prefrontal cortex (DLPFC), calculated separately for positive and negative EF_{normal} values for all montages. Horizontal lines within boxes represent median values, whereas lower and upper box hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentiles). Lengths of upper/lower whiskers extend to the largest/smallest values that do not exceed 1.5* the inter-quartile range; data beyond the end of whiskers are outliers.



Supplementary Figure 6. Spatial distribution of hotspot (strongest 5% EF_{normal} values) overlap for the Brunoni et al. (2013) montage in the flattened bilateral dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (MPFC), plotted separately for healthy participants and MDD patients (upper row: $EF_{normal+}$; lower row: $EF_{normal-}$). Statistical maps show nodes with control vs. patient differences that fall within the top or bottom 2.5% intervals with respect to a nonparametric permutation test (1,000 random assignments of participants in 2 groups). Red values indicate nodes with larger degree of hotspot overlap in the control group, whereas blue values depict nodes with substantially more hotspots within patients.

Supplementary Table 1. Tissue conductivities used for modeling electric field distributions

Tissue type	Conductivity (S/m)
Electrode rubber	0.1
Electrode sponge/gel	1.0
Skin	0.465
Eyeballs	0.5
Skull	0.01
Cerebrospinal fluid	1.654
Gray matter	0.275
White matter	0.126

Supplementary Table 2. Model selection for $EF_{intensity}$ values for the bipolar montages

Model ranking	Free parameter				LOOIC
	Hemisphere	Label	Montage	Group	
1	X	X	X	-	-27,407.3
2	X	X	X	X	-27,260.2
3	-	X	X	-	-23,368.9
4	-	X	X	X	-23,282.0
5	X	-	X	-	-16,502.3
6	X	-	X	X	-16,482.8
7	-	-	X	-	-16,144.1
8	-	-	X	X	-16,139.1
9	X	X	-	-	-13,034.4
10	X	X	-	X	-13,000.2
11	-	X	-	-	-12,922.2
12	-	X	-	X	-12,906.6
13	X	-	-	-	-11,504.4
14	X	-	-	X	-11,502.7
15	-	-	-	X	-11,463.7
16	-	-	-	-	-11,463.4

Supplementary Table 3. Model selection for EF_{normal} values for the bipolar montages

Model ranking	Free parameter				LOOIC
	Hemisphere	Label	Montage	Group	
1	X	X	X	-	-28,513.3
2	X	X	X	X	-28,449.0
3	X	X	-	X	-22,024.0
4	X	X	-	-	-22,009.2
5	-	X	X	-	-11,695.6
6	-	X	-	-	-11,660.8
7	-	X	-	X	-11,641.4
8	X	-	-	-	-11,612.3
9	X	-	-	X	-11,608.5
10	X	-	X	-	-11,601.4
11	-	-	-	-	-11,584.1
12	-	-	-	X	-11,582.3
13	-	-	X	-	-11,582.0
14	X	-	X	X	-11,574.4
15	-	-	X	X	-11,568.1
16	-	X	X	X	-11,555.6

Supplementary Table 4. Model selection for $EF_{intensity}$ values for the 4x1 montages

Model ranking	**Free parameter**				**LOOIC**
	Hemisphere	Label	Montage	Group	
1	X	X	X	-	-12,011.1
2	X	X	X	X	-11,941.5
3	X	X	-	-	-11,227.6
4	X	X	-	X	-11,191.9
5	-	X	X	-	-10,991.1
6	-	X	X	X	-10,953.4
7	-	X	-	-	-10,801.2
8	X	-	X	-	-10,790.6
9	X	-	X	X	-10,785.6
10	-	X	-	X	-10,783.2
11	X	-	-	-	-10,530.1
12	X	-	-	X	-10,528.4
13	-	-	X	-	-10,320.9
14	-	-	-	-	-10,319.0
15	-	-	X	X	-10,318.9
16	-	-	-	X	-10,318.8

Supplementary Table 5. Model selection for EF_{normal} values for the 4x1 montages

Model ranking	**Free parameter**				**LOOIC**
	Hemisphere	Label	Montage	Group	
1	X	X	X	-	-10,732.4
2	X	X	X	X	-10,697.0
3	X	X	-	-	-8,796.3
4	X	X	-	X	-8,767.1
5	-	X	X	-	-8,637.1
6	-	X	X	X	-8,602.1
7	-	X	-	-	-8,241.7
8	-	X	-	X	-8,225.2
9	-	-	X	-	-7,519.5
10	-	-	-	-	-7,518.1
11	X	-	-	-	-7,517.2
12	X	-	X	-	-7,516.6
13	-	-	-	X	-7,516.5
14	-	-	X	X	-7,515.7
15	X	-	-	X	-7,513.9
16	X	-	X	X	-7,509.2

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Paper III

The interplay between cognitive control, behavioral variability and mind wandering: Insights from a HD-tDCS study

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ABSTRACT

While the involvement of executive processes in mind wandering is largely undebated, their exact relationship is subject to an ongoing debate and rarely studied dynamically within-subject. Several brain-stimulation studies using transcranial direct current stimulation (tDCS) have attempted to modulate mind-wandering propensity by stimulating the left dorsolateral prefrontal cortex (DLPFC) which is an important hub in the prefrontal control network. In a series of three studies testing a total of $N = 100$ participants, we develop a novel task that allows to study the dynamic interplay of mind wandering, behavioural varibility and the flexible recruitment of executive resources as indexed by the randomness (entropy) of movement sequences generated by our participants. We consistently find that behavioural variability is increased and randomness is decreased during periods of mind wandering. Interestingly, we also find that behavioural variability interacts with the entropy-MW effect, opening up the possibility to detect distinct states of off-focus cognition. When applying a HD-tDCS brain stimulation montage to the left DLPFC, we find that propensity to mind wander is reduced relative to a group receiving sham stimulation.

Keywords: mind wandering, tDCS, attention, task-unrelated thought, behavioural variability, randomness, approximate entropy

1 Introduction

We spend a surprising amount of our daily lives thinking about things that are unrelated to what we are currently doing (Killingsworth & Gilbert, 2010), a state that has been characterized as mind wandering (MW). For example, we might be internally planning our next renovation project even as we are washing the dishes or reflect on a scientific problem while driving our car into the garage. Not paying attention to an ongoing task can have severe consequences and can result in accidents, e.g., in aviation (Casner & Schooler, 2014) or driving (Yanko & Spalek, 2014; Baldwin et al., 2017). In learning situations, excessive MW can negatively impact academic achievment in the classroom (Unsworth & McMillan, 2017). Furthermore, mind wandering appears to be related to mood (Ottaviani et al., 2015) and has also been related to psychiatric conditions such as depression (Hoffmann, Banzhaf, Kanske, Bermpohl, & Singer, 2016) and ADHD (Seli, Smallwood, Cheyne, & Smilek, 2015; Van den Driessche et al., 2017). In most everyday-situations, consequences of mind wandering are benign and are typically studied in situations that require sustained attention (Smallwood & Schooler, 2006).

It is, in general, difficult to establish a proper definition of mind wandering, a fact that is reflected in the multitude of different terms, such as “task-unrelated thoughts”, “mind wandering” or “spontaneous cognition”, used to study related phenomena (Callard, Smallwood, Golchert, & Margulies, 2013). One recent attempt to unify existing research has proposed a family-resemblances view of mind wandering (Seli et al., 2018), emphasizing that the definition of mind wandering may involve looking for similarities between the diverging operationalizations used in the literature and accepting that there may not be a single characteristic unifying all of them. However, this view has been criticised because of its all-encompassing and hence not selective viewpoint (Christoff et al., 2018). Other attempts establishing a working definition of MW have therefore attempted to delineate mind wandering from other types of spontaneous cognition, such as rumination or dreaming (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016) or to provide distinctions based on the underlying brain mechanisms (Mittner, Hawkins, Boekel, & Forstmann, 2016).

Furthermore, distinguishing between intentional (deliberate) and unintentional (spontaneous) mind wandering has been found to be important because these types of MW have different behavioural consequences and psychological and neural profiles (Seli, Risko, Smilek, & Schacter, 2016). In addition, a variety of factors have been found to be relevant for studying MW

including cognitive factors (e.g., working memory capacity; Kane & McVay, 2012), personal dispositions (e.g., neuroticism; Robison, Gath, & Unsworth, 2017) and context (e.g., motivation and affect) and efforts have been made to integrate them in a multi-faceted approach (Robison, Miller, & Unsworth, 2020). In the present study, we are less interested in studying between-subject individual differences but rather, we focus on the dynamical fluctuations of attention and executive control within a single experimental session. Based on experimental evidence that links MW to poor performance in tasks requiring executive control (Smallwood et al., 2004), it has been theorized that mind wandering is tightly linked to (the loss off) executive control (Smallwood & Schooler, 2006; McVay & Kane, 2010) even though the exact nature of this relationship is still unclear.

Hence, recent research has begun looking into the possibility of actively manipulating MW by means of non-invasively stimulating brain areas involved in executive control (Axelrod, Rees, Lavidor, & Bar, 2015; Chaieb, Antal, Derner, Leszczyński, & Fell, 2019). Most of these studies have focused on the dorsolateral prefrontal cortex (DLPFC; usually in the left hemisphere) which is one of the core brain regions consistently linked to executive functioning and hence highly likely to be related to maintaining sustained attention and avoiding mind wandering. Due to its extended size and accessible location near the surface of the brain, the DLPFC is a good target for non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS). This non-invasive brain stimulation method operates by injecting low-intensity currents (typically 1 or 2 mA resulting in electric fields of about 0.5 – 0.8 mV/mm; Opitz et al., 2016; Huang et al., 2017) into the brain through electrodes attached to the scalp. The tDCS method is safe with little adverse effects (Antal et al., 2017) and is typically assumed to operate by changing the resting membrane potential of pyramidal neurons perpendicular to the cortical surface (Filmer, Dux, & Mattingley, 2014). Importantly, the effect of tDCS is assumed to be polarity dependent: While anodal (inward-flowing) currents are supposed to elevate the neural resting membrane potential and hence result in higher excitabiliy of the neurons, cathodal (outward-flowing) currents are believed to have the opposite effect.

A multitude of tDCS studies has reported positive effects on many cognitive functions including attention (Coffman, Trumbo, & Clark, 2012), working memory (Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011) and language (Meinzer et al., 2014). However, different studies show little consistency in terms of the directionality of the effects and it has been questioned whether and to what extent there is sufficient evidence that tDCS affects cognitive functions at all (Horvath, Forte, & Carter, 2015; Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016). As a consequence, high-powered and pre-registered studies are gaining popularity in the tDCS literature (Minarik et al., 2016; Boayue et al., 2019; Filmer, Griffin, & Dux, 2019) because of their stronger potential to establish replicable results.

As mentioned above, in the field of mind wandering, a range of brain-stimulation studies attempted to non-invasively modulate mind-wandering propensity using transcranial direct current stimulation (tDCS) of the DLPFC (Chaieb et al., 2019). Initially, several studies reporting successful modulation of mind-wandering propensity using traditional non-focal, low-intensity tDCS over the DLPFC provided an optimistic outlook (Axelrod et al., 2015; Kajimura & Nomura, 2015; Kajimura, Kochiyama, Nakai, Abe, & Nomura, 2016). However, since then several studies have failed to replicate this effect (Boayue et al., 2019; Coulborn, Bowman, Miall, & Fernández-Espejo, 2020) including a large-scale, pre-registered direct replication study (Boayue et al., 2019), suggesting that the initial positive results that were based on very low sample-sizes might have been a false positive (but see Axelrod, Zhu, & Qiu, 2018; Csifcsák et al., 2019, for a discussion). Furthermore, those studies that did find an effect of tDCS on mind wandering were inconsistent with respect to the directionality of the effect, some finding an increase (e.g., Axelrod et al., 2015; Filmer et al., 2019) and some finding a decrease (e.g., Kajimura & Nomura, 2015; Chou, Hooley, & Camprodon, 2019) in mind-wandering propensity (see Chaieb et al., 2019, for a review).

In summary, there seems to be insufficient evidence for the effectiveness of tDCS over the DLPFC to modulate mind-wandering propensity. This failure to produce replicable results across studies may be due to various methodological reasons. First, the commonly used stimulation protocols may be ineffective. Second the universally applied SART task may not be optimal in studying the relationship between executive control and mind wandering because executive control is barely needed. And finally, the analytical methods applied in previous studies may be too coarse to allow localizing the possibly subtle effects of tDCS protocols. In the current study, we aim to improve all of these shortcomings to provide a more powerful experimental design for studying the relationship between executive functioning and mind wandering.

It has been questioned whether traditional stimulation montages using weak stimulation intensities (1mA is often used in the relevant studies; Axelrod et al., 2015; Boayue et al., 2019) provides strong and sufficiently focal fields to produce any neural effects at all (Huang et al., 2017). While we are not suggesting that commonly used tDCS protocols are entirely ineffective, it seems clear that higher electric fields are desirable in general to produce more tangible neural and behavioural effects (Vöröslakos et al., 2018). So far, no study has used a high-definition tDCS (HD-tDCS; Edwards et al., 2013) stimulation setup over the prefrontal cortex in a mind-wandering context despite its strong potential for increasing the focality of the stimulation (Datta et al., 2009; Dmochowski, Datta, Bikson, Su, & Parra, 2011; Boayue et al., 2019). HD-tDCS setups use multiple, smaller-sized electrodes positioned in strategic locations on the scalp, thereby shaping the electric field to more focally stimulate the target-region. Targeting the DLPFC, we implemented a ring-shaped 4-by-1 HD-tDCS stimulation protocol (Dmochowski et al., 2011; Villamar et al., 2013; Csifcsák, Boayue, Puonti, Thielscher, & Mittner, 2018) centered over

prefrontal electrode F3 that greatly increases both the focality and strength of the elicited electric field in the DLPFC (see Methods).

Furthermore, while the sustained attention to response task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) is omnipresent in the literature on mind wandering and has certainly produced many important insights, it is unclear whether this task is best-suited to study the relationship between executive control and mind wandering. Due to the low occurrence of target stimuli in this task (target-rates vary but are as low as 1 in 40 trials in the tDCS literature; Axelrod et al., 2018; Boayue et al., 2019), executive control is only rarely probed and cannot be tracked over the course of the experimental session. As a consequence, commission error rates (i.e., failed NoGo) are typically quite high indicating that employment of executive control may be low in general. Therefore, it is difficult to study the interaction of fluctuations in executive control and mind wandering in this task. Here we propose a novel, fast-paced paradigm that allows to study how executive control is employed over the course of the experiment at high temporal resolution. The task is based on the classical random-number generation task (RNGT; Baddeley, 1998) which is generally being used for measuring executive functioning. In a mind-wandering context, this task has been shown to be sensitive to attentional fluctuations (Teasdale et al., 1995). We combined this task with a standard finger-tapping procedure (similar to the metronome response task, MRT; Seli, Cheyne, & Smilek, 2013) where we asked our participants to rhythmically press one of two keys on the keyboard in a random sequence. This setup allows to investigate how behavioural variability is related to both executive functioning and mind wandering (Kucyi, Hove, Esterman, Hutchison, & Valera, 2017; Kucyi, Esterman, Riley, & Valera, 2016) and to study the relationship of these three variables dynamically over the course of the experimental session.

Finally, the effectiveness of tDCS stimulation on mind wandering is usually evaluated by comparing mean thought-probes across the entire experimental session between sham and active tDCS groups. As described in Boayue et al. (2019), this is problematic for three reasons: First, the ordinal thought-probe variable is treated as continuous which can be problematic (Liddell & Kruschke, 2018), second, information about within-subject variability is lost by the averaging process and thirdly, known influences on mind-wandering propensity are ignored (e.g., the well-established time-on-task effect; Thomson, Seli, Besner, & Smilek, 2014). Arguably, by explicitly modeling the ordinal data in a more realistic way, the statistical power for detecting the possibly subtle effect of tDCS on the outcome measures can be increased. For these reasons, analyzing thought-probes using Bayesian hiearchical ordered probit regression models is becoming more commonly used (Filmer et al., 2019; Boayue et al., 2019).

1.1 Overview

This paper develops a novel experimental paradigm that is designed to allow the tracking of attentional fluctuations at short time-scales and uses it to investigate the effectiveness of HD-tDCS on manipulating mind-wandering propensity. The purpose of study 1 was to establish a link between the randomness of the left-right finger-tapping sequences generated in our task and the use of executive resources. In addition, the parameters of the task, in particular the inter-stimulus-interval (ISI) and the parameters of our used measure of randomness, approximate entropy (Steve Pincus & Kalman, 1997), were optimized. In study 2, we introduced mind-wandering thought-probes into our task that were used to establish a link between behavioural variability, randomness and attentional fluctuations. Finally, in study 3, we investigated whether an optimized HD-tDCS brain-stimulation intervention over the DLPFC could change the degree of mind wandering experienced by our subjects.

2 General Methods

2.1 Participants

Participants were recruited at the university of Tromsø through standard procedures including fliers around campus and entries in student groups and other interest groups on social media networks. All studies were approved by the ethics committee at the institute for psychology at the university of Tromsø.

2.2 Finger-Tapping Random-Sequence Generation Task (FT-RSGT)

All studies used a novel Finger-Tapping Random-Sequence Generation Task (FT-RSGT). This task is a combination of a modified version of the random number generation task (Baddeley, 1998; Towse, 1998) and a finger-tapping task (Seli et al., 2013; Kucyi et al., 2017): It consists of a combination of rhythmic finger-tapping in response to an ongoing metronome and the generation of random sequences by pressing the two available response-buttons in a random sequence. The idea behind this task is as follows: Generating random sequences is a task that draws heavy on executive resources. As a consequence, we expect the randomness of the generated sequence to be related to the amount of executive resources diverted to it. In the context of mind wandering, this has been confirmed by the finding that sequences generated while mind wandering are typically less random (Teasdale et al., 1995). Furthermore, behavioural variability as measured by the deviation of the taps from the on-going metronome in finger-tapping studies has also been found to be an indicator of mind wandering (Seli et al., 2013; Kucyi et al., 2017) with behaviour becoming more variable when attention is drawn away from the task. By combining both measures in a

single experiment, the dynamic interplay of behavioral variability and executive control can be studied and related to mind wandering as measured by thought-probes.

Concretely, participants were instructed to press two buttons with their left or right index finger in a random order. In order to establish a comparable level of understanding of the meaning of "randomness" when applied to a sequence of button-presses, participants were carefully instructed using the flipping of a coin as an example. They were told that their button-presses should resemble the result of repeatedly flipping a fair coin and that, therefore, each of the two buttons should have equal probability of being pressed in each trial (see online materials). After receiving the explanation, subjects had to fill out a quiz asking them about various aspects of the procedure and they were allowed to continue only after correctly answering all questions.

Participants also had to match every single button press as accurately as possible to the occurrence of a rhythmic tone (440 Hz presented for a duration of 75 ms) that was presented to them via high-quality stereo headphones (Multi Function Headset 210, Trust International B.V., Dordrecht, Netherlands). The inter-stimulus interval (ISI) of the metronome tones was optimized in study 1. Finally, participants were randomly interrupted by thought-probes asking about the current state of their attentional focus ranging from being on-task to mind wandering (studies 2 and 3).

2.2.1 Measuring Randomness

Measuring randomness of a finite sequence is a non-trivial problem as, strictly speaking, entropy for a finite sequence is not defined. Rather, entropy is defined for a system that can generate sequences and any given generalization can be seen as stemming from an infinite number of generating systems. As a consequence, it is mathematically impossible to infer the entropy of a system from a finite sequence. As an example, consider a perfectly random process that flips a fair coin in every trial and outputs a 0 for heads and a 1 for tails. Given that perfectly random system, the sequence [1,0,1,0,1,0,1,0,1,0] that contains an obvious structure of alternating heads and tails has the exact same probability, $P = 0.5^{10}$, as, for example, this sequence [1,0,0,1,0,1,1,1,0,1]. In fact, any sequence of exactly ten items has that exact same probability. However, there are fewer sequences that have such obvious patterns and more sequences that look more random and hence, the chances to get a sequence with few repetitive patterns is relatively high if the system is indeed producing random sequences.

To circumvent this problem, we use a statistic called approximate entropy (AE; Pincus, 1991; Steve Pincus & Singer, 1996; Steve Pincus & Kalman, 1997) that is defined at the sequence level. This measure allows to evaluate the extent of irregularity in a sequence. Specifically, AE(m) measures the logarithmic frequency with which blocks of length m that are close together remain close together for blocks augmented by one position, with larger values of AE implying greater irregularity in the sequence. In other words, for a given sequence of numbers, AE(m) gives an indication of the predictability of the next item in a sequence given the previous sequence of m numbers. AE has proven useful across applications as diverse as analyzing the (ir-)regularity of physiological (e.g., EEG; Sabeti, Katebi, & Boostani, 2009) or financial market time series (Steve Pincus & Kalman, 2004).

Approximate entropy is parametrized by the parameter m that dictates the length of subsequences being evaluated. Hence, comparisons regarding the randomness of two sequences should be made for a fixed value of m (Pincus, 1991). Higher values of m require longer sequences for ensuring the validity of the calculation. In oder to establish the value of this parameter m that is most sensitive for detecting differences in the randomness of the sequences, we conducted study 1 and study 2 in which we compared the performance of different setting of this parameter.

2.3 Statistical Methods

We used exclusively Bayesian statistics because of their many advantages over classical frequentist methods (Wagenmakers et al., 2018). For all regression analyses, we used the R package `brms` (Bayesian Regression Models using Stan; Bürkner, 2017) with default, uniform priors for the regression coefficients. This package uses Hamiltonian Monte-Carlo (HMC) techniques implemented in Stan (Carpenter et al., 2017) to fit the models. We used 4 chains, each chain had a warm-up period of 1000 samples and 4000 post warm-up samples. We used the Gelman-Rubin diagnostic (Gelman, Rubin, et al., 1992) to ensure that all reported results had $\hat{R} \leq 1.05$. For model comparison, we used Leave-One-Out Information Criterion (LOOIC; Vehtari, Gelman, & Gabry, 2017, 5), where smaller scores of the LOOIC suggest a better model fit. Specifically, a model is considered better relative to another model if the LOOIC score is smaller, and if the ΔLOOIC score is at least the double of the corresponding LOOIC standard error.

When reporting regression coefficients, we report posterior mean b, 95% HDI and the evidence ratio (ER) in favor of a positive (ER_+) or a negative effect (ER_-). These ratios are calculated as the ratio of two probabilities: The probability of the effect being positive divided by the inverse probability of the effect being zero or negative (ER_+) or the inverse of that ratio (ER_-). For example, the statement $b = 0.09$ $[0.01, 0.18]$, ER_+=27.0 indicates a positive regression coefficient of 0.09 units with a positive 95% HDI going from 0.01 to 0.18 and an evidence-ratio of 27.0 in favor of a positive effect. The evidence ratio can be interpreted as an odds-ratio. In the previous example, we can for example state that it is 27 as likely that the effect is positive than that it is zero or negative.

2.3.1 Hierarchical ordered probit regression

In the mind-wandering literature, responses to thought-probes are often treated as continuous variables and mean and standard-deviation calculated per subject and session are used. This approach has been identified as problematic for several reasons (Boayue et al., 2019): it "wastes" data because within-subject variability is completely lost; it is a misspecification of reality as treating ordinal variables as continuous can have severe consequences (Liddell & Kruschke, 2018); and it ignores known modulating factors such as the time-on-task effect (Thomson et al., 2014). All of these factors can readily be integrated in more sophisticated analyses. Hence, we used the model developed by Boayue et al. (2019) that has already been applied in several studies (Filmer et al., 2019; Turi et al., 2019).

With this analysis method, the answers to our thought-probes was the dependent variable which was modeled as an ordinal response-variable. Each subject received a random intercept (and one for "experiment part" nested in participants of study 3) and we use behavioural variability, entropy of the sequences and current trial-number (as well as their interactions) as predictor variables.

3 Study 1

The first study served as a proof-of-concept that fluctuations in randomness as operationalized by approximate entropy as well as behavioural variability can be readily measured across the experimental session at high temporal resolution. We also aimed to establish that randomness measured by our FT-RSG task would be correlated to the classical version of the random number generation task as proposed by Baddeley (1998). Finally, we wanted to optimize the parameters of the experimental protocol (notably the inter-stimulus interval, ISI and the parameter of the AE measure) for our further studies.

3.1 Methods

3.1.1 Participants

We collected data from 19 students and employees (12 males) of the University of Tromsø with a mean age of 25.2 years (range from 21 to 42). All of the participants gave written informed consent before the start of the experiment and received a non-monetary compensation, worth around 40 Norwegian kroner for participation. The experimental instructions were given in English or Norwegian language, depending on the preference of the participant.

3.1.2 Design

We implemented five sessions of 5 minutes each using different inter-stimulus intervals including 0.3, 0.5, 0.75, 1.0, and 1.25 seconds. The order of presentation of these sessions was randomized across participants. After each session we asked our partipants to judge how random they thought the sequence they created over the preceding five minutes was. The answer was recorded using a 5-point Likert scale ranging from "very predictable" to "very random". To compare the FT-RSG task to the classical RNG-task used by Baddeley (1998), we implemented a version of that task in which participants had to press 10 instead of two buttons in a random order, with one finger assigned to one key. The duration of that task was set to 5 minutes and the inter-stimulus-interval was 1.0 seconds in accordance with the original study (Baddeley, 1998).

The experimental tasks were programmed with PsychoPy, Standalone version 1.83.04_win32 (Peirce, 2007). The keyboard was invisible to the participants during the task, since they had to place their head in the inbuilt chin- and forehead-rest of the eye tracking column of an infrared video-based eye tracker (iView X Hi-Speed 1250, SMI GmbH, Teltow, Germany). During this experiment, the eyes were not actually tracked but the setup was used for comparability to future studies. Participants were instructed to keep their eyes on a fixation cross (white on grey ground, height 0.15 degrees of visual angle), displayed in the center of the screen. Task instructions in the beginning of the experiment and the probe items during the course of the experiment were also presented on that screen (both in white letters on grey ground).

3.1.3 Procedure

Each experimental session started with the classical 10-digit version of the RNG task. Participants received a written explanation of randomness using an example in which 10 balls were randomly drawn out of a box and put back after every draw. Following the written explanation, the participants were asked to actually draw 10 times a ball out of a box of 10 different balls and to note down the results. The results of this process were discussed together with the experimenter to exemplify the concept of randomness. During the RNG task, participants had their hands placed on a specially prepared keyboard that only contained the ten used keys in an ergonomic arrangement. Participants were told to press those ten buttons in a random order. They were also instructed to respond synchronously with the ongoing tone of the metronome so that each button press would occurs together with the tone. After a training session of 50 trials, the actual 5-minute session of that task was started, consisting of 300 tones in total.

After finishing this task, the participants were given the explanation of randomness based on the example of flipping a coin discussed in the general methods above. Again, following the written explanation, participants were asked to actually flip a

coin 10 times and discuss the results of this process. In addition to the standard instructions, participants were also told that the rhythm of the tone would change after each break and that they would be asked to estimate how random the sequence that they created in the last block was. The FT-RSGT part of the experiment started with a one-minute training session using an ISI of 0.8 seconds. After that, the five blocks implementing different ISIs were presented in random order.

3.2 Results and Discussion

We started by investigating the distribution of the AE values to establish its usability for statistical analysis. We found that it was highly left-skewed (see Supplemental Materials) and we therefore implemented the transformation $-\log(\log(2)-\mathrm{AE})$ which we found to result in an approximately normal distribution of the outcome measure (see Supplemental Materials for details). All reported analyses are based on the transformed AE measure but we will refer to it as AE for simplicity.

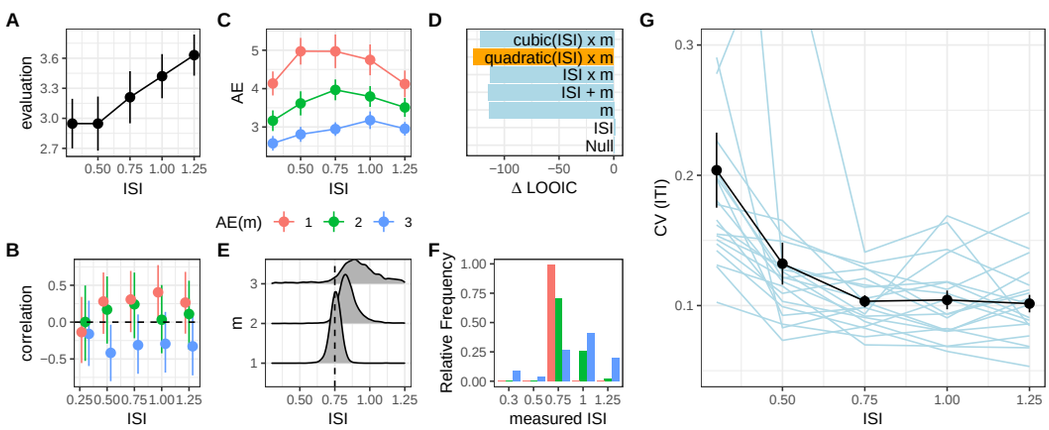

Figure 1. Results from Study 1. A: Perceived randomness of the sequences increases with longer ISIs. B: For all but the shortest ISIs, AE estimates from the finger-tapping task correlated with those from the standard RNG task for $m = 1$ and somewhat for $m = 2$. C: Randomness of the sequences quantfied by AE shows an inverse U-shaped relationship with ISI. D: A model incorporating a quadratic relationship yields the best fit in terms of model-selection (LOOIC). E: The ISI for which AE of the generated sequence was maximized according to the model from D. F: From the 5 ISI conditions actually measured in study 1, 0.75 sec was closest to the maximum estimated in E for $m = \{1,2\}$. F: The coefficient of variation (CV) of the inter-tap-intervals (ITI) approached an asympote for an ISI of 0.75 seconds. Blue lines represent data from each participant, whereas the black line represents the group mean.

One goal of the first study was to optimize the protocol. In particular, we wanted to find the ISI that would allow our subjects to maximize the randomness (AE) of their generated sequences. We hypothesized that ISIs that were too short would not allow for enough processing to randomize the tapping sequences. On the other hand, too long ISIs might encourage inattention and, hence also be detrimental to the randomness of the generated sequences. In addition, we wanted to make the ISI as short as possible in order to give a design with maximum possible temporal resolution with respect to extracting the ongoing involvement of executive resources. We therefore hypothesized that there would be a saturation point at which more processing time would not help, or might even hinder, the creation of random sequences.

The results of our analyses support that hypothesis (see Figure 1 C). The average AE values, calculated for each ISI condition and $m = \{1,2,3\}$ follow an inverted U-shape with the peak of the curve moving towards higher ISI for higher values of m. In order to more formally capture the optimal ISI at which the AE was maximized, we fitted a series of Bayesian linear mixed effects models with random-intercepts per subject treating AE as the dependent variable. We found, that entering the first two powers of ISI as well as m and their interactions to the model produced the best fit in terms of the model-selection (ΔLOOIC=-2.8, SE=1.3 relative to the next best model), see Figure 1 D. Using that model, we derived the theoretical ISI at which the curves for each m would reach their maximum, carrying the uncertainty from the Bayesian model through the calculation (i.e., the calculation was made for every posterior sample and the distribution of the results calculated). The results of this analysis are plotted in Figure 1 E. The peak of the curve was located between 750 ms and 1000 ms for all values of m. Next, we calculated which of the ISIs that we measured (i.e., 250, 500, 750, 1000 and 1250 ms) was closest to theoretical peak for each m. The results of these analysis are displayed in Figure 1 F. According to this analysis, the best ISI for optimizing AE

for $m = 1$ and $m = 2$ was 750 ms (99% of the values were closest to 750 ms for $m = 1$ and 71% for $m = 2$). For $m = 3$, the optimal ISI was most frequently closer to 1000 ms (41%).

We also investigated subjectively experienced randomness of the sequences. After each ISI-block, our subjects were asked to rate how well they thought they had performed at producing random sequences. Contrary to the actual randomness of the sequences, the results, displayed in Figure 1 A, indicate that subjects believed their sequences to become more random with increased ISIs. A Bayesian mixed linear regression model with self-evaluated randomness as dependent variable and ISI as (numeric) repeated measures predictor confirmed that trend, $b = 0.78\,[0.19, 1.34], \mathrm{ER}_{+} = 199$.

In addition, we opted to compare our FT-RSG task to the classical random-number generation task used by Baddeley (1998). We used robust Bayesian correlations[1] to quantify the correspondence between the classical RNG and our finger-tapping task. Interestingly, the degree of correlation seems to depend both on the choice of ISI for our finger-tapping task and the AE m-parameter (see Figure 1 B). For very short ISIs, there was no correlation between the randomness of the sequences generated in the two tasks (ISI=0.30, m=1: $\rho = -0.07\ [-0.53, 0.34]$, m=2: $\rho = -0.02\ [-0.52, 0.43]$, m=3: $\rho = -0.41\ [-0.78, -0.03]$). We interpret this finding such that the short time between taps did not allow our participants to exert executive control necessary to produce random sequences that would manifest in the AE measures. For longer ISIs, the correlations for $m = 1$ and $m = 2$ were positive (ISI=0.75, m=1: $\rho = 0.33\ [-0.07, 0.73]$, m=2: $\rho = 0.27\ [-0.18, 0.70]$; ISI=1.00, m=1: $\rho = 0.47\ [0.09, 0.79]$, m=2: $\rho = 0.05\ [-0.42, 0.50]$) while the correlations for $m = 3$ were consistently negative (ISI=0.75: $\rho = -0.34\ [-0.72, 0.07]$, ISI=1.00: $\rho = -0.34\ [-0.76, 0.05]$).

Finally, we measured how behavioural variability would change as a function of the used ISI in our task. We calculated the coefficient of variation (CV) of the sequence of inter-tap-intervals (ITI) for each subject (Figure 1 G). This measure of variability decreases monotonically until an ISI of 750 ms and then reaching a plateau on that level, indicating that behavioural variability was stable from 750 ms onwards. As a consequence of these analyses, we decided to continue using an ISI of 750 ms for the following studies. We also settled on using $m = 1, 2$ for calculating the AE scores and to use the transformation for the AE described above.

4 Study 2

The objective of study 2 was to evaluate to what extend the experimental design developed in study 1 allows to study the relationship between employment of executive function (operationalized by AE), behavioural variability and mind wandering. To that purpose, we conducted a longer experimental session featuring the optimal ISI of 750 ms determined in study 1. In addition, we included randomly interspersed thought-probes to assess the degree of mind wandering throughout the task. We predicted that periods of mind wandering would be characterized by less random sequences and a higher degree of behavioural variability.

4.1 Methods

4.1.1 Participants

21 subjects (7 males) with a mean age of 28 years (range from 21 to 57) participated in the experiment. All of the participants gave written informed consent before the start of the experiment and received a non-monetary compensation, worth 50 Norwegian kroner for participation. The experimental instructions were given in English or Norwegian, depending on the preference of the participant.

4.1.2 Design

The experimental task was identical to the FT-RGST task used in study 1 except that only a single ISI was used (750 ms) and the experimental session went on for 20 minutes. In addition, participants were intermittently prompted with a question asking them to estimate where their focus of attention was just before the question appeared. They answered by moving an arrow on a horizontal 6-point Likert scale ranging from “Clearly on-task” to “Clearly off-task”. The initial position of the arrow and the direction of the scale was randomized. Probes appeared randomly with a minimum of 20 and a maximum of 40 seconds between two probes. In total, there were 40 probes in each session.

4.1.3 Procedure

Participant were instructed in the same way as in study 1. As in study 1, subjects were placed in front of an eye-tracking device (iView X Hi-Speed 1250, SMI GmbH, Teltow, Germany) featuring a chin-rest. We planned to record eyetracking data and the eyetracker was therefore calibrated for each subject. However, due to a faulty device, the acquired eyetracking data was unusable and was not analysed. The training session was identical to study 1, comprising 50 trials, and an example of the thought-probes presented throughout the experiment was shown and explained. Finally, the participants started the experiment proper which lasted for 20 minutes.

[1] http://www.sumsar.net/blog/2013/08/robust-bayesian-estimation-of-correlation/

4.2 Results and Discussion

In study 2, we intended to investigate the relationship between entropy of the generated sequences, behavioural variability of the responses and mind wandering. First, we calculated the AE and BV values calculated using the last $n_{\text{back}} = 20$ trials (corresponding to 15 seconds) before encountering a thought-probe. For descriptive analysis, we then split probe-responses into on-task (response 1, 2 and 3) and off-task (response 4, 5 and 6) and calculated mean AE ($m = \{1,2,3\}$) and BV-scores within on- vs. off-task segments, see Figure 2 A. The pattern of increased behavioural variability (BV) and decreased entropy (AE) during periods of off-task is apparent for all values of m. Next, we re-calculated the AE ($m = 2$) and BV-scores for off- vs. on-task trials using varying numbers of trials preceding each probe ($n_{\text{back}} = \{10,15,20,25\}$), see Figure 2 B. The pattern is robust against the choice of n_{back} but seems to be strongest for $n_{\text{back}} = 25$.

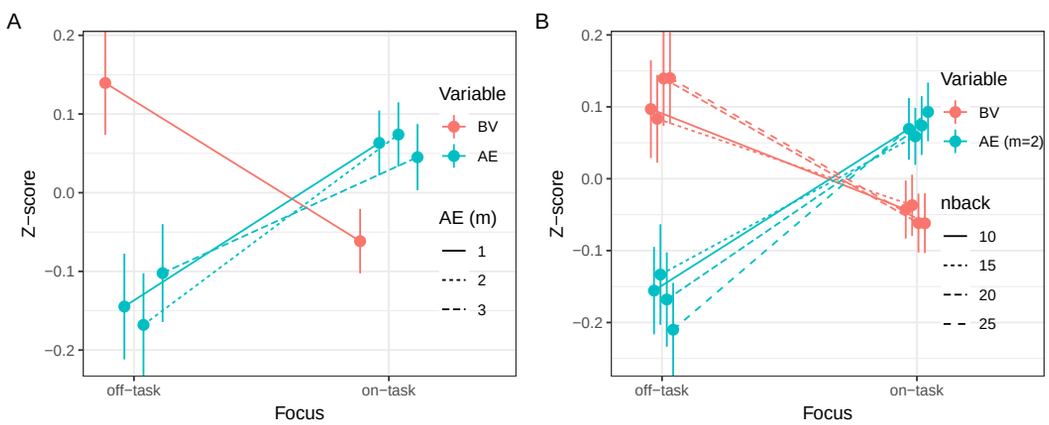

Figure 2. Results from Study 2. A, B: Behavioural variability is increased during off-task episodes while AE is decreased. This pattern holds for different choices of parameter m (A) and varying number of trials n_{back} (B).

Next we formally tested this pattern using a Bayesian hierarchical ordered probit model as described in the general methods. We first ran a model-selection procedure across 17 models that included different combinations of predictor-variables and their interactions (see Supplemental Figure 2A for details). We compared these models, according to their out-of-sample predictive performance using the leave-one-out cross-validation information criterion (LOOIC; Vehtari et al., 2017, 5). Based on this criterion, we calculated model-weights using two different methods: First, a method based on Akaike weights (Wagenmakers & Farrell, 2004) using the LOOIC instead of the AIC and second a method using Bayesian model-averaging (BMA; Yao, Vehtari, Simpson, Gelman, et al., 2018). Both of these techniques result in poster-probabilities p_{LOO} and p_{BMA} quantifying how likely it is that each of the models has the best out-of-sample predictive performance.

The two model-selection methods disagreed in their preferred models. While the LOOIC-procedure selected a model that included main effects of BV, AE ($m = 2$) and trial-number ($p_{\text{LOO}} = 0.35$, next best model: $p_{\text{LOO}} = 0.17$), the BMA procedure a model that also included the interaction between BV and AE ($p_{\text{BMA}} = 0.26$, next best model: $p_{\text{BMA}} = 0.23$). That last model was second-best in the LOOIC-procedure and we therefore chose this model as the winning one. This winning model had a Bayesian R^2 (Gelman, Goodrich, Gabry, & Vehtari, 2019) of $R^2 = 0.37$ $[0.33, 0.41]$. In this model, the coefficient for BV was positive ($b = 0.09$ $[0.01, 0.18]$, ER_+=27.0) indicating that as behavioural variability increased, so did off-task responses on the thought-probes. The coefficient for AE ($m = 2$) was negative ($b = -0.07$ $[-0.13, 0.00]$, ER_-=22.4) indicating that as the randomness of the sequences increased, mind wandering decreased. The effect of the trial-variable was positive ($b = 0.44$ $[0.38, 0.51]$), replicating the well-known time-on-task effect where mind wandering gets more likely later in the task. Finally, the AE$\times$ BV interaction was positive ($b = 0.05$ $[-0.02, 0.12]$, ER_+=7.0), even though its HDI did not exclude zero. The interpretation of this effect is that the positive relationship between BV and mind wandering was stronger for higher values of AE.

In order to establish the robustness of the main effects for AE and BV on mind wandering, we calculated the regression coefficients for all of the tested models, not only the winning one (see Supplemental Figure 2B). The coefficient for AE was negative for all fitted models and the coefficient for BV was positive for all tested models indicating that these effects were robust against analytical choices. We conclude that, in accordance with our predictions, AE and BV were related to MW in

opposing ways: While randomness (AE) was increased during on-task relative to periods of mind wandering, BV showed the opposite pattern. In addition, the positive AE $\times$ BV interaction in the model indicates that the the relationship between behavioural variability and mind wandering was particularly strong when entropy was high and executive resources were strongly recruited.

5 Study 3

In study 3, we wanted to investigate whether an optimized HD-tDCS protocol designed for achieving maximal field-strength and focality in the left DLPFC would be able to manipulate mind-wandering propensity in our task. We therefore implemented a protocol similar to that of study 2. The only changes were that the study consisted of two parts using the task from study 2, a baseline task before the brain-stimulation device was turned on and another block while stimulation was ongoing. We implemented a double-blind, sham-controlled design and randomly assigned half of our subjects to a sham and the other half to the real stimulation group. As described in the introduction, we expected mind-wandering propensity to be affected by the brain-stimulation protocol. The directionality of the effect was unclear *a priori* as previous studies found both tDCS-related increases and decreases in mind-wandering propensity.

5.1 Methods

5.1.1 Participants

A total of 60 participants (19 male; age $M = 22.4$ years, SD=2.5 years, range=$[19, 31]$ years) were recruited with flyers on the university campus, on social media networks and by personal contacts. Participants received gift-cards worth 200 Norwegian kroner (approx. 20 EUR) or course credits as compensation for taking part in the study. Inclusion criteria were a signed informed consent-form, aged between 18-50 years, no psychiatric/neurological condition (e.g., depression, bipolar disorder, epilepsy, migraine, severe head trauma, brain surgery) currently or in the past, not under the influence of psychotropic drugs (except caffeine and nicotine), not taking central nervous system medications (e.g., antidepressants, antiepileptic drugs), good or corrected eyesight and that they reported to have slept enough during the preceding night.

5.1.2 Design

In this study, participants completed two sessions of the FT-RSGT with a similar study design as in study 2. The first, "baseline", session was administered before the stimulation equipment was attached to the scalp and lasted for 10 minutes. The second, "online", session of the task was completed during active or sham stimulation and lasted for 20 minutes. The inter-stimulus-interval of the metronome tones (440 Hz) was set to 750 ms as in study 2. Approximately every minute (minimally 40 seconds, maximally 80 seconds, uniformly distributed), a thought-probe was presented asking how focused the participant was on the task (1="completely focused", 4="completely unfocused", 10 and 20 thought-probes in the baseline online sessions, respectively).

The study was double-blind with respect to the brain-stimulation procedure, i.e., neither the experimenter nor the particpants knew whether each participant was assiged to the active or sham stimulation condition. This was ensured using a randomization list assigning each participant a unique code. This code determined whether the stimulation device would output real or sham stimulation by using pre-specified stimulation protocols for each subject-code. In order to assess the efficacy of the blinding, we asked our participants to guess whether they received active or sham stimulation at the end of the experiment.

5.1.3 Brain Stimulation

In order to increase strength and focality of the tDCS intervention, we implemented a 4-by-1 ring arrangement of electrodes located over the left DLPFC. The anode was placed at location F3 and four cathodes were placed in a ring around it (locations C3, FT7, FP1 and Fz). This arrangement, when used with a stimulation intensity of 2mA, produces stronger and much more focal electric fields when compared to classical montages (see Figure 3) (Boayue et al., 2019). The used electrodes were PISTIM EEG&tCS Ag/AGCl electrodes (12 mm diameter) powered by a Startstim Neckbox (Startstim tCS, NE Neuroelectrics) and attached to the scalp using an electrode cap and conductive gel.

For comparison, we simulated both our target HD-tDCS setup and the montage used by Axelrod et al. (2015) using a set of publically available, high-resolution, realistic head models of healthy adults (Boayue, Csifcsák, Puonti, Thielscher, & Mittner, 2018). The simulation pipeline was based on the pre-released version of SimNIBS 2.1 (Saturnino et al., 2019). Conductivities for different tissue compartments were set as reported in our previous work (Boayue et al., 2018; Csifcsák et al., 2018): 0.465 S/m (skin), 0.01 S/m (skull), 0.5 S/m (eyeballs), 1.654 S/m (cerebrospinal fluid), 0.275 S/m (gray matter), 0.126 S/m (white matter). For the montage used in Axelrod et al. (2015) and Boayue et al. (2019), individual head models were fitted with electrodes with circular connectors (diameter: 0.5 cm) at the middle of the electrode pads (anode - F3: 4 x 4 cm and cathode - right supraorbital (RSO) area: 7 x 5 cm, both with a thickness of 1mm with 2.5mm sponge pocket). Stimulation intensity was set at 1 mA. For the HD-tDCS montage, electrode thickness was set to 1 mm + 2.5 mm gel thickness (anode: F3, cathodes: C3, FT7, Fp1, Fz). Stimulation intensity for the anode was set to 2 mA, with equal distribution of return currents for the 4 cathodes (0.5 mA for each). The electrodes were placed according to the International 10/20 system.

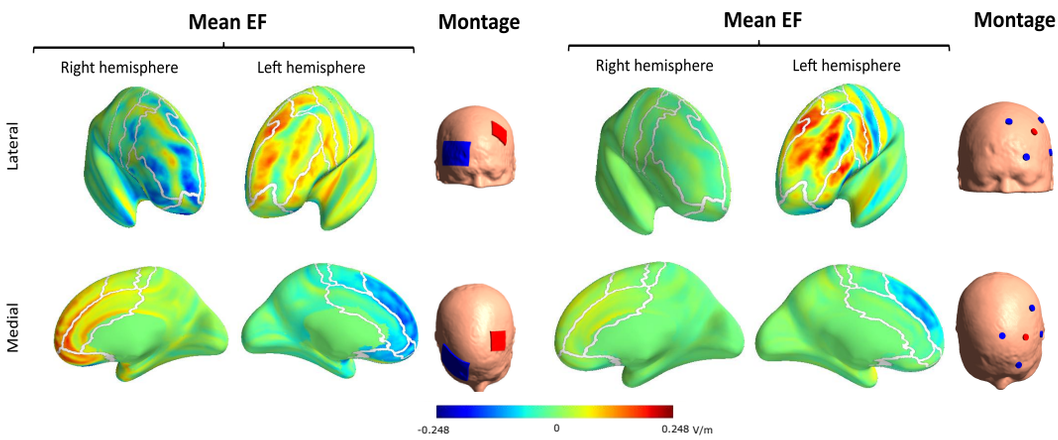

Figure 3. Simulation of the normal component of the electric field induced by Axelrod, Rees, Lavidor, and Bar (2015)'s setup (left) and our new protocol (right) averaged over N=18 individual datasets. While the traditional protocol features a broad and non-focal distribution of the electric field including both strong anodal and cathodal currents across both DLPFCs (left), our HD-tDCS protocol is both stronger and more focal.

We simulated both stimulation protocols for each of the subjects in our reference dataset (Boayue et al., 2018) and extracted the component of the electric field that is perpendicular to the cortical surface (normal component; Csifcsák et al., 2018). This normal component is believed to be the effective component of the E-field and it takes negative values for inward-going (cathodal) currents and positive values for outward-going (anodal) currents. This normal component was then averaged across the individual brains in order to account for inter-individual anatomical variability that has been shown to be an important determinant of the strength of the electric field (Opitz, Paulus, Will, Antunes, & Thielscher, 2015).

5.1.4 Procedure

Data were collected by two experimenters (authors IF and AEV) working together. The maximum total duration of the experiment was 90 minutes. Participants were required to set their mobile phones into flight-mode and to read and sign the informed consent form. Before continuing with the experiment, the experimenters measured the circumference of the head of the participant and selected a stimulation cap of the corresponding size. Using this cap, the locations of the five stimulation electrodes were located on the scalp and marked with a pen. These locations (F3, Fp1, Fz, C3 and T7) where then treated with a local anaesthetic cream (EMLA). During the time the local anesthetic needed to achieve full efficiency (20-30 minutes), subjects received instructions and performed the baseline session of the FT-RSGT (10 minutes).

We collected demographic information (age and sex), occupation as well as degree of experience with any musical instrument, because we assumed that musical training could impact our participants' ability to rhythmically respond to the ongoing metronome in the FT-RSG task. Participants were then presented with the explanation of what constitutes a "random sequence" using the flipping of a coin as an example used in studies 1 and 2. This was followed up by answering any questions the participants might have about randomness in the task. The participants received instructions on the FT-RSGT through the experimental software and then went through a training session that lasted for about 30 seconds. Finally, our subjects filled in a "mini-quiz" where they were asked to answer seven simple questions that were designed to measure whether they had understood the instructions with respect to randomness, mind wandering and the metronome. Wrong answers were followed up on and discussed before the participants were allowed to continue with the baseline session of the task.

After finishing the baseline session, any remaining EMLA cream was removed from the scalp and the electrode-locations cleaned with alocohol. PISTIM EEG&tCS electrodes were placed in positions F3, Fp1, C3, T7 and Fz on the cap and filled with conductive gel (Signa Gel, Parker Laboratories Inc., USA) before the cap was positioned on the participants' head. Next, electrodes where connected to the Startstim Neckbox (Startstim tCS, NE Neuroelectrics) which was fastened to the back of the cap. A connection to the stimulation computer was established through Bluetooth using the NIC software (version 2.0). It was ensured that all electrodes had impedances below 10 kΩ and the exact impedances were recorded for each participant and electrodes. In case one or several electrodes had too high impedances, the experimenters attempted to bring down impedance by pressing down the cap and/or inserting more gel through the top of the electrode. Once electrode preparation was finished, the stimulation protocol on the stimulation PC was activated (either sham or active, depending on the randomized subject-specific

protocol used) and the main task started (total duration 20 minutes). After 20 minutes, the stimulation protocol turned off by itself.

After the end of the task, our participants were asked to fill out the Norwegian version of the Mindfulness Awareness Scale (MAAS; Brown & Ryan, 2003). Finally, the stimulation electrodes were removed, our participants interviewed about their experiences during the task and debriefed. All materials used in this study and all raw data are available from our study repository at https://osf.io/nm2sz/.

5.1.5 Pre-Registration

Before conducting the study, we pre-registered the study plan, experimental materials and an analytic strategy targeted towards distinguishing between the executive function (e.g., Smallwood & Schooler, 2006) and the executive failure views (e.g., McVay & Kane, 2010) of mind wandering in a public repository at https://osf.io/4hvdf. This pre-registration does not cover the effect of brain-stimulation on mind wandering presented in the current study and the corresponding analyses are therefore exploratory.

The idea of the pre-registered analysis plan was as follows: The two dominant views of how executive functions are related to mind wandering, the executive function view (EFu; Smallwood & Schooler, 2006) and the executive failure view (EFa; McVay & Kane, 2010) make opposite predictions how an additional availability or shortage of executive resources should impact mind-wandering propensity: While the EFu view posits that an increase in the availability of executive resources should manifest in increased mind wandering, the EFa view predicts the opposite (i.e., fewer mind-wandering episodes). Based on that distinction, we wanted to 1) change the availability of executive resources using brain stimulation (i.e., either increase or decrease them operationalized by AE of the generated sequences) and 2) relate that change to increases or decreases in mind-wandering propensity.

As a consequence, our pre-registered analyses hinged completely on the ability of the HD-tDCS protocol to manipulate the availability of executive resources as measured by the AE of the sequences generated during stimulation. Therefore, we hypothesized that, the group receiving real stimulation should show higher or lower AE than the group receiving sham stimulation during the online sessions. We further constrained that should AE neither be increased nor decreased (i.e., tDCS was ineffective with respect to this measure), all further hypotheses relating to the relationship between MW and AE could not be tested. As reported in the results, tDCS did not change the randomness of the generated sequences and the pre-registered plan is therefore void. For the full set of hypotheses, please refer to the pre-registration document.

5.2 Results and Discussion

5.2.1 Blinding efficacy

In order to check whether blinding was effective, we asked our subjects to guess whether they received active or sham stimulation at the end of the experiment. Of the 30 subjects receiving sham stimulation, 20 guessed incorrectly that they had received active stimulation. Correspondingly, 19 out of 30 subjects receiving real stimulation correctly guessed that they received real stimulation. We calculated contingency table Bayes factors using an independent multinomial sampling plan (Morey & Rouder, 2018) and a prior concentration of $a = 1$ to assess the evidence for the hypothesis that the counts in the contingency table differed substantially. The Bayes-factor provided support for the null-hypothesis that the counts did not differ $\mathrm{BF}_{01} = 3.3$ (traditional χ^2-test: $\chi(1)^2 = 0.00, p = 1$). We conclude that blinding was effective for our novel protocol as opposed to the traditional protocol used in previous studies (Axelrod et al., 2015; Boayue et al., 2019) that has been shown not to be blinded effectively (Turi et al., 2019).

5.2.2 Pre-registered results

Our pre-registered analysis plan required us to first test, with a two-tailed t-test, whether application of the tDCS protocol would change recruitment of executive resources as reflected in the approximate entropy (AE) measure. Since we did not specifiy whether we would directly compare the groups' AE scores during stimulation or their respective changes from the preceding baseline session, we conducted both of these analyses. The two groups did not differ in the AE scores during stimulation, $\mathrm{BF}_{10} = 0.40$ ($\mathrm{M}_{\mathrm{sham}} = 3.0$, $\mathrm{M}_{\mathrm{real}} = 3.3$, $t(56.7) = 0.99, p = .32$). Neither did the comparison of the change in AE from baseline to stimulation session differ between the two groups, $\mathrm{BF}_{10} = 0.34$ ($\mathrm{M}_{\mathrm{sham}} = -0.26$, $\mathrm{M}_{\mathrm{real}} = -0.07$, $t(56.7) = 0.77, p = .44$).

Since our pre-registered analysis plan clearly specified that the other hypotheses were contingent on a significant difference between the stimulation groups in the AE measure, we did not conduct any of the other pre-registered analyses. However, we conducted further exploratory analyses using ordered probit regression models as described above (Boayue et al., 2019).

5.2.3 Effect of HD-tDCS on mind wandering

To analyze the impact the stimulation had on our participants' rate of mind wandering, we applied hierarchical ordered probit models treating the ordinal responses to the mind-wandering probes as dependent variable and using combinations of the following predictor variables: BV, AE ($m = 2$), trial, part (baseline vs. stimulation), stimulation (sham vs. real) and their interactions. All models had random intercepts per subject and for "part" (baseline vs. online) nested within each participant as

each participant went through a baseline and a stimulation session, respectively. In total, 22 models of increasing complexity were tested (see Supplemental Figure 3 for a list).

We used the same model-selection procedure as in study 2. Both the BMA and the LOOIC-procedures agreed on the preferred model, which included main effects for AE, BV, part, stimulation and trial as well as the AE $\times$ BV interaction and the part $\times$ stimulation interaction (BMA: $p_{\text{BMA}} = 0.28$, next best model $p_{\text{BMA}} = 0.17$; LOOIC: $p_{\text{LOO}} = 0.42$, next best model $p_{\text{LOO}} = 0.32$). This last interaction is the crucial measure for how stimulation affected mind wandering: Because every participant went through an identical baseline session, the effect of stimulation should not manifest in a main effect of stimulation (which averages across baseline and stimulation sessions) but in a part $\times$ stimulation interaction which describes the differences in how participants' mind wandering changed from baseline to stimulation session separately for the sham and the real stimulation groups.

The winning model had a Bayesian R^2 (Gelman et al., 2019) of $R^2 = 0.44\ [0.41, 0.46]$. As in study 2, the effect of BV was positive ($b = 0.12\ [0.05, 0.20]$, $\text{ER}_+ = 799$) indicating that higher BV came along with higher mind-wandering propensity. As in study 2, we clearly found the opposite effect for AE ($b = -0.13\ [-0.20, -0.06]$, $\text{ER}_- = 15999$), i.e., that more random sequences were associated with less mind wandering. We also replicated the positive interaction of AE and BV, $b = 0.09\ [0.03, 0.14]$, $\text{ER}_+ = 799$ indicating that high BV is predictive of mind wandering when AE is increased, but less so when executive performance is compromised. Also as expected, we found clear time-on-task effects both between the two sessions (baseline vs. stimulation, $b = 0.20\ [0.00, 0.41]$, $\text{ER}_+ = 33.2$) and within each of the sessions (trial: $b = 0.06\ [0.04, 0.07]$, $\text{ER}_+ = \infty$). Furthermore, we found an inconclusive main effect of real vs. sham stimulation, $b = 0.25\ [-0.32, 0.81]$, $\text{ER}_+ = 4.3$. Finally, the crucial part $\times$ stimulation effect was negative $b = -0.23\ [-0.50, 0.05]$, $\text{ER}_- = 17.4$ indicating that mind wandering was reduced in the real relative to the sham stimulation group during the active stimulation session.

In order to test the robustness of this effect of tDCS on mind-wandering propensity, we calculated the regression coefficient for each of the 22 tested models that included the part $\times$ stimulation condition (a total of 12 models; see Supplemental Figure 4B). For all models, the effect was negative with evidence-ratios ranging from 2.9 to 20.2 (mean $\text{ER}_- = 14.6$) indicating its robustness against analytical degrees of freedom.

6 Summary and Discussion

In a series of three studies, we developed a fast-paced experimental paradigm that allows the study of the dynamic interplay of mind wandering, executive control and behavioural variability within the course of an experimental session. We could show that our novel task is related to measures of executive control and that the extracted measures of approximate entropy and behavioural variability show the expected relationship to mind wandering propensity. In particular, in agreement with previous findings using different methods, behavioural variability was increased and randomness (indicating employment of executive resources) was decreased during periods of mind wandering relative to periods of focused attention (Seli et al., 2013; Teasdale et al., 1995).

Furthermore, we found evidence for the effectiveness of our HD-tDCS stimulation montage optimized to focally stimulate the left DLPFC, a region involved in the control of executive resources, in decreasing the propensity of mind wandering. In particular, subjects stimulated with real HD-tDCS reported lower mind wandering scores during stimulation than the group receiving sham stimulation. However, we acknowledge that our analysis purporting to these results were not pre-registered and therefore have to concur with our previous evaluation that "[...] it is important to replicate any [...] positive effects [of tDCS on mind wandering] before accepting them as facts" (Boayue et al., 2019). Pending the results of a high-powered, pre-registered study currently in progress in our group, the results reported here should therefore be taken as an encouraging but not definite finding that mind wandering can be decreased with HD-tDCS over the left DLPFC. Should the result prove to be replicable in a pre-registered study design, our finding could open up exciting possibilities for the treatment of psychiatric conditions that are characterized by maladaptive mind wandering (e.g., depression or ADHD; Hoffmann et al., 2016; Seli, Smallwood, et al., 2015; Van den Driessche et al., 2017).

The finding of reduced mind wandering during anodal tDCS above the left DLPFC might seem to be a surprising result, given previous work either pointing towards an effect in the opposite direction (Axelrod et al., 2015; Axelrod et al., 2018) or reporting a null-finding (Boayue et al., 2019). However, these studies applied less focal bipolar tDCS montages with the return electrode placed above the contralateral (right) supraorbital area, most likely resulting in strong stimulation-induced electric fields outside the target region, including medial prefrontal structures (see Figure 3). Therefore, tDCS protocols with bipolar electrode placement could have inadvertently modulated activity in the default-mode network (DMN; Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010) via medial prefrontal stimulation, confounding the putative causal link between left DLPFC activity and the occurrence of task-unrelated thoughts. In this respect, our study provides more straightforward evidence for the involvement of the left DLPFC in the onset of mind-wandering episodes because the DLPFC was stimulated exclusively.

Since the DLPFC is a key hub in the frontoparietal control network (FPCN; Christoff et al., 2016), we anticipated that active tDCS would also influence executive performance in our task, and thus, enable the distinction between EFa vs. EFu

theories of mind wandering. Even though the AE measure was not influenced by tDCS in our study, reduced mind-wandering propensity together with unchanged performance in the real stimulation group provides some support for the EFa view. Here, we speculate that improved executive control via anodal tDCS could have prevented involuntary shifts of attention towards mind wandering, while maintaining randomness of movement sequences. This outcome is incompatible with the EFu view, because if mind wandering and executive performance share resources, tDCS-associated enhancement in FPCN activity would have resulted in more task-unrelated thoughts without hindering task performance.

We also found evidence for an interaction between behavioural variability and entropy when predicting mind wandering. The interpretation of this novel finding is that the negative relationship between behavioural variability and mind wandering was strongest when approximate entropy (executive control) was also high and weaker in periods of low executive control. This finding resonates well with theories describing the dynamical evolution of mind wandering: When entropy is high, executive resources are being used to produce high-entropy sequences – in other words, subjects are concentrating on the task and perform well on it. An increase in BV is sensitive indicator of subjects losing their attentional focus (Seli et al., 2013) and can be seen as an early sign of a departure from a full task-focus and can occur with only minor or even no deterioration of task performance otherwise ("tuning out"; Cheyne, Solman, Carriere, & Smilek, 2009; Smallwood, McSpadden, & Schooler, 2007). However, even these initial and often brief departures from focused processing are usually accessible to introspection (Seli, Jonker, Cheyne, Cortes, & Smilek, 2015; Cheyne et al., 2009), hence we can expect a strong relationship between BV and self-reported mind wandering when AE is high. Values of sequence-entropy at the lower-end of the scale, however, might signal a more severe disconnection from the ongoing task ("zoning out"). In this state, subjects are hypothesized to be actively engaged in mind wandering (i.e., following task-unrelated trains of thoughts) which would be reflected in severely decreased performance measured in both behavioural variability and entropy and a weaker relationship between behavioural variability and mind wandering. In fact, it is even possible that behavioural variability could decrease in such a deeper state of mind wandering (resulting in a reversal of the BV–MW relationship) given that this state is governed by "autopilot"-like behaviour (Hawkins, Mittner, Forstmann, & Heathcote, 2019). This novel effect could only be studied because of our innovative design that allows to simultaneous assess the dynamic allocation of executive control and behavioural variability and it provides exciting opportunities for further investigations.

Speculatively, the finding that AE and BV interact in predicting mind wandering may point towards the existence of distinct types of mind wandering as proposed by Mittner et al. (2016). These authors propose on neural grounds that there should be at least two different mental states when losing focus from the ongoing task. The first of these states, labeled "off-focus", is supposedly characterized by its transient and subconscious nature. In this state, the narrow focus of attention applied to the current task is periodically broaded to allow the consideration of alternative behaviours, such as mind wandering. The off-focus state has been characterised as "explorative" in the sense that it allows to explore whether redirecting attention to other cognitive processes may be beneficial in the current situation. From that off-focus state, attention can be redirected into a full-blown mind wandering state. Compared to the transient off-focus state in which task-performance can be relatively unaffected, performance in full mind wandering is more severely impacted. Crucially, similar to the distinction between an initial "tuning-out" and a full "zoning-out" (Cheyne et al., 2009), that model describes the dynamical switching between on-task and mind wandering to be governed by the transition throught the off-focus state in a bi-directional way.

Our results can be interpreted in the framework of this model as follows: In the off-focus state, behavioural variability is increased relative to the on-task state but executive resources are still being fully allocated to the task at hand and the entropy of the sequences is therefore not impaired. We therefore find a regime in which there is a strong relationship between BV and mind wandering while AE is high (transition between on-task and off-focus states). During full mind wandering, on the other hand, executive resources are allocated to following internal trains of thoughts and hence the entropy of the generated sequences is reduced. In this state, BV is also generally increased but the transition between mind wandering and off-focus states is not characterized by changes in BV as performance is largely determined by autopilot-like behaviour.

Of course, without direct access to neural sources of information, this argument remains speculative. Future studies could therefore focus on bringing the reported experimental paradigm into an fMRI setting. Technically, employing the task in an fMRI design is not too challenging as the task was already designed to conform to standard fMRI requirements. For example, the reduced number of possible digits from nine to two allows to use the task with just two response-buttons commonly available in fMRI settings. Studying these effects in the fMRI has several benefits: First, the availability of brain contrasts can be used to validate the assumption that executive resources are increasingly being employed when sequences are more random by investigating whether brain regions involved in executive control show increased activity. Second, the brain signature of the proposed three-state configuration of mind states can be investigated directly. The neural model of mind wandering makes concrete assumptions about how various fMRI measures should change across the three states (Mittner et al., 2016). Identifying the three states using the behavioural signature developed in the current study therefore allows to directly validate whether these states conform to the predictions made by this model. For example, dynamic functional connectivity (Thompson et al., 2013) would be expected to be stronger in the off-focus state compared to both on-task and mind wandering and different

subnetworks of the DMN should show distinct activity patterns. As such, this approach could contribute to our understanding of the neural signature of mind wandering.

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Supplemental Material: Effectiveness of HD-tDCS on influencing executive control during mind wandering

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ABSTRACT

This is the supplemental material for ...

1 Distribution of AE-values

The values of the approximate entropy (AE; Pincus and Kalman (1997)) variable showed a clear right-skew (see Fig. 1, upper left). Shapiro-Wilks tests showed clear deviations from normality for all values of the AE-parameter m and this pattern is also apparent in the QQ-plots (Fig. 1, upper right). We therefore implemented the following transform:

$$\mathrm{AE}_{\mathrm{transformed}} = -\log\left(\log\left(2\right) - \mathrm{AE}_{\mathrm{raw}}\right).$$

The rationale for this transform is as follows: First, the skew is "inverted" by subtracting the raw values from the maximum possible AE (which is $\log(2)$ because we have only two response options; Pincus and Kalman (1997)). Next, these values are log-transformed to reduce the skew and finally, the result is multiplied with -1 to enable interpretation of the values as "increase of randomness". The resulting, transformed AE-values are much closer to being normally distributed as can be seen by the non-significant Shapiro-Wilks tests (Fig. 1, lower left) and the QQ-plots (Fig. 1, lower right).

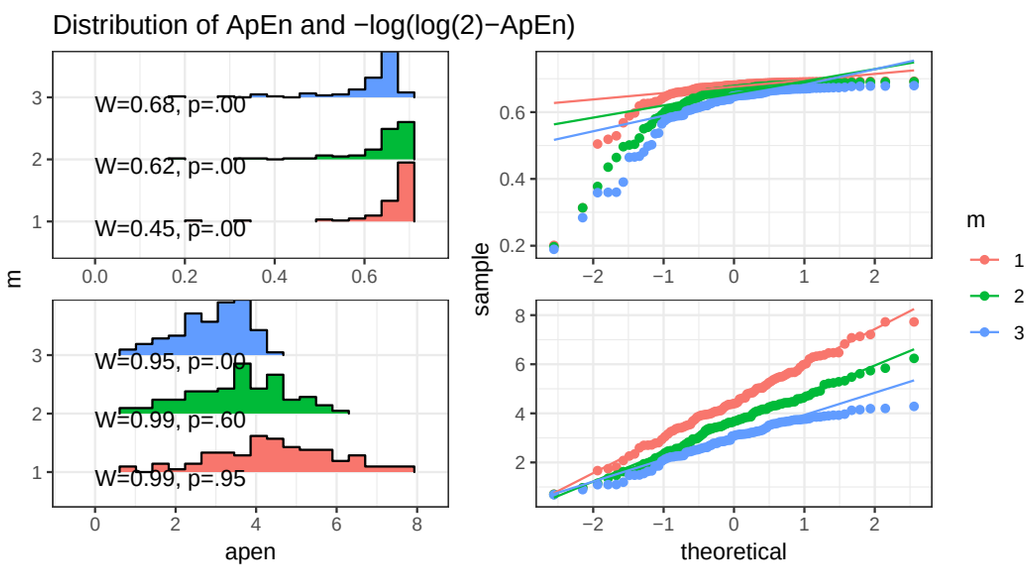

Figure 1. Distribution of raw and transformed AE-values.

2 Study 2

2.1 Model-selection

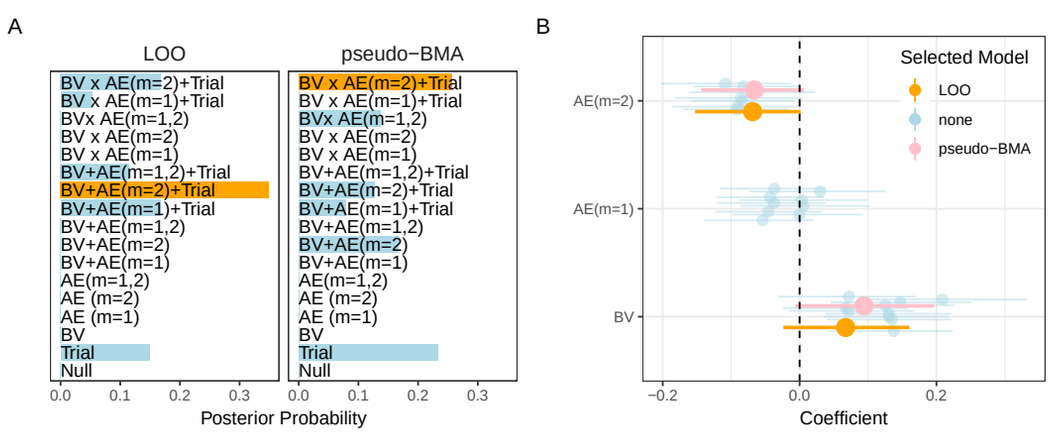

Figure 2. Model-selection results for study 2. A: Ordered probit models of increasing complexity were fit to the data. Model selection prefers models including both BV and AE with $m = 2$ but disagree on whether the BV$\times$ AE interaction should be included. B: Regression coefficients for BF and AE (m=1,2) from all models from A that include them. While AE is generally estimated to be negative (particulary for $m = 2$), BV is estimated to have a positive contribution across all models.

3 Study 3

3.1 Model-selection

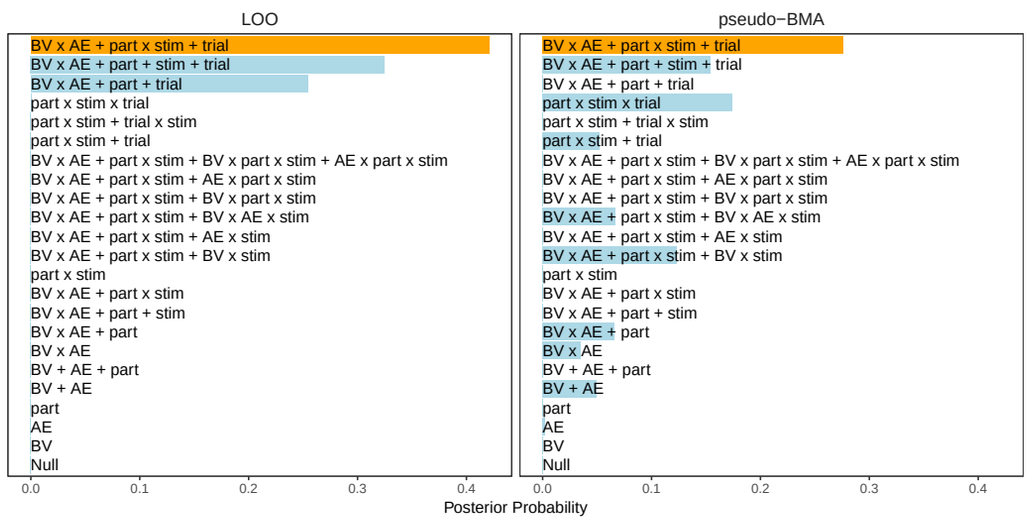

Figure 3. Model-selection results for study 3. Ordered probit models of increasing complexity were fit to the data and model-weights based on LOOIC and BMA were calculated.

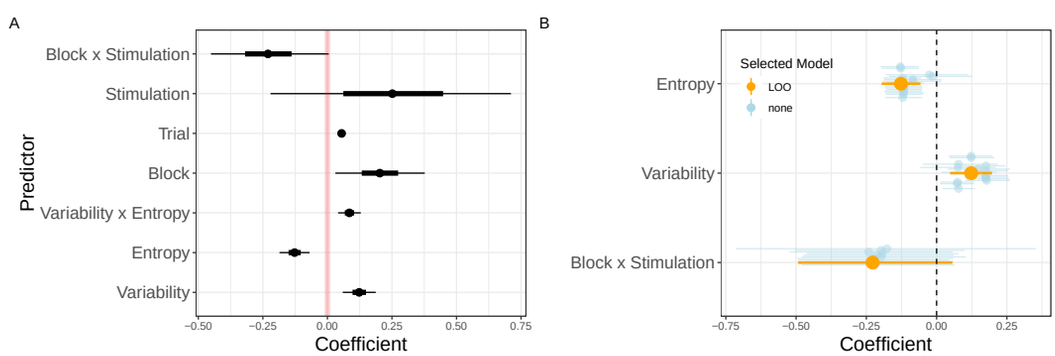

Figure 4. Model-coefficients study 3. A: All coefficients of the winning model. B: The coefficients for AE, BV and the crucial part × stimulation interaction for all of the tested models that included them.

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