MULTIMODAL INVESTIGATIONS OF SELF-REFERENTIAL COGNITION AND UNDERLYING BRAIN NETWORKS

By

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which modulates the resting state potential of neurons and is becoming widely used in both the research and clinical settings. However, to date, little is understood about the effects of tDCS on brain activity/connectivity or how this translates into behavioural changes. Mind-wandering is an interesting phenomenon due to its self-generated nature, which by definition is produced spontaneously rather than influenced by external stimuli. Therefore, it is of interest to the scientific community to understand if mind-wandering can be modulated externally via tDCS. Previous research has reported that tDCS is able to modulate self-referential cognitive processes, such as mind-wandering, assessed via subjective self-reports. Furthermore, modulations to core regions of the DMN, an intrinsic brain network typically associated with self-referential cognition, have been observed in a small number of studies applying tDCS to the right inferior parietal cortex. However, the literature is highly inconsistent, with failed replications and large variations in methodological designs, leaving the efficacy of tDCS in modulating mind-wandering unclear. Given the known association between mind-wandering and activation of the DMN, in addition to the link between impaired DMN connectivity and numerous neuropsychological disorders, it is of interest to understand the ability to modulate this intrinsically directed process with an external medium, such as tDCS. This thesis investigates the effects of tDCS on mind-wandering and underlying intrinsic brain networks. In Chapter 3, stimulation of right inferior parietal lobule failed to modulate objective and subjective reports of mind-wandering and we provide support for this lack of an effect with Bayesian analysis. Chapter 4 replicates this lack of behavioural effect with the addition of brain imaging data displaying no effect of tDCS on underlying brain activation and connectivity. Chapter 5 evaluates the effect of tDCS over the left dorsolateral prefrontal cortex on mind-wandering and on brain activation (BOLD, dynamic functional and effective connectivity). No effect of stimulation was found across all measures, and we provide evidence to support this null effect. Together, the empirical chapters presented in this thesis provide consistent evidence for the lack of an effect of tDCS in modulating mind-wandering propensity and in modulating underlying brain activity and add to the body of literature highlighting the unreliability of earlier positive reports of its effect.

Due to COVID-19, the trajectory of the thesis was then adapted to allow the analysis of existing datasets. Chapter 6 evaluates disruptions in effective connectivity in prolonged disorder of consciousness (PDOC) patients between the DMN and anterior forebrain mesocircuit (AFM). PDOC patients displayed overall reduced coupling within the AFM which led to loss of inhibition from AFM to DMN, mostly driven by posterior areas. In turn, the DMN showed disruptions in self-inhibition of the midline regions. Our results provide partial support for the mesocircuit model of consciousness.

This thesis is dedicated to
my late Mum and Nan
Julie Coulborn
&
Elaine Smith
My mind often wanders to you both
Thank you for everything

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KEY ABBREVIATIONS

AFM	Anterior Forebrain Mesocircuit
AMFG	Anterior Middle Frontal Gyrus
BMA	Bayesian Model Averaging
BMR	Bayesian Model Reduction
CRS-R	Coma Recovery Scale-Revised
CRT	Choice Reaction Task
DAN	Dorsal Attention Network
DCM	Dynamic Causal Modelling
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
ECN	Executive Control Network
EEG	Electroencephalography
FEM	Finite Element Method
FIC	Frontoinsular Cortex
FT-RSGT	Finger Tapping Random Sequence Generation Task
FWE	Family Wise Error
GLM	General Linear Model
HIPP	Hippocampus
INS	Insular
IPL	Inferior Parietal Lobule
ISI	Inter Stimulus Interval
LPFC	Lateral Prefrontal Cortex
MPFC	Medial Prefrontal Cortex
MSIT	Multi-Source Interference Task
MTG	Medial Temporal Gyrus
PCC	Precuneus / Posterior Cingulate Cortex
PDOC	Prolonged Disorder of Consciousness
PEB	Parametric Empirical Bayes
ROI	Region Of Interest
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
SART	Sustained Attention to Response Task
SMG	Supramarginal Gyrus
SN	Salience Network
SPM	Statistical Parametric Mapping
tDCS	Transcranial Direct Current Stimulation
TUT	Task-unrelated thought

LIST OF PUBLICATIONS

Below lists published work included in this thesis and outlines author contributions for each:

Paper 1

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Author contributions: SC and DF-E designed the research. SC supervised data collection and analyzed the data. SC and DF-E interpreted the data and wrote the manuscript. All authors contributed to the editing of the manuscript.

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Paper 2

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Chapter 1

INTRODUCTION TO MIND-WANDERING AND TRANSCRANIAL DIRECT CURRENT STIMULATION

1.1. Mind-wandering and its importance

Have you ever been undertaking a task, like driving a car or reading a book, and realised your mind has drifted to thinking about a previous holiday or plans later that day? This phenomenon is known as mind-wandering, whereby spontaneous shifts in attention move your focus away from the task at hand. The frequency of this shift in attention varies across individuals; however, it is thought to consume between a third and half of our daily lives (Killingsworth & Gilbert, 2010; Klinger & Cox, 1987; Song & Wang, 2012). Understanding why the mind wanders is still of considerable debate (Shepherd, 2019). Nonetheless, mind-wandering and self-generated thoughts have been associated with autobiographical planning of future events (Andrews-Hanna, Reidler, Huang, et al., 2010; Baird et al., 2011; Stawarczyk, Majerus, Maj, et al., 2011), creativity (Baird et al., 2012) and directed thinking (K. J. Gorgolewski et al., 2014). These processes have a beneficial element in that they help us prepare for the future and allow for new and inventive ideas.

On the contrary, mind-wandering is also linked to potentially negative side effects, such as disrupted learning (Wammes et al., 2016), poor task judgement and performance deficits (Antrobus et al., 1966, 1970; McVay & Kane, 2012), and reduced driving performance (Yanko & Spalek, 2014). Additionally, increased mind-wandering propensity is associated with several psychiatric disorders, including schizophrenia (Iglesias-Parro et al., 2020), depression (Hoffmann et al., 2016) and attention deficit hyperactivity disorder (Seli et al., 2015), to name a few. For this reason, research to understand the dynamic components of mind-wandering has recently exploded (Christoff et al., 2016; Murray et al., 2020). Furthermore, an ability to modulate this self-referential, inherently intrinsic process would undoubtedly be beneficial not only in real-world contexts but to clinical populations.

1.2. Defining mind-wandering

Early work from the 1960s began to investigate the concept of self-referential processes under the term “daydreaming” (Antrobus et al., 1966). Recently, the scientific terminology encompassing this internally directed process has diverged to include “task-unrelated thought”

(TUTs), “stimulus-independent thought”, and “spontaneous thought”. TUTs encompass ideation separate from the ongoing task demonstrating a failure in attentional focus (Giambra, 1989). Stimulus-independent thought refers to content unrelated to the immediate sensory input (Teasdale et al., 1993). Finally, spontaneous thoughts are mental states that freely arise with little constraint (Christoff et al., 2016). Mind-wandering, a term used widely in the scientific literature after its use by Smallwood & Schooler (2006) in their seminal paper, therefore incorporates a wide variety of mental states, with each term reflecting different aspects. To this effect, an ongoing debate surrounding the conceptual definition of mind-wandering still exists (Christoff et al., 2018; Seli, Kane, Metzinger, et al., 2018; Seli, Kane, Smallwood, et al., 2018).

Seli and colleagues advocate the family-resemblances framework to conceptualise mind-wandering (Seli, Kane, Metzinger, et al., 2018; Seli, Kane, Smallwood, et al., 2018). Here, the authors suggest that mind-wandering is considered a “heterogeneous, fuzzy-boundaried construct that coheres amid patterns of overlapping and non-overlapping features” (Seli, Kane, Metzinger, et al., 2018). Specifically, a graded membership is determined based on the number of common features (prototypicality), which captures all types of mind-wandering. For example, rather than categorising mind-wandering as explicitly relating to unintentional thought, there is no one defining feature that thoughts must have to be defined as mind-wandering; instead it is a collection of related experiences that share some, but not all, features (Seli, Kane, Metzinger, et al., 2018). Conversely, Christoff and colleagues reject the family-resemblances framework of mind-wandering, postulating it lacks a necessary defining feature that differentiates it from other types of thought (Christoff et al., 2018). Specifically, the authors suggest the family-resemblance framework fosters the use of mind-wandering to be used as an umbrella term, broadening the concept and allowing it to become more synonymous with overall “thought” (Christoff et al., 2018). Instead, they propose a dynamic framework with the defining feature of mind-wandering being “the relatively free and spontaneous arising of mental states as the mind wanders” (Christoff et al., 2016). The content of these mental states is constrained across two dimensions: deliberate and automatic. Deliberate constraints are those implemented through cognitive control and run along a continuum from minimal during dreaming, more so during mind-wandering, increased further for creative thinking, and maximal during goal directed thought. Automatic constraints are outside of cognitive control and are caused by affective and sensory salience (Christoff et al., 2016).

The debate surrounding the conceptualising of mind-wandering is ongoing. However, a review in 2016 found that most researchers (94.5%) defined mind-wandering as TUTs (Mills et al., 2018). Although commonly defined this way in the field, using the blanket of TUTs inevitably comes with its caveats. Specifically, this definition will undoubtedly capture incidences of thoughts being task-unrelated but which are not necessarily mind-wandering. For example, this definition captures episodes of external distraction caused by the environment, such as loud noises or touch sensations, which are task-unrelated but not stimulus-independent. The lack of a single gold-standard definition of mind-wandering does highlight the complex nature of conceptualising this multidimensional self-referential process. Furthermore, it demonstrates the difficulty in generalising across studies that classify mind-wandering episodes differently. Although a consensus has yet to be reached regarding the specific definition, researchers are strongly encouraged to clarify how they conceptualise mind-wandering and how it is operationally defined to participants (Seli, Kane, Metzinger, et al., 2018).

1.3. Variations of mind-wandering

According to Stawarczyk (2018), there are numerous phenomenological properties of mind-wandering (features that constitute the type of mind-wandering being experienced), including content, meta-awareness, and intentionality. The content of one’s mind-wandering arises along a temporal spectrum, such as thinking about past experiences, daydreaming about the present, and planning future events. Numerous studies have demonstrated that individuals are biased towards thinking about the future rather than the past or present (Andrews-Hanna, Reidler, Huang, et al., 2010; Baird et al., 2011, 2011; Smallwood et al., 2011; Smallwood & Schooler, 2015; Stawarczyk, 2018). The prospective bias is generally more prominent across age groups, however, reduced daydreaming, specifically future-oriented, is associated with increased age (Giambra, 1999; Maillet & Schacter, 2016). Individuals with high working memory capacity tend to mind-wander more frequently about future-oriented thought (Baird et al., 2011) and do so more frequently than individuals with lower working memory capacity (Levinson et al., 2012). Furthermore, an increased propensity to mind-wander, specifically prospectively, was found during low cognitively demanding tasks compared to high (Smallwood et al., 2009). These findings suggest an ability to use this spare cognitive capacity for autobiographical planning when task demands are low. Although less common, retrospective mind-wandering is associated with sadness and negative mood (Smallwood & O'Connor, 2011). This suggests that the content of mind-wandering is mediated by a multitude of factors, with potentially different costs and benefits.

Meta-awareness is another phenomenological feature of mind-wandering that has garnered attention, particularly given meta-awareness of one's mind-wandering is necessary during experimental paradigms that probe for task-unrelated thoughts (Schooler et al., 2004; Zedelius et al., 2015). Meta-awareness is the explicit knowledge that your mind has wandered from the immediate task (Schooler et al., 2011). Schooler et al., (2004) asked participants to read a passage of text and monitor their mental state to self-report occurrences of mind-wandering whilst intermittently presenting thought-probes which asked if they had been mind-wandering. The study found that although participants often caught periods of mind-wandering, they also reported mind-wandering when probed, indicating there were periods they were unaware of their mental state. Additional research captured mind-wandering via experience sampling and reported participants responded as being off-task on 43% of probes, of which they reported they were unaware where their attention was focussed 45% of the time (Christoff et al., 2009). Smallwood and colleagues demonstrated mind-wandering without awareness is strongly associated with response-inhibition failures compared to mind-wandering with awareness (Smallwood, McSpadden, et al., 2007, 2008). Together these studies demonstrate that a large portion of mind-wandering episodes occur without meta-awareness, which is problematic for studies relying solely on self-caught methods, with meta-awareness associated with unique neural signatures (Christoff et al., 2009) and impeding task performance differentially.

An additional phenomenological feature is intentionality, which refers to whether the episode of mind-wandering is caused by an uncontrolled or a deliberate shift in attention. These two types of mind-wandering appear to reflect unique and dissociated cognitive experiences (Giambra, 1995). Unintentional mind-wandering refers to spontaneous, uncontrolled periods of internally directed thoughts, whereas intentional mind-wandering reflects deliberate engagement in doing so. The penchant for intentional (deliberate) mind-wandering increases during an easy task, with unintentional more likely during complex tasks (Seli et al., 2016; Seli, Konishi, Risko, et al., 2018). A dissociation in intentionality has also been linked to clinical populations, with spontaneous, but not deliberate, mind-wandering associated with attention deficit hyperactivity disorder (Seli et al., 2015).

1.4. Operationalizing the study of mind-wandering

Mind-wandering has been studied in both the real world (Kane et al., 2007, 2017) and laboratory settings (Giambra, 1995), both typically via an experience sampling method. Here, participants are pseudo-randomly presented with a probe asking where their mind was immediately before the probe. In real-world settings, probes are presented randomly throughout the day with participants required to quickly assess their mental state before continuing their activities, such as “at the time of the beep, my mind had wandered to something other than what I was doing. Y / N” (Kane et al., 2007, 2017). In the lab, probes are presented throughout a task, which can be manipulated in complexity and cognitive demand, such as “where was your attention focussed just before the task? On-task / off-task” (Christoff et al., 2009). Despite the ease of implementing this technique in both settings, a divergence between how mind-wandering translates from the laboratory to the real world has been noted (Linz et al., 2021; Varao-Sousa et al., 2018). Specifically, laboratory-based mind-wandering appears to omit the fluid characteristics observed in more real-world observations. For example, making a cup of tea or knitting does not require the sustained attention demanded by lab-based tasks (Murray et al., 2020). Furthermore, unless highly attentive to one’s internal processes and aware of the transient fluctuations in mental states, people are likely to make inaccurate responses to probes, a factor highly influenced by individual differences (Seli et al., 2014). This, therefore, makes translating lab findings to real-world scenarios (and real-world findings into lab-based protocols) problematic. It is a common issue with lab-based research in psychological research, where well-constrained methodological designs are required to study intricate cognitive processes.

Despite this, considerable research has demonstrated the reliability and validity of laboratory-based observations of mind-wandering using the experience sampling method (Schubert et al., 2020). To date this is the primary and only direct method of garnering information about this internal, self-generated process. Researchers have previously manipulated cognitive load and investigated the effects of external influences on mind-wandering. Using the self-report probe method, participants are required to divulge their state of mind whilst undertaking various cognitive tasks, typically requiring sustained attention. The relationship between mind-wandering and sustained attention has been proposed to be accounted for by the perceptual decoupling theory of mind-wandering (Smallwood & Schooler, 2006). Here, mind-wandering is the result of redirecting attentional focus from the task to internally driven thoughts (Levinson, Smallwood, & Davidson, 2012). Conversely, the control failure theory posits mind-wandering results from an inability to maintain task-based attention leading to a temporary breakdown in attentional control (McVay & Kane, 2009). Both theories are still under investigation and sustained attention tasks have recently been widely adopted throughout the study of mind-wandering (Axelrod et al., 2015, 2018; Christoff et al., 2009; Filmer et al., 2019, 2021; Kajimura et al., 2019). These sustained attention tasks are typically not the focus of the research, however, are used to ensure participants are engaged with the task whilst promoting mind-wandering. Such tasks have included the choice reaction task (CRT) (Baird et al., 2011; Mason et al., 2007; Seli, Konishi, Risko, et al., 2018; Smallwood et al., 2011) and the N-back task (Turnbull et al., 2019). The CRT displays multiple stimuli with a different response required for each. The N-back task presents a sequence of stimuli, and the participant needs to decide if the current stimulus is the same as that presented N trials ago. Both tasks allow for the assessment of task demands on mind-wandering by manipulating working memory load by increasing the number of stimuli or using a larger N to increase cognitive demand. A subsequent variation, and possibly the most employed, is the sustained attention to response task (SART), which differs from the CRT and N-back by having a significantly lower level of cognitive load (Christoff et al., 2009; Robertson et al., 1997). The SART is a monotonous go/no-go task where participants press a button to each digit presentation, except a target digit that requires no response. The target appears in approximately only 5% of trials resulting in very low cognitive demand, which facilitates mind-wandering and promotes TUTs (Smallwood, McSpadden, et al., 2008), as opposed to studying the effect of task demands.

The common element of all these tasks is the use of regular probes to record the fluctuating mental states of participants. The probes used throughout these tasks vary in how they operationalise mind-wandering. For example, some studies use a binary "on-task" or "off-task" approach (Denkova et al., 2019; Kajimura et al., 2016, 2019; Zhou & Lei, 2018). This approach may be oversimplistic and inadvertently encapsulate mental states beyond those of mind-wandering as being "off-task". For example, thoughts pertaining to an external distraction, such as the noise of the MRI scanner or sensory distractions, will be included in "off-task" responses and therefore contaminate our ability to understand this self-referential process (Stawarczyk et al., 2014). In other studies, probes included a scale to report the extent of TUTs (typically from 1-minimum to 4-maximum) (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020; Filmer et al., 2019). Average rating across these studies for TUTs were around 2, with no specific definition of what constituted mind-wandering. Although this allows researchers to observe differences in the extent of TUTs, it again fails to delineate between the type of mind-wandering being experienced. Christoff et al., (2009) used a slightly longer 7-point Likert scale that rated the extent of being "completely on-task" to "completely off-task". Responses 1-3 were then categorised as "on-task" and 5-7 as "off-task", with a response of 4 eventually excluded. The authors report that participants chose option 4 on only 3% of occasions., which essentially created binary categories of "on-task" and "off-task" then used in the analysis.

To overcome some of the issues of oversimplistic probe responses, researchers have also provided more descriptive options relating to the content of mind-wandering. For example, Kajimura & Nomura (2015) gave seven choices (1. task content, 2. task performance, 3. past, 4. future, 5. state of being, 6. fantasy, 7. other) with responses 3-7 later grouped to reflect mind-wandering under the umbrella of "TUTs". The difficulty with this method is accurately explaining this to participants and obtaining reliable reports. Subsequent research presented two 4-point Likert scales allowing participants to rate how internally and externally oriented their thoughts were (1-minimum, 4-maximum for both internal and external) (Vanhaudenhuyse et al., 2011). Here, participants were periodically presented with a beep at which they responded to the probe. External was defined as the perception of environmentally sensory stimuli (visual, olfactory, auditory, and somatosensory), whereas internal was defined as environmentally stimulus-independent thoughts (e.g., wandering thoughts and autobiographical memories) (Vanhaudenhuyse et al., 2011). This method allowed for the discrimination between internally focused mind-wandering and those reflecting thoughts about the external environment. Vanhaudenhuyse et al., (2011) reported a negative correlation at the group-level between internal and external awareness with periodic shifts on average every 20s. It should be noted that the authors found substantial variability at the subject level for the strength of this anticorrelation. Ultimately, as previously mentioned, TUTs are what researchers are most interested in investigating throughout these studies (Mills et al., 2018). However, this does demonstrate the large variability and difficulty in operationalising subjective incidents of mind-wandering.

An alternative method of indirectly measuring mind-wandering comes from monitoring task performance. It is widely accepted that reduced task performance (during the SART, for example) is associated with increased mind-wandering. Specifically, mind-wandering is related to increased omissions (failing to respond) and errors (responding incorrectly) (Allan Cheyne et al., 2009; Hawkins et al., 2019; Smallwood et al., 2004) and longer reaction times to non-targets (Allan Cheyne et al., 2009; Cheyne et al., 2006; Hawkins et al., 2019; Leszczynski et al., 2017; McVay & Kane, 2009). Furthermore, increased time on task is associated with enhanced mind-wandering propensity (Stawarczyk, Majerus, Maj, et al., 2011). These task measures help validate episodes of mind-wandering captured via thought-probes and allow researchers to investigate this phenomenon objectively, whereby the individual may have been unaware of their mind-wandering. This may reveal further insight into occasions where meta-awareness is lacking, mitigating individual differences in the propensity to mind-wandering without awareness. Despite this, it should be noted that thought-probes are currently the only direct method of measuring the intrinsic process of mind-wandering.

1.5. Intrinsic brain networks

1.5.1. DMN

Recent advances in technology, such as the use of functional magnetic resonance imaging (fMRI), have allowed for the scientific study of the brain both at rest (Greicius et al., 2003) and whilst undertaking cognitive tasks (Christoff et al., 2009). These techniques enable the scientific exploration of the neural markers of mind-wandering (Christoff et al., 2009, 2016). fMRI is a non-invasive measure of neural metabolism, allowing investigations into the activation and functional correlation between brain regions (Ogawa et al., 1990; Raichle et al., 2001). One of the most influential findings of this technique was the discovery of intrinsic brain networks (groups of spatially separate regions that display coherent fluctuations in neural signal). The most commonly studied intrinsic network is the default mode network (DMN). The DMN comprises the precuneus / posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and bilateral inferior parietal lobules (IPL) (Buckner et al., 2008). This intrinsic brain network is predominantly active at rest (where the mind is free to roam with no task constraints) rather than during task completion, which initially gave rise to the term "task-negative network". However, this was later disputed, as it suggested the network was not involved in active cognitive processes (Spreng, 2012). Corroborating this, the DMN has since been shown to be active during creativity, episodes of mind-wandering and during self-generated thoughts (Andrews-Hanna et al., 2014; Beaty et al., 2015; Christoff et al., 2009). It is expected that the DMN would be recruited across various cognitive domains, particularly considering it consists of numerous, spatially independent brain regions.

Evidence from structural and functional MRI suggests the DMN is comprised of two subsystems: the medial temporal subsystem and the dorsal medial subsystem. The medial temporal subsystem comprises the hippocampus, parahippocampal cortex, inferior parietal lobules and ventromedial PFC. Conversely, the dorsal medial subsystem comprises the temporoparietal junction, temporal pole, lateral temporal cortex and dorsal MPFC. Both subsystems correlate highly with two midline core regions (PCC and anterior MPFC) (Andrews-Hanna et al., 2014). Following a meta-analysis of the available fMRI literature using NeuroSynth, the authors reveal the dorsal subsystem corresponds with mentalising, theory of mind and semantic processing. In contrast the medial temporal subsystem is associated with autobiographical thoughts, contextual retrieval and episodic memory (Andrews-Hanna et al., 2014). Additional research posited that the PCC gathers information related to the internal and external environments, whereas the MPFC evaluated this information for decision-making processes (Raichle et al., 2001), which suggests diverging roles between the subsystems which are driven by the two core midline regions. This indicates a multifaceted role of the DMN, with dissociated sub-divisions related to diverging component processes and therefore highlights the complex nature of investigating these neural processes.

The DMN has been widely investigated in relation to several psychiatric and neurological conditions. Disruptions to this network are associated with depression (Veer et al., 2010), attention deficit hyperactivity disorder (Broyd et al., 2009), schizophrenia (Zhou et al., 2018), Alzheimer's disease (Buckner et al., 2008), and disorders of consciousness (Crone et al., 2015; Fernández-Espejo et al., 2012). As previously outlined, disrupted mind-wandering propensity is associated with a number of these conditions, including schizophrenia (Iglesias-Parro et al., 2020), depression (Hoffmann et al., 2016) and attention deficit hyperactivity disorder (Seli et al., 2015), which highlights the potential synergy between the DMN and self-referential processes and the importance of understanding the neural dynamics of both.

1.5.2. Intrinsic brain networks and mind-wandering

The primary function of the DMN appears to be its direct involvement with self-referential processes, including mind-wandering and ongoing internal mentation (Andrews-Hanna, Reidler, Huang, et al., 2010; Christoff et al., 2009; Mason et al., 2007; Raichle et al., 2001). Furthermore, activation of the DMN is typically reduced as the difficulty of a memory load task increased (McKiernan et al., 2003), suggesting decreased engagement of the DMN as cognitive demands increase. Research comparing conditions of repeatedly practiced and novel working memory tasks again demonstrated increased DMN activation to more practised tasks where cognitive engagement is reduced (Mason et al., 2007). This corroborates previous research that demonstrated reduced mind-wandering during high working memory tasks (McVay & Kane, 2012). A subsequent technique used a retrospective questionnaire following resting-state fMRI to ask participants to gauge the percentage of time spent in five spontaneous thought domains (auditory mental imagery, visual mental imagery, somatosensory awareness, inner musical experience, and mental manipulation of numbers) (Chou et al., 2017). For the analysis, participants were grouped into high versus low percentile for each domain. One of the main issues with this technique is that the full rs-fMRI times series is used for analysis instead of individual occurrences of each spontaneous thought type. More commonly used now, and arguably more reliable is the method of experience sampling via the use of thought-probes, whereby participants periodically assess where their thoughts were throughout the scan (Christoff et al., 2009). This technique allows for a direct association between behavioural responses and neural activation throughout the scan.

DMN activation has been demonstrated across various domains of self-referential thinking, ranging from remembering past events (Svoboda et al., 2006), autobiographical planning (Buckner & Carroll, 2007), and thinking about others (Amodio & Frith, 2006), all of which fall under the umbrella of mind-wandering. Despite consistent recruitment during self-referential processes, the function of the DMN is not constrained to this phenomenon. For example, the DMN - specifically recruitment of the MPFC - is found during working memory tasks (Vatansever et al., 2015), typically associated with the frontoparietal network. Furthermore, the MPFC is recruited during simple reaction time tasks (Burgess et al., 2007; Gilbert et al., 2005). Overall, these studies suggests recruitment of the DMN is not specific to self-referential processes, with activation also found during more conventional 'external' tasks.

Equivalently, mind-wandering itself is not solely captured by the DMN alone. Recent research has demonstrated that this phenomenon also recruits other cortical areas of the brain. During probe-sampling, Christoff et al., (2009) found episodes of mind-wandering, particularly those that participants were not meta-aware of, recruited activation of both the DMN and ECN. Specifically, for the ECN, they report activation of the bilateral dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), two core regions of this network. The ECN is routinely involved with undertaking cognitively demanding tasks, such as attentional and mental reasoning tasks (e.g., Stroop; (Dobrynina et al., 2018)), response inhibition tasks (e.g., go/no-go; (Christoff et al., 2009)) and working memory tasks (e.g., n-back; (Mencarelli et al., 2019)), all of which display reduced performance with mind-wandering (Unsworth & McMillan, 2014). Cooperation between the DMN and ECN has been proposed in a framework attempting to understand the development and production of internally directed, task-unrelated thoughts (Smallwood et al., 2012). Additionally, the left DLPFC showed increased neural activity during episodes of "off-task" thinking throughout a 0-back (low demand) task; however displayed greater activity for episodes of "on-task" thinking during the 1-back (high demand) task (Turnbull et al., 2019). This suggests the DLPFC may act in a context-specific manner, prioritising off- and on-task thoughts depending on cognitive demands. A divergence between activation following spontaneous and deliberate mind-wandering has also been observed, with deliberate (intentional) episodes resulting in dual activation of DMN and ECN (but less so for spontaneous) (Golchert et al., 2017). A meta-analysis of 24 fMRI studies examining mind-wandering revealed consistent activation of DMN alongside non-DMN regions, specifically, dorsal ACC (part of the salience network (SN), DLPFC (a critical node of the ECN), left mid insula, secondary somatosensory cortex, lingual gyrus and temporopolar cortex (Fox et al., 2015). These results, therefore, indicate the experience of mind-wandering is not solely related to activation of the DMN, while the type of mind-wandering - and the conditions under which it arises - can recruit non-DMN regions, particularly those associated with the ECN.

Other intrinsic brain networks include the salience network (SN) and the dorsal attention network (DAN). The DAN comprises the intraparietal sulcus and frontal eye fields and is typically active when attention is focussed externally, specifically during voluntary orienting of visuospatial attention (Corbetta et al., 2008). The DAN is thought to be associated with goal-directed and stimulus-driven attention (Corbetta & Shulman, 2002); therefore, recruitment during visually based cognitive control tasks is expected (Lanssens et al., 2020). The SN consists of the dorsal ACC and anterior insular and is responsible for filtering information to maintain goal-directed behaviour by shifting attention between internal and external focus via projections to DMN and ECN (Menon, 2011). Mindfulness relates to attentional experiences pertaining to the present moment and has been associated with brain activity across regions of the DMN, SN and ECN. Specifically, mindfulness scores correlated with functional connectivity between all three networks (Doll et al., 2015). Although mindfulness is a separate phenomenon from mind-wandering, an overlap between the networks employed during both is likely given the shared self-referential properties. Therefore, given the complex nature of mind-wandering, it is expected that this phenomenon would recruit and encompass a wide range of brain networks as the mind shifts from goal-directed to self-referential processes.

1.5.3. Anticorrelated intrinsic networks

Early research discovered an anticorrelation between some intrinsic brain networks, specifically between the DMN and both DAN and ECN (Fox et al., 2005). Subsequent research aimed to investigate the mediation between these networks by employing a rest condition, a continuous self-paced/attended sequential finger tapping condition, and a movie watching condition to engage the DMN, DAN and ECN (Gao & Lin, 2012). During finger tapping, the ECN exhibited positive correlations with DAN and negative correlations with DMN. During movie watching, the ECN was anticorrelated with the DAN and positively correlated with the DMN. The results provided more evidence for the anticorrelation of these intrinsic networks and suggest that the ECN regulates the relationship between DAN and DMN (Gao & Lin, 2012). These anticorrelations in neural activity may mirror the relationship observed between the anticorrelations in behavioural responses to the mind being externally and internally directed, as previously demonstrated (Vanhaudenhuyse et al., 2011). Supporting this, in a second experiment, Vanhaudenhuyse et al., (2011) asked participants to periodically rate how internal and external their thoughts were during fMRI. They observed correlations between activation in DMN regions (PCC and hippocampus) and internal responses, and ECN regions (DLPFC) correlated with external responses. Interestingly, they found activation of the IPLs (part of the DMN) for external awareness, demonstrating a dissociated role between midline and parietal regions of the DMN.

Despite this, the view that an anticorrelation exists between these networks may be slightly oversimplistic and has subsequently been challenged. Notably, the method used by Fox et al., (2005) and Goa & Lin (2021) relied on global signal regression, and its use has been highly debated. Global signal regression is predominantly used on rs-fMRI to remove artefacts driven by motion and respiration (Li et al., 2019). The technique has been shown to induce negative signals in fMRI analysis and is suggested to be the underlying cause of the observed anticorrelations (Murphy et al., 2009). Specifically, Murphy et al., (2009) demonstrated that negatively correlated voxels were only visible after global signal regression (opposed to without). Additionally, a meta-analysis of studies demonstrating an anticorrelation between intrinsic brain networks found the DMN and DAN to be independent, not anticorrelated, when global signal regression was not included (Dixon et al., 2017). The authors established that the DMN does demonstrate weak anticorrelations with the DAN but only with the medial temporal subsystem, associated with the PCC, not the dorsal medial subsystem. Furthermore, they conclude that the relationship between these two networks fluctuates over time and may be mediated by interactions with the ECN (Dixon et al., 2017). These mediations may be driven by positive connectivity between the ECN and DAN to allow external focus, and positive connections between the ECN and DMN to support internally directed cognition; the latter may also help explain aforementioned dual ECN and DMN activation observed during episodes of mind-wandering (Smallwood et al., 2012; Spreng et al., 2010). Therefore, further research is necessary to delineate the relationship between these intrinsic networks and understand their role in cognitive processes such as self-referential thought.

1.6. Brief overview of tDCS

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique and is now one of the most widely used neuromodulation techniques administered in both research and clinical settings (Dubljević et al., 2014). It delivers a low constant current (usually between 1-2mA for 20 minutes) to the brain, typically administered by placing two electrodes on the scalp, although new techniques, such as high definition tDCS (HD-tDCS), use a multi-electrode set-up to improve focality (Mikkonen et al., 2020; Nitsche et al., 2008). Stimulation shifts the resting membrane potential of neurons with anodal (positive) stimulation increasing cortical excitability and cathodal reducing it (Nitsche & Paulus, 2000). tDCS, therefore, allows us to make inferences about the role of cortical regions in cognitive functions. However, it should be noted that this classical view of an anodal-excitatory and cathodal-inhibitory effect has been challenged, particularly within the cognitive domain (Jacobson et al., 2012). Early work from motor studies found effects of single-session tDCS can last up to 1-hour post-stimulation, and more recent work using prefrontal stimulation found neural and behavioural effects lasted up to 5-hours on a forced-choice target discrimination task (Reinhart & Woodman, 2014). These lasting effects allow researchers to investigate the consequences of stimulation with tasks and behavioural measures.

Following some success in the motor field, researchers began to investigate the effects of brain stimulation on cognitive function. Encouragingly, tDCS demonstrated improvements to working memory (Brunoni & Vanderhasselt, 2014; Polizzotto et al., 2020), speed and accuracy on an adapted 2-back paced auditory serial addition task (Wiegand et al., 2019), and enhanced planning abilities (Dockery et al., 2009). Furthermore, tDCS has demonstrated promise across numerous patient populations, including schizophrenia (Hoy et al., 2014), depression (Meron et al., 2015), Parkinson’s (Benninger et al., 2010), stroke (Schlaug et al., 2008) and disorder of consciousness (Aloi et al., 2021).

Using multimodal brain imaging techniques, subsequent research has begun to investigate the neurological effects of tDCS to uncover the mechanisms behind the behavioural and clinical observations. Anodal stimulation of left DLPFC at rest, compared to sham, has suggested resting-state functional connectivity changes in the DMN and ECN (Keeser et al., 2011). Using concurrent fMRI and tDCS, anodal stimulation of the right inferior frontal gyrus improved response inhibition during the stop-signal task with increased activation of the SN observed in participants with high fractional anisotropy within the SN (Li, Violante, Leech, Hampshire, et al., 2019). Concurrent stimulation of right IPL and left DLPFC during a creative thinking task induced functional and effective connectivity changes within the DMN as detected by electroencephalography (EEG) (Koizumi, 2020). Furthermore, a recent systematic review of 16 studies found tDCS induces brain activation changes in patients with neuropsychiatric disorders (Chan & Han, 2020). Specifically, they note that tDCS appears to normalise aberrant brain activation in schizophrenia and substance abuse patients. Together, the results of these multimodal imaging studies suggest an ability to externally modulate underlying activity with tDCS inducing neural changes in the brain, both at rest and whilst undertaking cognitive tasks, that can have significant clinical importance.

Despite these initial findings, concerns of the efficacy of this method have begun to surface, with a meta-analysis in 2015 suggesting there was little-to-no reliable effect on cognitive/behavioural measures (Horvath et al., 2015). A subsequent review found unreliable evidence of neurophysiological effects of tDCS beyond those of motor-evoked potentials (Horvath et al., 2015a). However, it should be noted that this meta-analysis has been highly criticised as being overly pessimistic and failing to highlight some of the successful replications within the field (Filmer et al., 2020). However, inconsistent results are prominent. For example, DLPFC-tDCS increased working memory capacity in one study and decreased it in another (Tremblay et al., 2014). Furthermore, tDCS allows researchers and clinicians to manipulate and define numerous parameters (such as electrode placement, polarity, current intensity, and duration of stimulation). This flexibility in administration has resulted in a lack of standardisation of methods and an inability to effectively compare studies (Reinhart et al., 2017). Hence, meta-analyses are problematic due to heterogeneity in study designs and inclusion criteria.

One of the significant contributors to the lack of reliability and replicability in the tDCS field is likely driven by large interindividual differences in response to tDCS. A comprehensive review demonstrated that numerous factors are attributed to this variability in individual responsiveness, notably, baseline cognitive function and brain anatomy (Li et al., 2015). Baseline cognitive function refers to participants' initial abilities prior to intervention and has been shown to significantly influence the responsivity to tDCS. In a visual short-term memory task, tDCS over the right posterior parietal cortex improved performance for participants who performed poorly at baseline, however, no improvement was found for those who displayed high performance pre-stimulation (Tseng et al., 2012). Additional research only observed effects of tDCS on visual sensitivity when the group was split between good and poor performers at baseline, with only the poor performers significantly impaired by tDCS (Learmonth et al., 2015). Collectively, this research indicates that baseline levels of cognitive function mediate the effects of tDCS, which may relate to neuronal or behavioural ceiling effects (Li et al., 2015).

Somewhat related to baseline cognitive function is the neurological state of the brain during stimulation. tDCS can be delivered at rest, where the mind is unconstrained and free to wander, or whilst performing a task, with varying neurophysiological effects (Stagg et al., 2011). In the cognitive domain, performance enhancements in a serial addition task following left DLPFC tDCS were observed when stimulation was paired with high working memory task (3-back) compared to both sham and low working memory task (1-back) during tDCS, thus indicating cognitive demands during stimulation influence effects of post-stimulation performance (Gill et al., 2015). The interaction between stimulation and brain state was further investigated during two motor practising tasks: facilitatory and non-facilitatory. Results demonstrated tDCS-induced plasticity in the motor cortex was task-dependent with reduced learning during the facilitatory task and increased during the non-facilitatory. These findings indicate the effects generated by tDCS are dependent on excitability changes induced by the task and when concurrent modulatory approaches are combined it may hinder neuroplasticity (Bortoletto et al., 2015). Further brain-state dependent effects of tDCS have been demonstrated on brain activity and connectivity even in the absence of behavioural modulations. Stimulation of the right inferior frontal gyrus was delivered at rest and during the CRT. In the rest condition, tDCS increased activation of the DMN and deactivated the SN. Whereas, when stimulation was delivered concurrently with the CRT, tDCS increased activation in the SN (Li, Violante, Leech, Ross, et al., 2019). This, and other research, indicates the large variability in the effects of tDCS relating to the brain state during stimulation. Studies currently use a combination of tDCS at rest and tDCS concurrent with task. Therefore, differences in brain state and susceptibility to stimulation may be a contributing factor to the lack of consistency in the literature.

Differences in brain anatomy have repeatedly been shown to have marked effects on current density (Opitz et al., 2015). Much of the electric current is shunted by the scalp, and the proportion reaching the brain is influenced by skull thickness (Opitz et al., 2015). Furthermore, idiosyncratic cortical folding greatly influences the electric field (Opitz et al., 2015). Simulation software packages (such as SimNIBS (Saturnino et al., 2019; Thielscher et al., 2015) and ROAST (Huang et al., 2019)) are now available to create individual current simulations by manipulating various parameter settings (e.g., current intensity, electrode size and placement). This technique can be used to assess differences in responsivity to tDCS following data collection by comparing modelled current density in specific regions with task performance. For example, participants who showed tDCS-induced enhancements in working memory tasks were estimated to have larger current density over the DLPFC compared to other participants, suggesting the inconsistent behavioural outcomes may be attributed to anatomical differences (Kim et al., 2014). The software does allow simulations in reference head models, which enables researchers and clinicians to more specifically tailor tDCS protocols to target specific brain regions based on an a priori hypothesis. Additionally, modelling current density can allow individually tailored montage and dosage to take into consideration anatomical difference and control the current density over the targeted regions (Thair et al., 2017). However, this can be costly as individual structural magnetic resonance images are required to generate segmented head models. Given that approximately only 25% of the applied current to the scalp enters the brain (Vöröslakos et al., 2018) and this is largely influenced by skull thickness (Akhtari et al., 2002), individual differences in anatomical morphology have a significant influence on current density and therefore the validity of these models is crucial to the field. Comparing in-vivo intra-cranial recordings with simulated electric fields are considered the gold-standard in validating these methods which is notoriously difficult due to the ethical considerations of such invasive techniques. Indeed, to-date, only a handful of studies have managed to investigate the validity of these simulations. Despite this, a small number of studies have used surgical epilepsy patients to test simulated electric fields against intra-cranial recordings during stimulation (Huang et al., 2017; Opitz et al., 2018). Notably, Huang et al., (2017) tested 10 epilepsy patients and found high correlations between simulated electric field magnitudes and intra-cranially recorded values (for both cortical, r = 0.86, and depth, r = 0.88, electrodes). Opitz et al., (2018) studies two epilepsy patients and observed slightly lower correlations with one participant's electric field being underestimated, whereas the second being too high. A prevailing issue with intra-cranial measurements is that such invasive techniques change the volume conduction properties in the head (Puonti et al., 2020). Non-invasive approaches of reconstructing transcranial electric stimulation have also been investigated (such as, magnetic resonance current density imaging) with the initial results from five subjects showing a moderate underestimation of current densities (Göksu et al., 2018).

1.7. tDCS and mind-wandering

Recently, research has investigated the ability of tDCS to modulate mind-wandering and the underlying brain networks associated with it (see (Chaieb et al., 2019) for a review). An ability to externally modulate mind-wandering is of great interest to neuroscience and clinical psychology given its inherently intrinsic, self-referential basis, which is unique to each individual. **Table *1.1*** lists the available published articles investigating the use of tDCS on mind-wandering propensity and summarises the study design and reported effects of tDCS for each. **Table *1.2*** lists the studies that included fMRI analysis.

1.7.1. tDCS targeting DLPFC

Initial reports of tDCS modulating mind-wandering came from stimulation of the left DLPFC (Axelrod et al., 2015), with the active anodal electrode over the left DLPFC and the return over the right supraorbital area. Fourteen participants completed both anodal and sham DLPFC-tDCS conditions during the SART with interspersed probes rating their TUTs (4-point Likert scale). The task was administered during and after 20 minutes of 1mA tDCS. A second experiment assessed whether effects of tDCS were region-specific using a between-subjects design with three conditions: anodal-DLPFC (11 participants), sham-DLPFC (10 participants), and anodal-occipital cortex (10 participants). The authors found anodal stimulation of the left DLPFC increased mind-wandering propensity compared to both control conditions (Axelrod et al., 2015). They observed no change in SART performance as measured by reaction times to non-targets and commission errors to targets, suggesting the DLPFC plays a vital role in regulating mind-wandering by enhancing working memory capacity to allow for increased mind-wandering without impeding task performance. However, a commentary on these findings highlighted the role of meta-awareness in self-report methods of capturing mind-wandering, suggesting stimulation of the DLPFC may have influenced the meta-awareness of mind-wandering rather than its propensity (Fox & Christoff, 2015). Axelrod and colleagues subsequently conducted a replication study to address these critiques using a similar design with the addition of a meta-awareness probe (1 minimal – 4 maximal) and a larger sample size (between subjects, total N= 85) (Axelrod et al., 2018). The study also used a larger electrode size for the target (7 x 5cm compared to 4 x 4cm) with a longer stimulation period (30 minutes). Axelrod et al., (2018) replicated their initial findings of increased TUTs in anodal compared to control conditions, without influencing task performance or meta-awareness, suggesting mind-wandering propensity could indeed be modulated by DLPFC-tDCS, and this was not regulated by meta-awareness.

An additional commentary on the seminal paper by (Axelrod et al., 2015) suggested that due to the location of the return electrode over the right supraorbital cortex (7 x 5cm) and coarse density of current flow, the tDCS may have influenced several cortical areas (Broadway et al., 2015). This is particularly true of larger electrodes sizes which reduce focality and increase inter-subject variability in electric field distribution (Laakso et al., 2017). Specifically, Broadway and colleagues posit that the cathode may have been stimulating the DMN directly via the MPFC, resulting in increased mind-wandering. A recent simulation study corroborated this assumption with bipolar montages targeting left DLPFC and right supraorbital area resulting in modelled electric fields of comparable strength in both the DLPFC and the MPFC (Csifcsák et al., 2018). **Figure 1 A)** displays a visual representation for the E-field distribution under a similar montage to Axelrod et al., (2015) and demonstrates the large current dispersion across the frontal areas of the cortex. It is worth noting here that the spatial specificity of most bipolar tDCS montages is very coarse. **Figure 1 B) and C)** display the E-field distribution for two alternative montages (electrodes placed over the right IPL and left DLPFC in B) and right IPL and left cheek in C)) both of which demonstrate a severe lack of spatial specificity of current flow, with several regions being stimulated simultaneously. This lack of spatial specificity across montages highlights the difficulty in understanding which regions or networks are driving any effects of tDCS. Therefore, the inclusion of fMRI to corroborate the spatial localisation of the effects is a useful tool for the field to adopt, where possible.

Throughout this thesis when referring to tDCS over different brain areas, we are referring to the placement of the electrode and not to the direct stimulation of that region alone.

Despite this initial success, a large-scale, pre-registered replication study (Boayue, Csifcsák, Aslaksen, et al., 2020) did not replicate the initial findings (Axelrod et al., 2015). Using a multi-site between-subjects design with 192 participants, the authors provide Bayesian evidence for the lack of an effect of tDCS. Additional research using a similar protocol during the same task (SART) could not to replicate the anodal-tDCS results (Filmer et al., 2019). However, Filmer and colleagues did observe increased mind-wandering compared to sham when using 2mA cathodal stimulation (Filmer et al., 2019). These results demonstrate a lack of polarity-specific effects of tDCS given both anodal and cathodal stimulation apparently increased mind-wandering. They, therefore, question the interpretation of the initial results by Axelrod et al., (2015) who posited anodal stimulation up-regulated the DLPFC, allowing increased mind-wandering without impeding task performance. However, it should be noted that Filmer et al., (2019) measured mind-wandering post-tDCS only, with stimulation delivered at rest (whereas Axelrod et al., (2015) delivered tDCS during SART), therefore the differences in brain states during stimulation may contribute to the contradictory effects.

Additional research used 2mA anodal HD-tDCS over the left DLPFC during a novel finger tapping random-sequence generation task (FT-RSGT) and observed reduced mind-wandering propensity compared to sham (Boayue, Csifcsák, Kreis, et al., 2020). These results are in the opposing direction to Axelrod et al., (2015, 2018) who found anodal stimulation increased mind-wandering. HD-tDCS offers a more focussed approach to the typical bipolar montage by using smaller electrodes positioned strategically on the scalp to shape the electric field over the targeted region (Csifcsák et al., 2018). Although promising, the use of HD-tDCS, with double the current intensity and a novel task compared to the initial research by Axelrod et al., (2015), make it difficult to pinpoint whether the focality, higher electric fields, or underlying brain state during stimulation (or a combination) account for the observed differences in polarity-specific effects. Overall, failure to reproduce results and lack of consistency in both the findings and methodological protocols has resulted in insufficient evidence to determine the efficacy of DLPFC-tDCS on modulating mind-wandering propensity.

1.7.2. tDCS targeting intrinsic networks

In addition to the research targeting the DLPFC, further research has incorporated alternative stimulation sites to modulate mind-wandering. Kajimura & Nomura (2015) delivered anodal and cathodal stimulation (alongside a sham condition) to the left lateral prefrontal cortex (LPFC) and right IPL simultaneously, targeting the ECN and DMN, respectively. It is worth noting that the electrode placement for the left LPFC was slightly more lateral/anterior and larger than the previous research stimulating the ECN (EEG 10/20 position AF7, 7 x 5cm for Kajimura and Nomura (2015) compared to position F3 (left DLPFC), 5 x 5cm for (Axelrod et al., 2015; Boayue, Csifcsák, Aslaksen, et al., 2020; Filmer et al., 2019)). Participants were given 20 minutes 1.5mA tDCS (at rest) in either an anodal, cathodal, or sham condition before completing a perceptual load task with interspersed thought-probes (7 response options, see **Table *1.1***). The perceptual task requires visual detection of target letters placed amongst non-target letters, which are to be ignored, with low and high perceptual load conditions (one and five distractor letters, respectively). In addition to this, a flanker letter appeared under equal probability, which would be congruent or incongruent to the target letter. Kajimura & Nomura (2015) found anodal right IPL/cathodal left LPFC stimulation led to reduced mind-wandering propensity compared to cathodal right IPL/anodal left LPFC stimulation. No difference for either condition was found with sham. The study used a between-subjects design with mind-wandering propensity assessed post-stimulation, therefore, the observed differences may be attributed to individual differences in baseline levels of mind-wandering. Regarding the effect of tDCS on task performance, the study found a significantly reduced flanker effect in low-load conditions for anodal right IPL and approaching significance for cathodal right IPL stimulation both compared to sham. The authors suggest that although anodal and cathodal stimulation have different mechanisms, they had the same modulation of interference and distractor processing on the task.

Subsequent research aimed to investigate the polarity-specific and dosage-dependent effects of tDCS on mind-wandering by dual stimulation of the ECN and DMN (Filmer et al., 2021). Electrodes (5 x 5cm) were placed over the left DLPFC (F3) and the right IPL with participants randomly assigned to one of five conditions: sham; 1mA anodal left DLPFC; 2mA anodal left DLPFC; 1mA cathodal left DLPFC; or 2mA cathodal left DLPFC (return over right

IPL). Post-tDCS at rest, participants completed the SART with interspersed probes rating TUTs (Likert scale 1-7). Filmer et al., (2021) observed increased mind-wandering for anodal-DLPFC stimulation at both 1 and 2mA compared to sham. Interestingly, the effects were not linear with dosage, as predicted, instead a slight reduction (although not significant) in mind-wandering was observed in the 2mA condition compared to 1mA. A significant increase in mind-wandering was observed between 1mA anodal DLPFC and cathodal DLPFC conditions. Task performance, as assessed by target accuracy, was found to be influenced by tDCS and dosage, with reduced accuracy found for higher doses of tDCS, independent of polarity. This result shows a dissociation with effects found for mind-wandering (polarity-specific, but not dosage) and indicates variations in performance may not reflect changes in mind-wandering, perhaps modulated by other attentional processes. The results from Filmer et al., (2021) support the initial findings from Kajimura & Nomura (2015) and suggest anodal DLPFC/cathodal IPL stimulation increases mind-wandering. However, a direct comparison between the studies is not possible due to numerous methodological differences, including electrode size, task used, assessment of TUTs, and the placement of the left prefrontal electrode. These findings suggest an effect of tDCS; however, due to the dual network stimulation, it is unclear whether stimulation of the ECN or the DMN (or both) was necessary to elicit such modulations. See **Figure 1 B)** for a visual representation of the E-field distribution using this montage.

Examining the neural bases of tDCS-induced modulations in mind-wandering propensity, Kajimura and colleagues conducted a follow-up study of their original work (Kajimura et al., 2016). Here, they included resting-state fMRI pre- and post-stimulation to assess changes in connectivity within the DMN induced by tDCS. The stimulation protocol and task were the same as that used earlier (Kajimura and Nomura, 2015); however, probes were amended to a binary choice (“on-task” and “off-task”). The authors replicate their original findings, observing reduced mind-wandering following anodal right IPL stimulation (return over left LPFC) compared to cathodal (not sham). No effect was reported on task performance. The rs-fMRI analysis observed modulations in the effective connectivity within the DMN following anodal right IPL stimulation. Specifically, they found reduced coupling to the PCC from both the right IPL and MPFC. In the cathodal condition, they found increased coupling from the MPFC to the PCC. Kajimura et al., (2016) conducted mediation analysis to assess whether the effects of tDCS on mind-wandering were mediated by changes in the effective connectivity of the DMN. The coupling from the right IPL to the PCC inhibited mind-wandering in the anodal condition, whereas the connection from the MPFC to PCC facilitated it. These results suggest manipulations to the PCC (specifically via the right IPL and MPFC) play a vital role in mind-wandering. Given the observed modulation from the MPFC here and the aforementioned commentary on the large electrode size and electric field distribution over the frontal cortex (Broadway et al., 2015), Kajimura et al., (2016) may in fact have stimulated the MPFC, opposed to the targetted LPFC, which would suggest modulations in mind-wandering are being driven by changes in the DMN alone. A notable limitation of this study is that mind-wandering was assessed only after stimulation (and following a 6-minute resting-state scan) with baseline levels of mind-wandering taken on a separate day, leaving the observed effects of tDCS susceptible to inter-subject variability in mind-wandering.

Subsequent research from this lab directly stimulated the IPL with the return electrode placed over the contralateral cheek (Kajimura et al., 2019). (See **Figure 1 C)** for simulated E-field distribution). Participants were split into right or left IPL groups, each completing anodal (1.5mA) and sham conditions at least one week apart. Mind-wandering was again assessed post-stimulation only using the binary “on-task” or “off-task” categories during the SART. Anodal right IPL stimulation reduced mind-wandering compared to sham, with no effect on task performance. Anodal left IPL stimulation had no effect on mind-wandering but reduced reaction times to SART. Reduced mind-wandering in the right IPL group suggests the previous modulations in studies which placed electrodes over this region (and the prefrontal cortex) (Filmer et al., 2021; Kajimura et al., 2016; Kajimura & Nomura, 2015) were being driven through stimulation of the DMN via the IPL. The authors included rs-fMRI pre- and post-stimulation and found increased coupling from the MPFC to bilateral medial temporal lobes and right middle temporal gyrus and reduced coupling from bilateral IPLs to both medial temporal lobes after anodal IPL stimulation. Although promising, these results are yet to be replicated. In addition, numerous studies have demonstrate large inter-subject variability in individual mind-wandering propensity at baseline (Killingsworth & Gilbert, 2010; Klinger & Cox, 1987; McVay & Kane, 2009; Song & Wang, 2012). Therefore, given the small sample size (14 in right IPL condition), limited number of probes (10), and lack of baseline levels of mind-wandering pre-stimulation used by Kajimura et al., (2019), the effect may be driven solely by inter-subject variability.

Chou et al., (2020) also attempted to modulate mind-wandering via stimulation of the IPL. They assessed mind-wandering before and after 30 minutes of HD-tDCS over bilateral IPL, applying 1mA anodal stimulation to both hemispheres simultaneously with the target electrodes over P3 and P4. Participants were presented with thought-probes throughout a Multi-Source Inference Task (MSIT) asking whether their attention was on the task or something else, then probing whether off-task content was about the past, present or future and whether it was positive, neutral, or negative. No effect of tDCS on mind-wandering propensity was observed, however, they did report an effect on the content of mind-wandering, with cathodal stimulation reducing the frequency of negative past thoughts. Given the IPLs are primarily coupled with regions in the DMN medial temporal subsystem, which is associated with thinking about the past and the future (Andrews-Hanna, Reidler, Sepulcre, et al., 2010), bilateral simulation of the IPLs may have driven the observed reduction in mind-wandering about the past. However the effect of cathodal HD-tDCS was in the opposite direction to what Chou et al., (2020) hypothesised (cathodal stimulation would increase mind-wandering about the past) based on previous research observing increased connectivity within the medial temporal subsystem following inhibitory low frequency repetitive TMS to the left IPL (Eldaief et al., 2011). The differences in stimulation method and montage and task could account for the lack of effect on overall propensity as compared to solo right IPL stimulation by Kajimura et al., (2019). Furthermore, only eight thought-probes were included per run of the task, which may have been insufficient to accurately capture changes in mind-wandering.

Additional research has attempted to directly stimulate the DMN by placing the cathode over the MPFC and an extracephalic electrode over the right deltoid (Bertossi et al., 2017). In a between-subjects design (N=24 per group), they found cathodal stimulation of the MPFC (2mA for 15 minutes) reduced mind-wandering during a CRT task compared to sham and occipital stimulation. This is consistent with research indicating ventromedial PFC damage reduced mind-wandering in patients with lesions to the ventromedial PFC compared to controls and patients with lesions outside the ventromedial PFC (Bertossi & Ciaramelli, 2016). Furthermore, they found no modulation of task performance. This suggests tDCS over multiple regions of the DMN (right IPL and MPFC) can modulate mind-wandering. Given that both cathodal stimulation of the MPFC and anodal stimulation of right IPL (Kajimura et al., 2019) reduced mind-wandering propensity, it would suggest that within the DMN, the MPFC is involved with increasing mind-wandering, whereas the right IPL reduces it. It is worth noting here that Bertossi et al., (2017) only found an effect in men and little explanation is currently available as to why the effects of tDCS would be gender-specific.

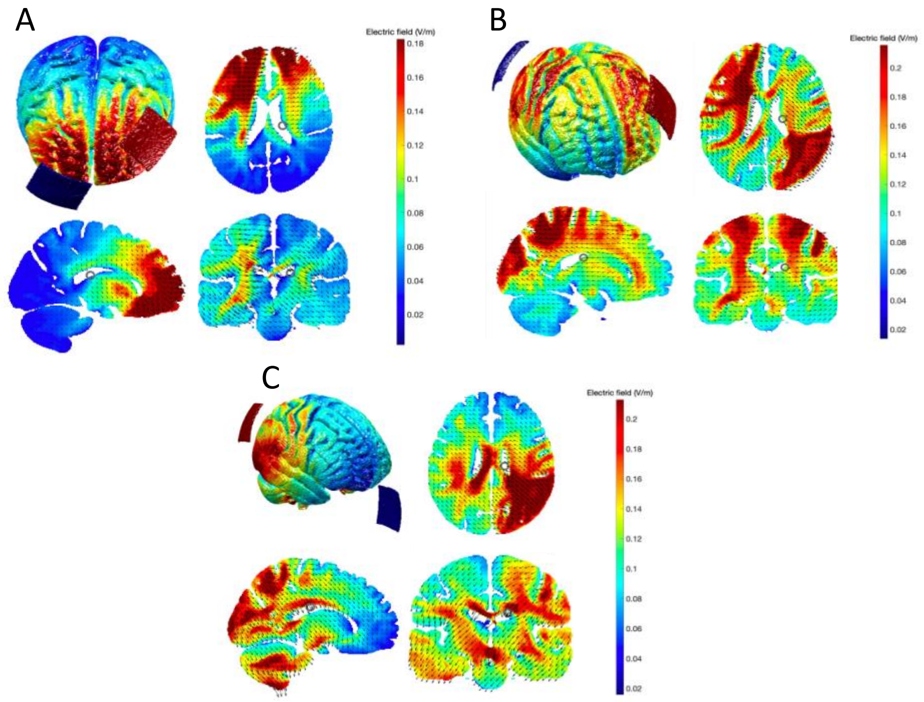

Figure 1: Computational models produced with the open-source tool ROAST for the simulation of transcranial direct current stimulation (tDCS). The current magnitude and distribution was simulated using the default 'MNI152_T1_1mm' template based on delivering 1.5mA current using bipolar montages with electrode size 5 x 5cm (anode, red patch; cathode, blue patch). A) Anode electrode over the left DLPFC (F3) with cathode placed over the right supraorbital area (Fp2) (similar to Axelrod et al., (2015)). B) Anode placed over the left DLPFC (F3) with cathode placed over the right IPL (P4) (similar to Kajimura et al., (2016, 2018) and Filmer et al., (2021)). C) Anode electrode over the right IPL (P4) with cathode over contralateral cheek (similar to Kajimura et al., (2019)). Colour chart on the right represents the magnitude of the electric field in Volts per meter. The default conductivities were used for the simulation (white matter 0.126 S/m; gray matter 0.276 S/m; cerebral spinal fluid 1.65 S/m; bone 0.01 S/m; skin 0.465 S/m; air 2.5e-14 S/m; gel 0.3 S/m; electrode 5.9e7 S/m).

1.7.3. Summary of tDCS effects

Overall, the literature on tDCS to modulate mind-wandering demonstrates a lack of replicability, uncertainty of polarity-specific effects, and a lack of consistent study design.

Specifically, variations in the administration of tDCS include electrode size and position, brain state during stimulation, cognitive task (and therefore varying cognitive processes recruited), and length of stimulation. Additionally, various methods of operationalising mind-wandering/TUTs have been used with inconsistent control of baseline propensity resulting in susceptibility to influences of inter-subject variability (Killingsworth & Gilbert, 2010; Klinger & Cox, 1987; McVay & Kane, 2009; Song & Wang, 2012). Furthermore, the literature demonstrates a lack of consistent effects on task performance in terms of polarity specificity and in relationship with mind-wandering. Together this has resulted in limited insight into the efficacy of modulating mind-wandering via tDCS, the interplay between mind-wandering and executive function, and on our understanding of which networks and regions may be responsible for driving any modulations. Therefore, this demands tightly controlled studies using within-subjects design and inclusion of baseline levels of mind-wandering to mitigate subject variability. Furthermore, only two studies have investigated the effects of tDCS on the neural correlates of mind-wandering using fMRI (Kajimura et al., 2016, 2019) (see **Table *1.2***). Therefore, more research employing TDCS is needed to delineate its neural basis of and ability to modulate this phenomenon. This provides the motivation for the current research project.

Table 1.1: *Studies using tDCS to modulate mind-wandering propensity.*

Authors	Stimulation site: anode	Stimulation site: cathode	Stimulation conditions	Control condition(s)	Design (No of participants)	Task	Probes	Timing of task	Findings / Effect of tDCS on mind-wandering	Effect of tDCS on task performance?
Axelrod (2015)	Left DLPFC (F3)	Right supraorbital	1 mA 20 min 7 x 5 cm cathode, 4 x 4 cm anode	Exp 1: Sham, 2min Exp 2: Occipital (Oz, anode vs Cz), Sham	Exp 1: Within (14) Exp 2: Between: anode F3 (11), anode Oz (11), sham (10)	SART	TUTs (1-4)	During and post-stimulation	Increased TUTs compared to both control conditions.	None
Kajimura (2015)	Left LPFC (AF7) / right IPL (P4)	Right IPL / left LPFC	1.5 mA 20 min 7 x 5 cm	Sham, 30s stimulation	Between: anode (24), cathode (24), sham (25)	Perceptual load (flanker) task	1. task content, 2. task performance, 3. past, 4. future, 5. state of being, 6. fantasy, 7. other. 3-7 classed at TUTs	Post-stimulation	Anodal IPL significantly reduced TUTs compared to cathodal IPL (no difference with sham)	Flanker effect for tDCS compared to sham
Kajimura (2016)	Left LPFC (AF7) / right IPL (P4)	Right IPL / left LPFC	1.5 mA 20 min 7 x 5 cm	Sham, 30s stimulation	Between: anode (20), cathode (19), sham (21)	Perceptual load (flanker) task	Were you thinking about something (Y/N) - where was you attention (on/off task)	Post-stimulation	Anodal IPL significantly reduced off-task compared to cathodal IPL (no difference with sham)	None
Bertossi (2017)	Right deltoid	MPFC	2 mA 15 min 5 x 5 cm cathode, 4 x 7 cm anode	1) Sham, 30s 2) Occipital (cathode, Oz)	Between (24 each)	Choice reaction time task	TUTs (0-100) If > 0: past, present, future, external, time not clear, unaware & self, other, unrelated to people	Pre- and post-stimulation	MPFC tDCS reduced off-task compared to sham and occipital in men only	None

Axelrod (2018)	Left DLPFC (F3)	Right supraorbital	1 mA 30 min 7 x 5 cm anode, 5 x 5 cm cathode	1) Sham, 2min 2) Occipital (Oz, anode vs Cz)	Between: F3 (30), Oz (27), sham (28)	SART	TUTs (1-4) Then also awareness (1-4).	During and post-stimulation	Increased TUTs compared to both control conditions	None
Kajimura (2019)	Right IPL (P4) / left IPL (P3)	Contralateral cheek	1.5 mA 20 min 7 x 5 cm	Sham, 30s stimulation	Mixed: randomly assigned to anode, P4 (13) or anode, P3 (14). Both completed sham	SART	Where was your attention 'on/off task' 'aware/unaware'	Post-stimulation	Reduced off-task for right IPL compared to sham. No effect on awareness	RT decreased for left IPL comparted to sham
Filmer (2019)	Left DLPFC (F3) / right orbitofrontal	Left DLPFC (F3) / right orbitofrontal	1 mA anode F3 1 mA cathode F3 1.5 mA cathode F3 2 mA cathode F3 20 min, 5 x 5 cm	Sham 15s stimulation	Between (30 per group)	SART	TUTs (1-4)	Post-stimulation	2mA cathode F3 increased TUTs compared to sham	None
Boayue (2020)	Left DLPFC (F3)	Right supraorbital	1 mA 20 min 7 x 5 cm cathode, 4 x 4 cm anode	Sham (15s fade in/out)	Between (total 192)	SART	TUT (1-4)	During and post-stimulation	No effect of stimulation on TUTs	None

Chou (2020)	Right IPL (P4) / left IPL (P3)	Right IPL / left IPL	HD-tDCS 2 mA (1mA right, 1mA left) IPL 30 min returns over right: P8, CP2, O2; left: P7, CP1, O1, 3.14 cm	Sham (15s fade in/out)	Between (30 per group)	MSIT	Were you thinking about the task or something else? Past, present, or future? Positive, neutral, or negative?	Pre- and post-stimulation	None for off-task propensity. Cathode decreased frequency of negative past thoughts	None
Boayue (2020)	Left DLPFC (F3)	C3, T7. FP1, Fz	HD-tDCS 2 mA 20 min, 12mm	Sham	Between (30 per group)	FT-RSGT	TUTs (1-4)	Pre- and during stimulation	Reduced TUTs compared to sham	None
Filmer (2021)	Left DLPFC (F3) / right IPL (P4)	Left DLPFC (F3) / right IPL (P4)	1 mA anode F3 2mA anode F3 1mA cathode F3 2mA cathode F3, 20 min, 5 x 5 cm	Sham, 30s stimulation	Between (30 per group)	SART	TUTs (1-7)	Post-stimulation	1mA and 2mA anode F3 stimulation increased TUTs compared to sham. 1mA anode F3 increased TUTs compared 1mA cathode F3	Reduced target accuracy in both anodal and cathodal conditions

DLPFC, dorsolateral prefrontal cortex; LFPC, lateral prefrontal cortex; IPL, inferior parietal lobe; MPFC, medial prefrontal cortex; TUTs, task-unrelated thoughts; SART, sustained attention to response task; MSIT, multi-source interference task; FT-RSGT, finger tapping random-sequence generation task; tDCS, transcranial direct current stimulation

Table 1.2: *Studies including fMRI to investigate modulating mind-wandering via tDCS*

Authors	Stimulation site: anode	Stimulation site: cathode	Stimulation conditions	Control condition(s)	Design (No of participants)	fMRI acquisition	Observations
Kajimura (2016)	Left LPFC (AF7) / right IPL (P4)	Right IPL / left LPFC	1.5 mA 20 min 7 x 5 cm	Sham, 30s stimulation	Between: anode (20), cathode (19), sham (21)	rs-fMRI pre- and post-tDCS	Anodal right IPL tDCS reduced rIPL-PCC and MPFC-PCC coupling and inhibited /facilitated mind-wandering respectively. Cathodal right IPL tDCS increased MPFC-PCC coupling
Kajimura (2019)	Right IPL (P4) / left IPL (P3)	Contralateral cheek	1.5 mA 20 min 7 x 5 cm	Sham, 30s stimulation	Mixed: randomly assigned to anode, P4 (13) or anode, P3 (14). Both completed sham	rs-fMRI pre- and post-tDCS followed by SART & fMRI	Anodal right IPL tDCS induced regional amplitude and effective connectivity changes in the DMN compared to sham

Note: behavioural results for these studies are displayed in ***Table 1.1***. LFPC, lateral prefrontal cortex; IPL, inferior parietal lobe; MPFC, medial prefrontal cortex; PCC, precuneus/posterior cingulate cortex; tDCS, transcranial direct current stimulation; DMN, default mode network

1.8. Disorders of consciousness [1]

The two dimensions of consciousness are wakefulness and awareness. A disorder of consciousness refers to impairments to one or both dimensions. Following damage to the brain, typically from traumatic (car accident, severe fall) or non-traumatic (stroke, heart attack) injuries (Turner-Stokes & Wade, 2004), patients that show a complete failure in the arousal system (impairments in both domains) are classified as being in a coma (Jellinger, 2009). After an initial period of coma (around two to four weeks), patients typically progress to a prolonged period of disordered consciousness. With recent advances in medicine and technology, an increasing number of patients survive brain damage and subsequently remain in a prolonged disorder of consciousness (PDOC) (Blume et al., 2015; Monti et al., 2010).

Techniques including fMRI have been used to investigate the neural bases of PDOC. Specifically, research has demonstrated structural (Fernández-Espejo et al., 2011; Fernández-Espejo et al., 2012), functional (Boly et al., 2009; Cauda et al., 2009), and effective connectivity (Crone et al., 2015) impairments in the DMN in these patients. Given the association between the DMN and internal, self-referential processes, it is unsurprising that this network is damaged in this patient group. The thalamus, heavily involved in relaying sensory signals to the cortex, is another focal region in the study of consciousness (Child & Benarroch, 2013; Stein et al., 2000). Research has demonstrated focal damage to the thalamus in PDOC, with specific structural and functional damage observed between the thalamus and the DMN (Fernández-Espejo et al., 2012; Lant et al., 2016). A number of studies have shown that deep-brain and ultrasonic stimulation of the thalamus improved clinical diagnostic scores in some patients (Cain et al., 2021; Schiff et al., 2007; Vanhoecke & Hariz, 2017). The thalamus is a central node of the mesocircuit, a subcortical network also comprising two regions of the caudate: globus pallidus and striatum. Schiff proposed a mesocircuit hypothesis of consciousness,

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[1] Due to COVID-19, the original planned trajectory of the thesis could not be followed. Instead, I have analysed an existing fMRI dataset comprising a group of healthy volunteers and patients with prolonged disorder of consciousness. I will briefly describe here some of the background literature on this topic which constitutes the work presented in Chapter 6.

whereby disorders of consciousness are purported to result from an imbalance in the anterior forebrain mesocircuit (AFM) (Schiff, 2010). Specifically, Schiff postulates that excessive inhibition of the thalamus from the globus pallidus (via projections from the striatum) results in loss of excitatory output from the thalamus to cortical regions. Corroborating this theory, structural and metabolic impairments have been observed between the DMN and AFM in a group of PDOC patients (Fridman et al., 2014; Lant et al., 2016). To date, however, little is understood of the possible disruptions to functional and effective connectivity of the AFM in PDOC. Further research is needed to allow for more accurate diagnosis, prognosis, and rehabilitation techniques.

Currently, diagnosis relies solely on the patient’s responses to external stimuli being behaviourally assessed and graded by clinicians. To help standardise this, a number of diagnostic scales have been produced, including the JFK Coma Recovery Scale-revised (CRS-R), which is the current gold-standard method and the most commonly used across the clinical community (Kalmar & Giacino, 2005). The CRS-R comprises 25 items across six subscales (auditory, visual, motor, oromotor, communication, and arousal). For example, in the visual domain, participants are assessed on their ability to present spontaneous eye opening to speech, pain, or no eye opening at all. Some patients display intermittent communication through either verbal or gestural responses (typically yes/no responses). The results of such assessment lead to a diagnosis along a spectrum including vegetative state and minimally conscious state. The term vegetative state is used for patients that may still demonstrate wakefulness (sleep-wake cycles and eye opening) but lack awareness of the self or the environment. Conversely, patients in a minimally conscious state demonstrate inconsistent and fluctuating signs of awareness (e.g., at the lower end of the spectrum, visual pursuit, and at the upper end, the ability to follow simple commands). Clinical evaluation may also consider observations from family and health workers alongside clinical notes; however, these, and the CRS-R, all rely upon the patient’s ability to demonstrate awareness behaviourally. Understanding the neural markers of PDOC, such as the specific structural, functional, or effective connectivity impairments, may provide more accurate insight into patients' diagnostic and prognostic state and allow for more individually tailored rehabilitation going forward. There is thus a need to develop methods of assessing the brain states that underlie PDOC, specifically using brain imaging methods. This – and the known overlap in brain networks involved in mind-wandering and in PDOC –

provides my motivation to include a study on network connectivity in PDOC into this thesis originally focussed on mind-wandering.

Chapter 2

This thesis is comprised of 4 empirical chapters. Chapters 3-5 specifically focus on investigating modulating mind-wandering propensity and underlying brain activation via tDCS. Chapter 6 focusses on functional connectivity analysis of fMRI data, and its methods will be discussed in the main body of Chapter 6. Chapter 3 and 4 explore the effect of tDCS over the right IPL by comparing mind-wandering propensity and task performance pre- and post-stimulation on two separate cohorts. Chapter 4 includes concurrent fMRI to explore the effects of mind-wandering on underlying brain activation and effective connectivity. Chapter 5 explores the effect of tDCS over the left DLPFC on mind-wandering and task performance. We again use concurrent fMRI in Chapter 5 and explore the effects of tDCS on underlying brain activation, and functional and effective connectivity. A summary of the tDCS protocols, task designs and analysis pipelines are summarised below, highlighting any similarities and differences.

2.1. tDCS protocols in the current thesis

Table *2.1* summarises the stimulation protocols for each of the studies presented in Chapters 3, 4, and 5. All three used a within-subjects design, with participants completing all conditions. Each session was a minimum of 1-week apart to allow for sufficient wash-out of any effects of tDCS. We administered tDCS via a NeuroConn DC-Stimulator (MRI compatible for Chapters 4 and 5) for all three studies, using 5 x 5 cm electrodes with a 10s fade-in / fade-out period.

The studies in Chapters 3 and 4 have similar designs and brain stimulation parameters, Chapter 3 being behavioural-only, whereas Chapter 4 includes fMRI. In both Chapters 3 and 4, participants received 1.5mA of tDCS at rest for 20-minutes with the active electrode placed over the right IPL and the return over the left cheek. Chapter 3 used a double-blind, sham-controlled (with anodal and cathodal conditions) design. In Chapter 4 only the participant was blind to stimulation condition as the MRI compatible machine did not have the blinding function enabled. Chapter 4 also only included anodal and cathodal conditions. Furthermore, the method used to facilitate conductance between the electrode and the scalp was different across studies to ensure MRI compatibility: Chapter 3 used saline-soaked sponges and Chapter 4 used ten20 conductive paste.

In Chapter 5, participants received 1.8mA anodal and sham stimulation over the left DLPFC (with the return over the right supraorbital area) for 20-minutes whilst completing a task in the scanner. Ten20 conductive gel was used to facilitate current flow. Participants were blind to the condition.

Throughout all studies, we tested tDCS on participants for 30s to ensure the set-up was administered correctly and to check that the impedance was below 15kΩ. In Chapters 4 and 5, which included concurrent tDCS-fMRI, electrodes were covered with approximately 2mm of Ten20 conductive gel and were placed onto participants before entering the scanner and remained in place throughout the whole session. The routing of the wires when the participant was in the scanner came out of the back of the bore and around to the control room. The NeuroConn DC-Stimulator was left disconnected until stimulation was delivered. Following stimulation, the device was disconnected. Across all studies we did not have any participants that did not tolerate the tDCS/fMRI session.

For the sham conditions, after fading-in, stimulation was delivered for 30s before fading out to give the sensations of stimulation. Following each session, participants completed a post-tDCS questionnaire which asked them to indicate whether they thought they had received real or sham stimulation and assessed their perception of the physical sensations during stimulation (pain, discomfort, intensity, tingling, burning, and itching). To locate the placement of electrodes, we used the commonly employed 10/20 EEG system (Thair et al., 2017). We fitted an EEG cap on the participant with the appropriate region(s) marked on the scalp before removing the cap and putting the electrodes in place (see **Table *2.1*** for more details). For the extracephalic electrode in Chapters 3 and 4, we placed the electrode in the centre of the left cheek. Electrodes were then held in place using self-adhesive tape. Impedances were monitored throughout stimulation and kept below 15kΩ.

Table 2.1: *Summary of stimulation protocols used in this thesis*

Study	Target	Return	Current & duration	Conditions	Conductive gel & electrode size	Task	Study type
Chapter 3	Right IPL (P4)	Left Cheek	1.5mA 20 mins	Anodal, cathodal, sham	Saline 5 x 5 cm	Before & after tDCS	Behavioural
Chapter 4	Right IPL (P4)	Left Cheek	1.5mA 20 mins	Anodal, cathodal	Ten20 5 x 5 cm	Before & after tDCS	Behavioural & fMRI
Chapter 5	Left DLPFC (F3)	Right supraorbital (Fp2)	1.8mA 20 mins	Anodal, sham	Ten20 5 x 5 cm	Before and during tDCS	Behavioural & fMRI

IPL, inferior parietal lobule; DLPFC, dorsolateral prefrontal cortex; tDCS, transcranial direct current stimulation

2.2. Task and probes

2.2.1. SART

We used the sustained attention to response task (SART) in all experimental chapters (3-5). This is a simple go/no-go task where participants need to press a button to the presentation of non-target digits and refrain from responding to target digits, balancing speed with accuracy (Robertson et al., 1997). Specifically, a number (0-9) is presented on a screen which the participants need to respond to as quickly and accurately as possible using a button press, except for the target number, 3, for which they need to refrain from pressing. We recorded reaction time after the presentation of non-target stimuli and accuracy of refraining from pressing to target stimuli. Specifically, we defined errors as a button press in response to a target (commission error). Mean reaction time to non-targets and proportion of commission errors for each run of the task were then used for statistical analysis.

Chapters 3 and 4 use an identical experimental design as seen in **Figure *3.2***. The target number 3 appeared in 5% of trials in a pseudo-random order (as used in Christoff et al., (2009)). Each digit was displayed for 2s. Between each stimulus, the screen displayed a fixation cross for 20ms. Throughout the task, we presented a total of 20 thought probes that asked the participant to reflect on what they were thinking immediately prior to the probe. Each thought-probe appeared at pseudo-random intervals to avoid expectation effects (30, 40, 50, 60, 70, 80 or 90s; mean=60s), similar to Kajimura et al., (2019) (~40-80 seconds). Participants responded to the probes by a button press on a scale of 1-4 (max to min) for how externally and internally distracted their thoughts were (two responses required per probe). We instructed them to rate min in both scales in occasions where they were fully on-task. More information on these **Thought probes** can be found in the next section. Each run of the task lasted for 20-minutes. To encourage mind-wandering, participants completed two practice runs of the task, lasting 40-minutes, on each session (outside the scanner for Chapter 4) as per (Christoff et al., 2009). In Chapter 3, participants were sat in a quiet room and fitted with earplugs to reduce external distraction, with window blinds closed during task completion and throughout delivery of tDCS (at rest). In Chapter 4, participants completed the practice runs outside the scanner in a windowless, quiet room. All other conditions were completed in the scanner.

Chapter 5 used a slightly modified version of the task as seen in **Figure 5.2**. The task included 535 non-targets (95.4%) and 26 targets (4.6%) which never appeared in the final 10s prior to a thought-probe. All stimuli were displayed for 1 second, followed by a fixation cross, also displayed for 1s. Throughout the task, we presented 32 thought-probes at pseudo-random intervals (20, 30, 40 and 50s; average 35s). These read ‘Where was your attention focused just before the probe?’. The participants responded by indicating whether they were “on-task” or “off-task”. They had 4s to make a response before the SART began again. The task lasted for 20 minutes and 14 seconds. Participants completed all runs of the task whilst in the MRI scanner.

2.2.2. Thought probes

Initially, we intended to differentiate between TUTs that are stimulus-dependant and stimulus-independent (Stawarczyk, Majerus, Maj, et al., 2011), thereby isolating mind-wandering as stimulus-independent, task-unrelated thought. Stimulus-dependent thoughts are driven by an external distraction (e.g., sound of the scanner) and stimulus-independent thoughts are internal and decoupled from sensory information (e.g., thinking about last evenings meal or a future holiday) (Antrobus et al., 1966). This was guided by research which observed an anti-correlation between thoughts being internally or externally focussed, with each being associated with differential brain activation (PCC and hippocampal areas for intrinsic and fronto-parietal for extrinsic) (Vanhaudenhuyse et al., 2011). Recent research demonstrated that off-task responses to thought-probes during SART are likely to be reflecting both mind-wandering and external distractions (Robison et al., 2019). As our aim was to assess the effects of tDCS on mind-wandering specifically, we instructed participants to provide subjective rates specifically for the extent of task-unrelated thoughts that were internally or externally oriented (mind-wandering and external/sensory distractions respectively). To accomplish this separation, in Chapters 3 and 4, we ask participants to respond to two probes, each on a scale of 1-4 (max to min), to declare how much of their thoughts were either on-task or (depending on the probe) internally or externally directed. We instructed participants that internally directed thoughts were related to “times where you are mind-wandering, such as thinking about personal memories, future plans or fantasising (daydreaming)” and externally directed thoughts “refers to any thoughts directed at external influences, such as the noise of the scanner or an itch on your arm”. We first categorised the responses to the thought-probes into four categories: “mind-wandering”; “environment”; “on-task” and “both high”. For this, we considered a response of 1 or 2 in the 4-point scale to be high and a response of 3 or 4 to be low. We then classified responses of low internal and high external thoughts as “environment”, those of high internal and low external thoughts as “mind-wandering”, those of low internal and low external thoughts as “on-task”, and those for high on internal and high on external as “both high”. Frequency of occurrence for each of these responses was then used for statistical analysis.

After analysing the data for Chapter 4, we observed no group level brain activation related to the task. As we categorised thought-probe responses into four groups based on the two 4-point Likert scales (described above), this led to a very low number of probe responses to some categories which resulted in low power in some individuals to accurately capture brain activation at the level of the GLM. Therefore, we wanted to adapt the probes for Chapter 5 to minimise this and attempt to observe task-related brain activity.

The three main modifications we made to the task in Chapter 5 were: increased number of thought-probes per run; reduced probe response complexity to a binary “on-task” / “off-task” option; and removal of the 40-minute practice session. We increased the number of thought-probes per run from 20 to 32 to increase the power for the GLM analysis. Justifying these changes, recent research using a semantic version of the SART (words rather than numbers are used as targets and non-targets) investigated the effect of modifying the frequency of probes and the number of probe options to thought-probe responses and task performance (Robison et al., 2019). They found no difference in probe responses or task performance when the frequency of probes was doubled. In a subsequent experiment they observed no difference in behavioural measures when two, three or five response options were given for thought-probes. Additionally, they included an external and a mind-blanking option in the three and five option conditions, however they accounted for less than 1% of responses each (Robison et al., 2019). Therefore, we decided to reduce the average time between probes (from an average of every 60s to 35s) and increase the total number of probes (from 20 to 32). Christoff et al., (2009) initially used a 7-point Likert scale rating TUTs, these were later classified as “on-task’ (1-3) or “off-task” (5-7) with mid-point (4) responses disregarded and only accounted for 3% of total responses. Subsequent research combining the SART with experience sampling and fMRI also adopted a binary “on-task” / ”off-task” response option (Denkova et al., 2019; X. Zhou & Lei, 2018), as did research investigating effects of tDCS on mind-wandering (Kajimura et al., 2016, 2019). Therefore, we adopted the binary choice in line with this previous research. Regarding removing the 40-minute practice runs of the task, this decision was primarily made due to the large drop-out and task disengagement experienced in Chapter 3. Specifically, four participants failed to complete all three sessions and five participants had to be removed from the analysis as they had at least one period of failing to respond to the task for more than 30s. Participants removed from the analysis had informally informed the researchers that the disengagement / drop-out was due to the extensively long sessions. The 40-minute practice sessions were originally included to match Christoff et al., (2009) and encourage mind-wandering, however, to mitigate high participant attrition and to match the tDCS literature, we removed the extensive practice session. Instead we adopted a very short practice which included three practice trials, similar to previous research (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020; Filmer et al., 2019).

Mind-wandering was categorised as occasions of “off-task” responses and participants were given the following information: “Task-unrelated thoughts are thoughts which are irrelevant to the experiment and do not help with task execution (e.g., thoughts that relate to personal memories or future plans). Mind-wandering and being off-task is perfectly normal during this type of task so please be as honest and accurate as possible when answering the probes." Frequency of occurrence of "on-task" responses in each run of the task was then used for statistical analysis.

2.3. Behavioural data analysis

Classical frequentist statistics have been the backbone of quantitative psychological research for many years now. These tests create a test-statistic (e.g., t-value), with the associated probability (p-value) of observing this test-statistic assuming the null hypothesis is true (Quintana & Williams, 2018). Therefore, the p-value tells the researcher how likely this outcome would be if the null hypothesis were correct. If the probability is small enough, as determined by an alpha level (typically lower than 0.05), researchers then reject the null hypothesis and accept the alternative (Kruschke & Liddell, 2018). The alpha-level tries to balance the occurrence of false-positive (Type I) and false-negative (Type II) errors (Quintana & Williams, 2018). However, the acceptance or rejection of hypotheses is one of the main critiques of frequentist statistics. Results are often misinterpreted, and accepting the alternative hypothesis based on p-values lower than 0.05 is logically invalid – the lack of evidence for the null is not evidence for the alternative (Wagenmakers et al., 2018). Although this method provides insight into how unlikely the null hypothesis is, it cannot demonstrate whether the data provides support for the null hypothesis. Furthermore, it does not indicate if a dataset is sensitive enough to observe the given effect unless a power analysis is performed in advance (Hoenig & Heisey, 2001).

Conversely, Bayesian statistics offers an opportunity to overcome both of these issues. Bayes factor hypothesis testing quantifies the degree to which the data favours one of two hypotheses by considering the prior odds (Wagenmakers et al., 2018). This prior belief is updated based upon the available data, which allows for evidence to be quantified and monitored as data is acquired (Quintana & Williams, 2018). Given this, Bayesian statistics can quantify evidence for the null hypothesis as both models (null and alternative) are tested to inform which more accurately predicts the data. JASP software (JASP Team, 2020) implements Jeffreys-Zellner-Siow priors as default, which assumes effect sizes are likely to be small (Love et al., 2019). The use of appropriately informed priors based on previous data is recommended, where possible, to reduce the likelihood of type II errors from overly conservative constraints. However, it has been found that varying prior specifications had relatively modest effects on Bayesian estimates (Gifford & Swaminathan, 1990). Throughout this thesis we use the default priors in JASP. As Bayesian statistics allows data to be evaluated as it accumulates, researchers have begun to use this to determine when to cease data collection (known as the stopping rule) (Steel, 2003). Here, data is analysed throughout the collection period until a pre-determined level of evidence is observed in support of either the null or alternative hypotheses. We implemented this technique in Chapter 6 (as outlined in our preregistration: **https://osf.io/8um5s/).**

For the frequentist tests, we set the level of significance at $p = 0.05$. For the Bayesian test, we evaluated both the presence and the absence of an effect by comparing how different models explain the data given the factors of interest (Stafford et al., 2019). We used a Jeffrey-Zellner-Siow Bayes factor (JZS-BF10) to contrast the strength of the evidence for models reflecting the null and interactions (Rouder et al., 2012). For ease of interpretation, we include BF_{10} for those >1 and invert them as BF_{01} for those <1. We also calculated a Bayes factor for the exclusion of the variable of interest (BF_{excl}) by comparing all models that exclude the interaction with all models that include it. A JSZ-BF between 0.33 and 3 is considered to be weak/anecdotal evidence for an effect; 3–10: substantial evidence; 10–100: strong evidence; >100: very strong evidence (Jeffreys, 1998).

This thesis uses both frequentist and Bayesian methods to analyse behavioural data in Chapters 3-6 using JASP (JASP Team, 2020; Love et al., 2019).

2.4. Dynamic causal modelling

DCM is a Bayesian model comparison procedure which compares models of time series data to infer causal architecture of coupled or distributed systems. The resulting effective connectivity parameters are based on probable models of linked neuronal activity which examine causal interactions between brain regions for specific experimental designs. DCM uses nonlinear (bilinear) designs to identify generative models of the measured neural activity which for fMRI is the haemodynamic measurements. Overall, the resulting output is the most plausible effective connectivity among hidden neuronal states that explains connectivity among haemodynamic responses (Friston et al., 2014). Throughout this thesis we use spectral DCM to analyse fMRI data independently of the task. Spectral DCM requires specification of a plausible model which allows the estimation of the model parameters that quantify effective connectivity (Esménio et al., 2019; Friston et al., 2014).

After the model specification, we took the first level individual (within-subjects) estimated fully connected DCMs to the second level (between-subjects) analyses using parametric empirical Bayes (PEB) (Friston et al., 2016). PEB is a hierarchical approach to model how individual subject’s connections relate to the group level by using the individual DCMs as priors (first level) to constrain the variables in the Bayesian linear regression model (second level) (Zeidman et al., 2019). This method allows individual subjects’ variability in connection strengths to then influence the group (second level) analysis. After group level connection strengths (parameters) have been estimated, hypotheses are tested by comparing evidence for different variations of these parameters in a process known as Bayesian model comparison. This was achieved by repeatedly removing one of the parameters from the full model, therefore producing reduced forms of the full model. To achieve this, we used Bayesian Model Reduction (BMR) which enables an efficient (greedy) search which prunes connections from the full model until there are no more improvements in model-evidence. Parameters from the best models following BMR were then taken, weighted by their model evidence, and combined using Bayesian model averaging (BMA). To define statistical significance, we applied a threshold of a posterior probability > 0.95 (strong evidence) for each connection. For more information on BMR and BMA, see Friston et al., (2016) and Zeidman et al., (2019).

We used bilinear, one state fully-connected spectral DCMs and the PEB framework in SPM12 to assess effective connectivity in Chapters 4-6.

2.5. Dynamic functional network connectivity

Functional connectivity refers to the correlated relationship of temporal activity between spatially separated regions in the brain. Moving beyond the classic static descriptions of functional connectivity, dynamic functional network connectivity (dFNC) analysis allows researchers to quantify changes to the relationship between these regions over time and provides a rich insight into the dynamic properties of brain networks (Hutchison et al., 2013). Using a sliding window approach on the fMRI data, changes in functional connectivity are clustered using k-means which categorises dynamic functional connectivity patterns of n samples into a number of clusters (k). This results in k number of distinct reoccurring activity patterns know as ‘brain states’. dFNC provides information on the frequency (how often a state occurs) and the dwell time (length of time spent in a particular state before switching) of each state. These ‘brain states’ refer to a set of typically re-occurring functional states over a period of time and are thought to represent different internal states of the brain. Notable differences have been observed between the typical functional connectivity over long periods and repeated patterns characterised by dFNC (Allen et al., 2014). Specifically, this early research questioned descriptions of a single canonical DMN and its anticorrelations with other networks (such as, the task positive network) therefore cementing dFNC as a notable method of delineating the relationship between intrinsic network connectivity. Evidence using various tasks has indicated a strong relationship between functional states and ongoing cognitive processes which allows for a convergence between functional states and mental states (Gonzalez-Castillo et al., 2015). Furthermore, resting-state and task-based studies have begun to investigate the dynamic properties of mind-wandering to characterise the occurrence and patterns of ongoing thoughts using time-varying functional connectivity analyses (Karapanagiotidis et al., 2018; Kucyi & Davis, 2014; Mooneyham et al., 2017). Denkova et al., (2019) employed this technique on functional MRI data collected whilst participants undertook the SART (without tDCS stimulation). They observed five reoccurring ‘brain states’ over three key intrinsic brain networks (DMN, ECN and SN) (Denkova et al., 2019). We employ dFNC analysis using the GIFT toolbox in Chapter 5 with a similar pipeline to Denkova et al., (2019), see **Dynamic functional network connectivity** for more details. It should be noted that dFNC is not assumption free, with a priori knowledge required to categorise states of brain activity. For example, the number of clusters (k) as brain states, the length of the sliding windows and the step size (typically TR) will all influence the resulting connectivity states and their frequency and dwell time (Zhou et al., 2019).

Chapter 3

EFFECT OF TDCS OVER THE RIGHT INFERIOR PARIETAL LOBULE ON MIND-WANDERING PROPENSITY[2]

3.1. Abstract

Mind-wandering is associated with switching our attention to internally directed thoughts and is by definition an intrinsic, self-generated cognitive function. Interestingly, previous research showed that it may be possible to modulate its propensity externally, with transcranial direct current stimulation (tDCS) targeting different regions in the default mode and executive control networks. However, these studies used highly heterogeneous montages (targeting the dorsolateral prefrontal cortex (DLPFC), the right inferior parietal lobule (IPL), or both concurrently), often showed contradicting results, and in many cases failed to replicate.

Our study aimed to establish whether tDCS of the default mode network, via targeting the right IPL alone, could modulate mind-wandering propensity using a within-subjects double-blind, counterbalanced design. Participants completed a sustained attention to response task (SART) interspersed with thought-probes to capture their subjective reports of mind-wandering before and after receiving anodal, cathodal, or sham tDCS over the right IPL (with the return over the left cheek). We found evidence for the lack of an effect of stimulation on subjective reports of mind-wandering (JZS-BF01 = 5.19), as well as on performance on the SART task (errors (JZS-BF01 = 6.79) and reaction time (JZS-BF01 = 5.94). Overall, we failed to replicate previous reports of successful modulations of mind-wandering propensity with tDCS over the IPL, instead providing evidence in support of the lack of an effect. This, and other recent unsuccessful replications call into question whether it is indeed possible to externally modulate spontaneous or self-generated cognitive processes.

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3.2. Introduction

Mind-wandering refers to the diversion of one's attention away from ongoing task demands towards self-generated or spontaneous internally directed thoughts (Smallwood & Schooler, 2015). We typically spend 25-50% of our waking hours engaged in mind-wandering (Killingsworth & Gilbert, 2010; Song & Wang, 2012), and yet the focus of cognitive neuroscientific research has largely been on goal-oriented and externally directed thoughts (Callard et al., 2013). Over recent years however, there has been increasing interest in elucidating the neural correlates of mind-wandering and determining whether it is possible to modulate this spontaneous process using external sources, such as transcranial direct current stimulation (tDCS).

Most research suggests that mind-wandering relies upon activation of the default mode network (DMN) (Christoff et al., 2009), which includes the medial prefrontal cortex (mPFC), posterior cingulate cortex/precuneus (PCC) and bilateral inferior parietal lobule (IPL) (Boly et al., 2009). Nevertheless, there is evidence that mind-wandering can also lead to activation of the executive control network (ECN) (Christoff et al., 2009; Golchert et al., 2017). The ECN is characteristically involved with undertaking cognitive demanding tasks, such as response inhibition tasks (e.g., go/no-go; (Christoff et al., 2009)), attentional and mental reasoning tasks (e.g., Stroop; (Dobrynina et al., 2018)) and working memory tasks (e.g., n-back; (Mencarelli et al., 2019)), all of which see their performance greatly reduced with mind-wandering (Unsworth & McMillan, 2014). While the above studies (Christoff et al., 2009; Golchert et al., 2017) suggest both the DMN and ECN may indeed interplay in the generation of mind-wandering, their individual contributions, and the specific dynamics of the relationship with each other, still remain unclear.

To our knowledge, seven recent studies tackled this question by using tDCS to investigate causal roles of DMN and ECN in mind-wandering (Axelrod et al., 2015, 2018; Bertossi et al., 2017; Boayue et al., 2020; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Mind-wandering was measured via experience sampling techniques, whereby participants self-reported their internal state in response to thought-probes (Giambra, 1995; Smallwood & Schooler, 2006) periodically presented during a tedious and monotonous task (Christoff et al., 2009; Kajimura et al., 2016). In two different studies totalling 132 participants across different stimulation conditions, Axelrod and colleagues (2015, 2018) reported a successful modulation of mind-wandering after tDCS over the left dorsolateral prefrontal cortex (DLFPC). Specifically, they found that anodal tDCS lead to an increase in mind-wandering during a sustained attention to response task (SART). The authors attributed this modulation to the ECN’s involvement in mind-wandering. However, a recent multi-centre registered report with a large sample (n=192) was unable to replicate Axelrod et al., (2015, 2018) findings, and instead provided evidence supporting the lack of an effect of DLPFC-tDCS on mind-wandering propensity (Boayue, Csifcsák, Aslaksen, et al., 2020).

Subsequent research reported successful modulations of mind-wandering after concurrent stimulation of the DLFPC and right IPL (Kajimura et al., 2016). Due to the nature of the montage, which targeted regions in both DMN and ECN, the authors were unable to conclude which network was driving the observed changes. However, in a subsequent study, they reported modulation of mind-wandering during a SART task via stimulation over the right IPL only, using a return electrode over the left buccinator muscle (Kajimura et al., 2019). Specifically, anodal stimulation decreased mind-wandering compared to sham. The authors related this effect to changes in the effective connectivity of the DMN at rest. Although promising, these studies do not offer conclusive evidence for the effect of tDCS over the IPL on mind-wandering due to a number of limitations. Specifically, they failed to control for polarity, including only anodal and sham conditions. Most importantly, their design does not provide adequate control for individual variability on mind-wandering propensity, in that they only measured mind-wandering after tDCS without considering baseline levels.

To address these limitations, here we aimed to further investigate whether tDCS stimulation of the right IPL can indeed modulate mind-wandering propensity in a 3-session, within-subjects design in which we could compare anodal, cathodal and sham stimulation. We used a SART task interspersed with thought-probes both before and after tDCS. We hypothesised that anodal stimulation would result in a reduction in mind-wandering propensity compared to sham, and that the effect would be reversed for cathodal stimulation.

3.3. Method

3.3.1. Participants

Thirty-three participants volunteered to take part in the study from an opportunity sample at the University of Birmingham. Participants provided written consent and received course credits for their participation. Before their inclusion in the study, we screened all participants for tDCS safety. The University of Birmingham's Science, Technology, Engineering and Mathematics Ethical Review Committee provided ethical approval for the study.

Four participants failed to complete all sessions and their data was removed from the study. We also removed the data from a further participant after they reported at the end of their first session that they had not understood the task. After performing quality control on the remaining data, we removed five participants who failed to respond for 30 seconds or more of the go/no- go task, suggesting lack of engagement and compliance with the task instructions. We analysed the remaining 23 participants' data (6 male, aged 18-23 (M=19.83, SD=1.34)). Our sample size was determined based on previous studies using tDCS over IPL to modulate mind-wandering (Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Our numbers of participants per condition was comparable to previous between-subjects studies (Kajimura et al., 2016; Kajimura & Nomura, 2015) and two-fold greater than the only previous within-subject study (Kajimura et al., 2019).

3.3.2. Materials

3.3.2.1. Brain Stimulation

We administered tDCS via a NeuroConn DC-Stimulator (neuroCare Group GmbH), using 5 x 5 cm rubber electrodes covered with saline-soaked sponges. We placed one electrode over P4 (according to the standard 10-20 system for electroencephalography electrode placement) and the other over the left cheek, as used in (Kajimura et al., 2019) (NB. their electrode size was 5x7cm). The position of the electrodes was reversed for the anodal and cathodal conditions (i.e., anodal electrode over P4 or the left cheek respectively) and counterbalanced for the sham condition (i.e., half of the participants received an anodal montage and the other half received a cathodal montage in a counterbalanced order). Before applying the electrodes, we cleaned the skin with alcohol wipes. To identify the location of P4 on each participant and session, we used a customised EEG cap, and marked P4 with a pen on the participants scalp. After that, we removed the cap and fixed the electrodes in place using coban tape.

Participants received 20 minutes of continuous 1.5mA stimulation with 10 seconds fade-in and fade-out periods, as per previous research (Kajimura et al., 2019). We monitored impedance and made sure it stayed below 15 kΩ. For the sham condition, stimulation was delivered for 30s before fading out to give the sensation of active stimulation. We used a double-blind design, using the 'study mode' feature of the device (i.e., each stimulation session was linked to an arbitrary code which would be entered into the machine and deliver real or sham stimulation that would be blind to the researcher and participant). This is in contrast to Kajimura et al., (2019) where only participant-blinding was used. At the end of each stimulation session, participants completed a post-tDCS perception questionnaire in which they reported their perceived sensations and their impression about whether they had received real stimulation or sham.

3.3.2.2. Electric field estimation using SimNIBS

We created a finite element method (FEM) head model using SimNIBS v2.1.0 (www.simnibs.org) using conductivity values for various tissues as described in (Opitz et al., 2015), and modelled on the electrode montage previously described (P4 and left cheek, 1.5mA). This confirmed that our montage resulted in a peak electric field strength over the right inferior parietal lobule as displayed in **Figure 3.1**.

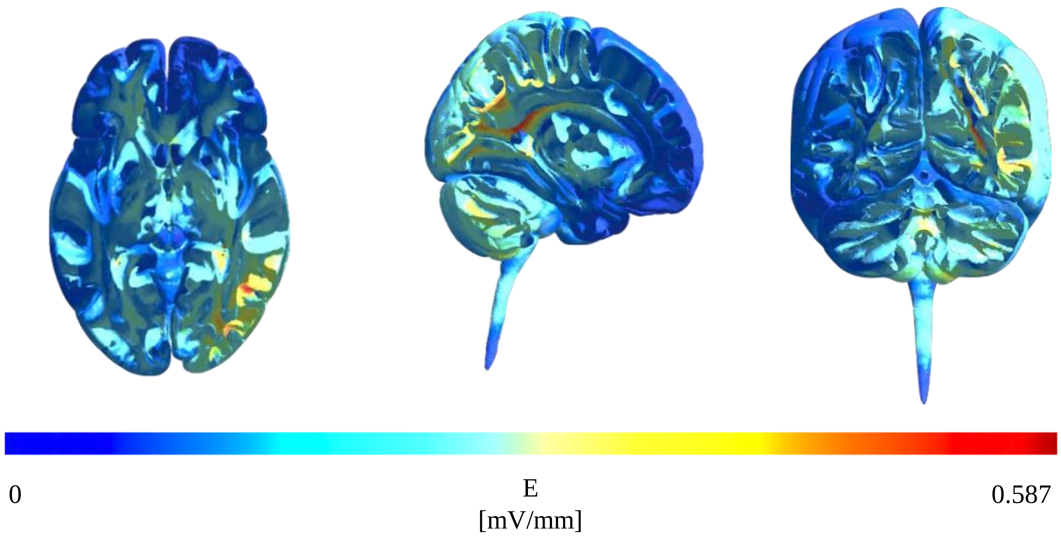

Figure 3.1: Modelling of electric field strength showing maximum field strength over the right inferior parietal lobule in the axial (a), sagittal (b) and coronal (c) planes. Default conductivity values were used for the simulation (white matter 0.126 S/m; gray matter 0.275 S/m; cerebral spinal fluid 1.654 S/m; bone 0.01 S/m; scalp 0.465 S/m; eyes 0.5 S/m; silicone rubber 29.4 S/m; saline 1.0 S/m).

3.3.2.3. Sustained Attention to Response Task (SART) and Thought-Probes

We administered a sustained attention to response task similar to that used by Axelrod et al., (2018), Christoff et al., (2009) and Kajimura et al., (2019), with periodic thought-probe sampling. The monotonous nature of this task helps to promote high incidences of mind-wandering, while allowing to record them both objectively (through reaction times and errors) and subjectively (through thought-probes). We delivered the task using MATLAB 2015b and Psychtoolbox-3 on either a Windows 7 computer (processor: Intel Core i5) or a Macbook Air (macOS High Sierra; 2 GHz Intel Core i7). Each participant used the same computer for all three of their sessions. As seen in **Figure *3.2***, we instructed participants to press the space bar as quickly and accurately as possible to the display of a numerical stimulus (0-9), except for the target number 3, where they had to refrain from responding. The target number 3 appeared in 5% of trials in a pseudo-random order (as used in Christoff et al., (2009)). Each digit was displayed for 2s (Christoff et al., 2009) in white Arial size 35 font on a black background in the centre of the screen. Between each stimulus, the screen displayed a fixation cross for 20ms. This is in contrast to Kajimura et al., (2019), where digits were displayed for 1s followed by 1s ISI, and included ~3.3% targets. Throughout the task, we presented a total of 20 thought probes that asked the participant to reflect on what they were thinking immediately prior to the probe. While previous studies of tDCS in mind-wandering typically used binary on-task / off-task categories (Axelrod et al., 2015, 2018; Kajimura et al., 2016, 2019), recent research demonstrated that off-task responses to thought-probes during SART are likely to be reflecting both mind-wandering and external distractions (Robison et al., 2019). As our aim was to assess the effects of tDCS on mind-wandering specifically, we instructed participants to provide subjective rates specifically for the extent of task unrelated thoughts that were internally or externally oriented (mind-wandering and external or sensory distractions respectively).

Each thought-probe appeared at pseudo-random intervals to avoid expectation effects (30, 40, 50, 60, 70, 80 or 90s; mean=60s), similar to Kajimura et al., (2019) (~40-80 seconds). Participants responded to the probes by a button press on a scale of 1-4 (max to min) using a standard keyboard, with ‘s’, ‘e’, ‘r’, ‘g’ keys for mind-wandering and ‘h’, ‘u’, ‘i’, ‘l’ for external distractions. We instructed them to rate min in both scales in occasions where they were fully on-task. We placed stickers over the key letters to indicate the appropriate number. The task lasted approximately 20 minutes.

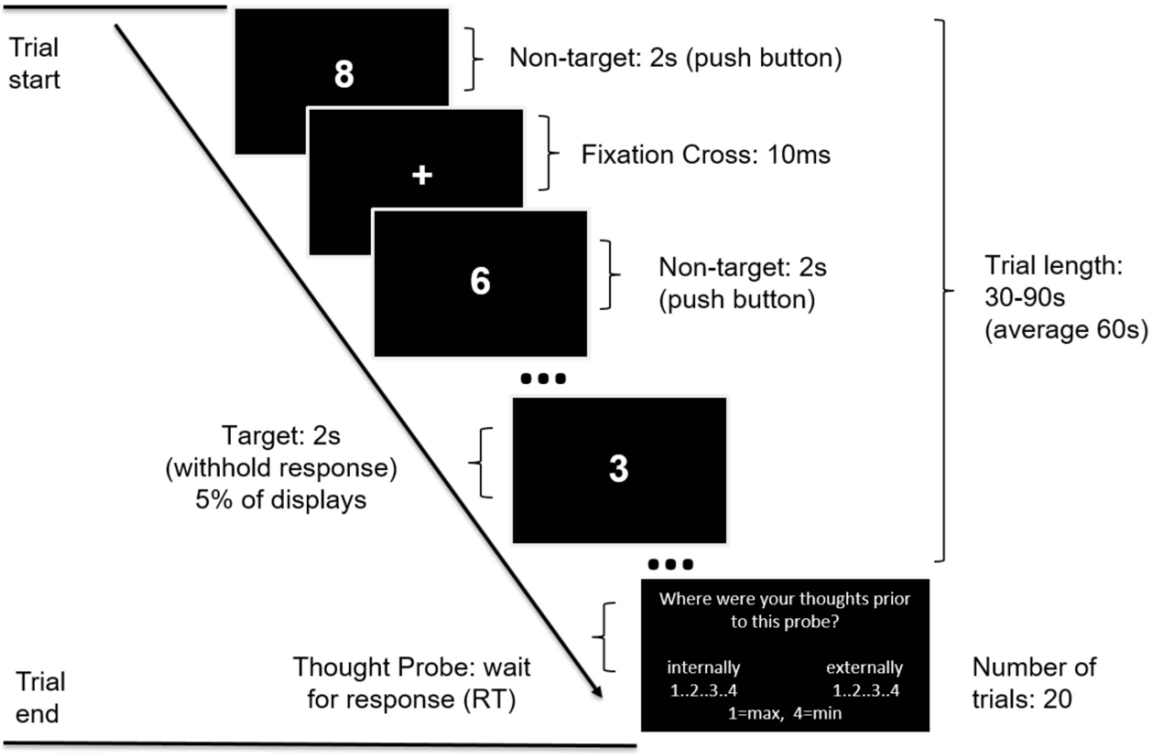

Figure 3.2: Flow diagram of the SART experimental design

3.3.3. Design & Procedure

The experiment followed a double-blind, within-subjects design. Participants completed three conditions: anodal stimulation, cathodal stimulation, and sham, in a counterbalanced order and spaced a minimum of 1 week apart (range = 7-23 days, mean = 8.04, SD = 2.62). While previous research typically included anodal and sham conditions only (Kajimura et al., 2019), we were interested in determining whether the reported effects were polarity specific, as this would allow us to establish that any found effects are site specific (Parkin et al., 2015). At the start of each session, participants completed two practice runs of the SART for a total of 40 minutes to familiarise themselves with the task and encourage greater levels of mind-wandering as done in Christoff et al., (2009). Participants then completed a baseline run of the SART followed by 20 minutes of stimulation at rest and concluded with a final post-stimulation run of the SART. It is worth highlighting here that previous research by Kajimura et al., (2019) only included post-stimulation runs of the SART and a very brief practice at the start of the session (not included in their analysis).

For the duration of the full session, participants wore earplugs to reduce external noise distraction. To further reduce auditory and visual distraction, testing was conducted in a quiet room with window blinds closed.

3.3.4. Statistical Analyses

3.3.4.1. Responses to Thought-Probes

We first categorised the responses to the thought-probes into three categories: 'mind-wandering'; 'environment'; and 'on-task'. For this, we considered a response of 1 or 2 in the 4-point scale to be high and a response of 3 or 4 to be low. We then classified responses of low internal and high external thoughts as 'environment', those of high internal and low external thoughts as 'mind-wandering', and those of low internal and low external thoughts as 'on-task'. Occurrences of high (1 or 2) to both internal and external were considered invalid responses and disregarded, this appeared for 18/23 participants and accounted for 8.22% of total responses. Finally, we calculated the frequency/percentage of responses in each of the three categories after these invalid responses were removed.

3.3.4.2. Performance in the SART

We recorded reaction time after the presentation of non-target stimuli and accuracy of refraining from pressing to target stimuli. Specifically, we defined errors as a button press in response to a target. We interpreted increased commission errors (to targets) and longer reaction times to non-targets as suggestion of greater levels of mind-wandering.

3.3.4.3. Data analyses

We used frequentist and equivalent Bayesian comparisons (with default priors) on JASP (JASP Team, 2020). To test the effect of tDCS on our variables of interest (i.e., frequency of mind-wandering, environment, and on task thoughts, as well as mean reaction time for correct responses to non-targets and number of commission errors on SART), we conducted repeated measures ANOVAs with stimulation (anodal, cathodal, sham) and session (baseline, post-tDCS) as factors. Finally, to assess the effectiveness of our blinding method, we performed a Chi-Squared test for the association between received and perceived stimulation type (real or sham). We also analysed perception of sensations caused by tDCS (intensity, discomfort, tingling, pain, burning, itching) using a one-way repeated measures ANOVA.

For the frequentist tests, we set the level of significance at $p = 0.05$. For the Bayesian test, we evaluated both the presence and the absence of an effect by comparing how different models explain the data given the factors of interest (Stafford et al., 2019). We used a Jeffrey-Zellner-Siow Bayes factor (JZS-BF10) to contrast the strength of the evidence for models reflecting the null and interactions (Rouder et al., 2012). For ease of interpretation, we include BF_{10} for those >1 and invert them as BF_{01} for those <1. We also calculated a Bayes factor for the exclusion of the variable of interest (BF_{excl}) by comparing all models that exclude the interaction with all models that include it. A JSZ-BF between 0.33 and 3 is considered to be weak/anecdotal evidence for an effect; 3–10: substantial evidence; 10–100: strong evidence; >100: very strong evidence (Jeffreys, 1998).

3.4. Results

3.4.1. Mind-Wandering Responses

While the data violated tests for normality, we still employed ANOVA, as this has previously been shown to be robust enough even when assumptions of normality are not met (Schmider et al., 2010). See **Table *3.1*** and **Figure 3.3** and **Figure 3.3** for summary statistics.

Table 3.1: *Percentage of each response type ('mind-wandering', 'on-task' and 'environment') to thought-probes and performance on SART. The data are group means (standard deviations in parenthesis).*

	Baseline			Post-stimulation		
	Sham	Anodal	Cathodal	Sham	Anodal	Cathodal
Mind-wandering (%)	43.14 (33.85)	43.78 (31.89)	43.27 (30.09)	33.82 (33.23)	35.60 (28.88)	41.83 (35.87)
Environment (%)	9.44 (11.54)	15.59 (17.31)	13.34 (9.72)	13.47 (12.47)	14.01 (15.25)	9.73 (11.44)
On-task (%)	47.42 (33.17)	40.62 (32.36)	43.38 (31.58)	52.72 (32.45)	50.40 (30.14)	48.44 (35.29)
Commission errors (%)	51.98 (19.98)	53.21 (15.80)	53.06 (12.70)	49.45 (20.76)	54.06 (15.32)	51.70 (16.46)
Reaction times (s)	0.659 (0.142)	0.668 (0.133)	0.662 (0.137)	0.647 (0.141)	0.638 (0.142)	0.655 (0.150)

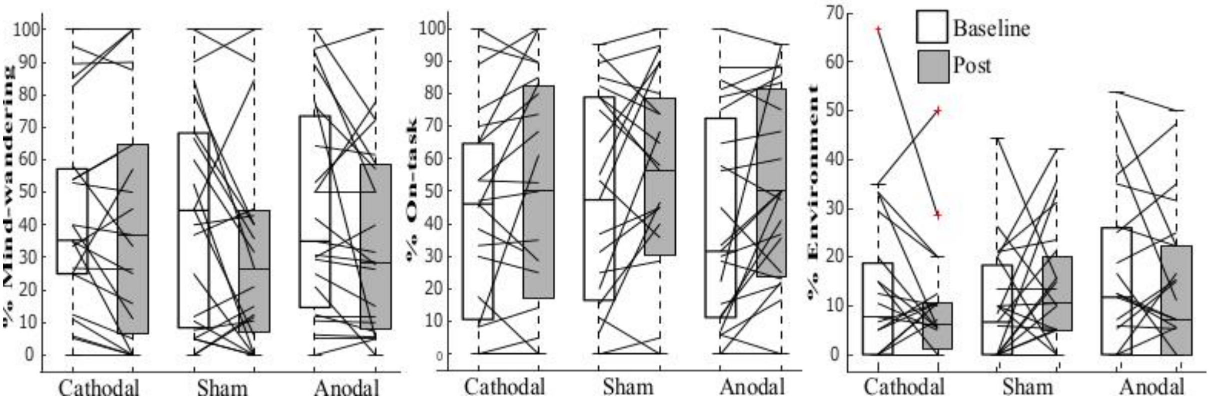

Figure 3.3: Line graphs with box plots displaying the variability in subjective responses of (a) 'environment', (b) 'on-task' and (c) 'mind-wandering' before and after tDCS in cathodal, sham and anodal conditions. All measures exhibited great variability at baseline and in response to tDCS across all 3 stimulation conditions.

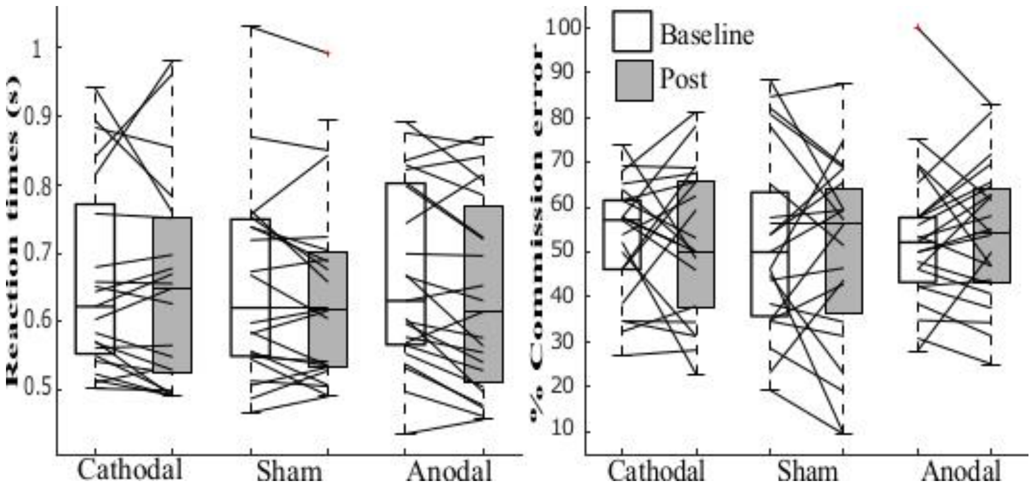

***Figure 3.4**:* Line graphs with box plots displaying the variability in task performance for (a) mean reaction time for correct response to non-target and (b) percent commission errors before and after tDCS in cathodal, sham and anodal conditions. All measures exhibited great variability at baseline and in response to tDCS across all 3 stimulation conditions.

A repeated measures ANOVA modelled the main effects of stimulation (anodal, cathodal and sham) and session (baseline, post-tDCS), as well as the interaction between them, for percentage of 'mind-wandering', 'environment' and 'on-task' responses to probes and commission errors, and mean reaction time (s) to correct responses in the SART. Both frequentist and Bayesian analyses revealed no main effects for responses of 'environment', errors on SART and no interaction for any of the measures studied. Moreover, Bayesian analyses provided support for the lack of an effect of tDCS (strong to very strong evidence for the null as compared to the full model across all variables, and substantial evidence for the model excluding the interaction). see **Table *3.2***.

We found a significant main effect of session in 'mind-wandering' propensity in our frequentist ANOVA but inconclusive evidence for this effect in our Bayesian analyses (F(1,22) = 4.87; p = 0.038, η_p^2 = 0.181, BF_{10} = 1.04), and no significant post-hoc differences for cathodal ((t(22) = 0.48, p = 0.666, BF_{01} = 4.191), sham (t(22) = 1.90, p = 0.081, BF_{01} = 1.100) and anodal (t(22) = 1.86, p = 0.076, BF_{01} = 1.044). We also found a significant main effects of session for 'on-task' responses, which was supported by both our frequentist and Bayesian analyses (F(1,22) = 6.03; p = 0.022, η_p^2 = 0.215, BF_{10} = 3.14), and with a significant increase post-tDCS for anodal (t(22) = 2.366, p = 0.027, BF_{10} = 2.147) but not cathodal (t(22) = 1.382, p = 0.181, BF_{01} = 1.980) or sham (t(22) = 1.156, p = 0.260, BF_{01} = 2.528). For SART performance, we found a main effect of session for RT to correct response to non-targets (F(1,22) = 5.741; p = 0.026, η_p^2 = 0.207, BF_{01} = 1.74), with significantly faster RTs post-tDCS for anodal (t(22) = 2.938, p = 0.008, BF_{10} = 6.173) but not cathodal (t(22) = 0.470, p = 0.643, BF_{01} = 4.136) or sham (t(22) = 1.239, p = 0.228, BF_{01} = 2.320).

Table 3.2: *Bayesian and frequentists repeated measures ANOVA for the interaction of stimulation (anodal, cathodal and sham) and session (baseline and post-stimulation) effects on subjective and objective measures of mind-wandering.*

	JZS-BF_{01} for the null vs full	BFexcl(interact)	F	df	η_p^2	P-value
‘Mind-wandering’ (%)	43.43	5.19	1.149	2,44	0.050	0.326
‘Environment’ (%)	115.06	3.67	2.629	2,44	0.107	0.083
‘On-task’ (%)	13.75	6.40	0.485	2,44	0.022	0.619
Commission errors (%)	244.46	6.79	0.425	2,44	0.019	0.656
Mean reaction time (s)	126.90	5.96	1.005	2,44	0.044	0.374

3.4.2. Post-tDCS Questionnaire

Table *3.3* displays the proportion of sessions perceived to have had active stimulation, from the post-tDCS perception questionnaire. A Chi-squared test revealed no significant association between participants received and perceived stimulation type (real or sham) (X^2(1) = 1.232, p = 0.267; $BF_{01\ \text{independent multinomial}}$ = 1.82, N = 69).

Additional perceptual scales also revealed no significant difference between each type of stimulation as assessed by a one-way repeated measures ANOVA of stimulation (anodal, cathodal, and sham). These include rating of intensity of stimulation (F(2, 42) = 1.99, *p* = 0.150, η^2 = 0.059; BF_{01} = 1.39); discomfort (F(2, 42) = 1.57, *p* = 0.221, η^2 = 0.043; BF_{01} = 2.13); tingling (F(2, 42) = 0.18, *p* = 0.840, η^2 = 0.004; BF_{01} = 7.14); pain (F(2, 42) = 0.60, *p* = 0.553, η^2 = 0.017; BF_{01} = 4.76); burning (F(2, 42) = 0.35, *p* = 0.707, η^2 = 0.008; BF_{01} = 5.88); and itching (F(2, 44) = 0.07, *p* = 0.934; BF_{01} = 7.69). Thus, there was no evidence that participants were able to differentiate between receiving active stimulation or sham (note that BF was inconclusive and therefore there is no conclusive evidence that they were not able either). For all perceptual scores except intensity (where results were inconclusive), there was evidence in support for the physical sensations not differing.

Table 3.3: *Contingency table displaying the frequency of perceived stimulation type against actual stimulation received.*

		Actual	
		Real	Sham
Perceived	Real	34	14
	Sham	12	9

3.5. Discussion

In the present study, we found evidence that tDCS over the right IPL was unable to modulate behavioural incidences of mind-wandering during a SART task. Specifically, we failed to identify a polarity specific effect on either subjective reports of mind-wandering, or errors and reaction times on the task. In fact, our Bayesian analyses provided strong to very strong evidence for the lack of an effect of stimulation in any of our objective and subjective measures of mind-wandering. Specifically, when comparing the null vs the full models, there was strong evidence for the lack of an effect of tDCS based on incidences of ‘mind-wandering’ and very strong evidence when considering commission errors and reaction times on the task. Furthermore, when looking specifically at the effect of the interaction, we found substantial evidence for the models excluding the interaction as compared to those including it for all three measures, again suggesting no effect of tDCS on objective or subjective reports of mind-wandering. We therefore suggest that, against our hypothesis, neither anodal nor cathodal tDCS over the right IPL can influence mind-wandering propensity.

Our findings also contradict earlier reports by Kajimura et al., (2019) showing that stimulation of the right IPL via tDCS could modulate mind-wandering propensity during a SART task. This could be due to differences in the operationalisation of subjective incidences of mind-wandering. While Kajimura et al., (2019) used a binary ‘on-task’ or ‘off-task’ as possible responses to the thought-probes, we used Likert scales and recorded the level of two types of task unrelated thoughts: mind-wandering and environmental distraction. Previous studies suggest that off-task responses can reflect both mind-wandering and external distraction

(Robison et al., 2019) and that both elicit activity on the DMN as compared to on-task instances (Stawarczyk, Majerus, Maquet, et al., 2011). It is thus possible that our observed lack of effect is due to measuring these two processes independently. This however seems unlikely as, while they both engage the DMN, mind-wandering is associated with greater activity in this network (Stawarczyk, Majerus, Maquet, et al., 2011). Moreover, most of the distraction observed in our study was due to mind-wandering (with only 9-15% dedicated to external distractions), and our analyses confirmed the lack of an effect for 'on task' incidences too. Nevertheless, we cannot rule out that differences in the subject's experience elicited by the thought probes themselves may have played a role in the discrepancy of findings across both studies. It should be noted that our study was not designed as a direct replication of (Kajimura et al., 2019), which alongside other differences discussed above, was conducted in the MRI scanner, and therefore should not be interpreted as such.

Despite the differences in our operationalisation of subjective reports of mind-wandering, we were also able to investigate mind-wandering objectively by looking at reaction times and errors on task. According to previous research, the specific methodology used for collecting thought probes (i.e., frequency, framing, or type of responses), or in fact the inclusion of thought probes at all, does not influence the behavioural performance in the task the probes are embedded (Robison et al., 2019; Wiemers & Redick, 2019). Therefore, our reaction times and errors should be comparable to those in previous studies using SART. Similarly than for 'mind-wandering' incidences, we found substantial evidence for the lack of an effect of tDCS over performance in the SART (both accuracy and RT). This is in line with previous studies reporting non-significant effects on accuracy or RTs (Axelrod et al., 2015, 2018; Kajimura et al., 2019).

More importantly, Kajimura et al., (2019) compared mind-wandering reports after tDCS only, between sham and anodal conditions separated by at least a week. It is therefore possible that their results simply reflect subject variability in mind-wandering propensity. Indeed, in our study, we observed a large variability in mind-wandering propensity at baseline (ranging from 0-100% across participants), which is also consistent with previous reports of mind-wandering outside of the influence of tDCS (Unsworth & McMillan, 2014; Vannucci & Chiorri, 2018). Moreover, Kajimura et al., (2019) findings are based on groups of 13 subjects.

It is known that small sample sizes can greatly overestimate effect sizes and increase the likelihood of false positives (Lorca-Puls et al., 2018). To overcome these limitations, in the current study, we used a within-subjects design including both baseline and post-tDCS runs on each polarity session with a larger sample size that is almost two-fold greater (23). We therefore suggest that our design allows for a more robust attribution of the effects (or in this case the lack of) to tDCS. We nevertheless acknowledge that further studies with much larger samples are needed before definite conclusions about the lack of effects of tDCs in mind-wandering can be made. Related to this, it is worth highlighting that, while our Bayesian and Frequentists analyses broadly produced comparable results, there were also some minor inconsistencies (e.g., some of the main effects in our ANOVAs had significant p values but inconclusive BFs). Bayesian statistics are more conservative and known to yield more robust results in studies with relatively small samples (Stegmueller, 2013), and therefore their interpretation should be preferred here. Crucially, as discussed above, both approaches led to consistent results in support of the lack of effect of tDCS in responses to thought probes or performance in the SART.

It is possible that other tDCS montages can still successfully modulate mind-wandering. Indeed, some studies have reported modulation of mind-wandering by stimulating the DLPFC (Axelrod et al., 2015, 2018). While the DLPFC is not part of the DMN, it is a central node of the executive network, and therefore an up regulation of this network may allow higher levels of mind-wandering while maintaining the same level of task performance. Crucially, these findings were not replicated in a recent large-scale study (Boayue, Csifcsák, Aslaksen, et al., 2020). Other studies have suggested that dual stimulation of the DLPFC and right IPL can elicit changes in subjective reports of mind-wandering (Kajimura et al., 2016; Kajimura & Nomura, 2015). However, these results are yet to be replicated outside the original lab. In either case, the disparity of findings may reflect the well-known inter-subject variability in responsiveness to tDCS (Dyke et a., 2016; López-Alonso et al., 2014) and highlight the need to conduct well powered replications.

A further possible explanation to our lack of effects and the lack of consistency across reports relates to administering tDCS while the participant is at rest. Recent research suggests neuronal activation of the regions targeted for stimulation may be necessary in order for tDCS to influence the network sufficiently (Kadosh, 2013). For example, studies have shown greater enhancement in performance on a working memory task only when stimulation occurred simultaneously as compared to sham stimulation or tDCS at rest (Andrews et al., 2011). Similarly, tDCS over M1 has greater influence on motor learning when applied concurrently with the task, as compared to pre-task only (Karok & Witney, 2013). Future studies could therefore engage participants in a task known to induce mind-wandering, while administering tDCS, in an effort to engage the DMN during stimulation and increase the likelihood of modulating its activity.

Leaving the discussion about effects of tDCS aside, our analysis of the thought probes across conditions revealed some unexpected findings. On the basis of prior literature (e.g., (McVay & Kane, 2009)), we expected to find an increase on mind-wandering in our second run on the SART across conditions (related to having spent more time on the task). In contrast, we failed to show reliable differences for mind-wandering and found contradicting evidence in support of a decrease of on-task responses. We attribute this to the extensive practice run at the start of each sessions, which would have had a greater effect on our baseline than our post stimulation runs. Indeed, previous studies using similarly extensive training also failed to identify reliable changes in thought-probe responses with time spent on the task (McVay & Kane, 2009). To further assess this, we conducted additional analyses comparing the first half of each run with the second half. In agreement with the literature, we identified the expected increase in in mind-wandering (t(137) = 2.07, p = 0.040, BF01 = 1.33) and reduction of on-task responses (t(137) = 3.33, p = 0.001, BF10 = 17.75). This suggests our reported main effect of session was in fact likely explained by the practice session and therefore should not be interpreted as being in contradiction with previous literature.

Overall, we failed to replicate previous research suggesting stimulation of the right IPL alone is capable of modulating mind-wandering propensity and instead provide evidence against an effect, observed through both objective and subjective measures. This, and other recent unsuccessful replications (Boayue, Csifcsák, Aslaksen, et al., 2020), call into question whether it is indeed possible to exert external influence over spontaneous cognitive processes. Future studies should include brain imaging to further understand what influence tDCS is exerting on the target networks and elucidate whether the reported inconsistency in behavioural effects is indeed reflecting unsuccessful neural modulations or subthreshold changes in brain activity.

Chapter 4

MODULATING MIND-WANDERING AND INTRINSIC BRAIN NETWORKS VIA RIGHT INFERIOR PARIETAL LOBULE TDCS

4.1. Introduction

In this chapter, we were interested in understanding the neural basis of mind-wandering and observe any effects of tDCS on associated brain networks. Specifically, we used the exact task and design as the behavioural study in Chapter 3 on a new cohort of participants and included concurrent tDCS-fMRI. To further understand the neural changes elicited by tDCS, we applied anodal and cathodal tDCS to the right IPL (return left cheek) during fMRI using a within subject's design. The SART with interspersed thought-probes has previously elicited BOLD activation in regions of the DMN during periods of mind-wandering (Christoff et al., 2009; Stawarczyk, Majerus, Maquet, et al., 2011). To date, however, no research has examined the effect of tDCS on BOLD during this task.

Using multimodal imaging techniques, research has begun to investigate and observe effects of tDCS on brain activation and connectivity. Resting state-fMRI revealed tDCS modulated large-scale brain networks with active stimulation of the DLPFC increasing synchrony in the ECN and reduced synchrony in the DMN (Peña-Gómez et al., 2012). Subsequent research delivered online stimulation during a visual working memory task and recorded rs-fMRI pre- and post-stimulation under two stimulation conditions: anodal left DLPFC and cathodal right IPL, with the return over the supraorbital area for both conditions (Šimko et al., 2021). Accuracy and functional connectivity increased in the DLPFC condition whereas no effect on behaviour was found in the right IPL condition and it is unclear if right IPL-tDCS modulated functional connectivity as no analysis is reported (Šimko et al., 2021). Research stimulating the right inferior frontal gyrus at rest and during a CRT found tDCS modulated activity and functional connectivity across brain networks in a brain-state and polarity specific manner without observing any effects on behavioural performance (Li, Violante, Leech, Ross, et al., 2019). More recently, EEG signals during a creative thinking task were recorded before and after tDCS over the left DLPFC (anode) and right IPL (cathode) with participants completing both active and sham conditions (Koizumi, 2020). Although they observed no effects of tDCS on task performance, EEG analysis revealed active stimulation increased functional connectivity between the PCC and IPL with effective connectivity analysis revealing a decreased delta band flow within the DMN (Koizumi, 2020). Together the research demonstrates an ability to detect tDCS-induced neuronal changes using multimodal neuroimaging methods, including fMRI, even in the absence of behavioural effects thus indicating even subtle changes, which may not be strong enough to modulate behaviour, can be observed.

We analysed the behavioural objective and subjective responses to the task using both frequentist and Bayesian statistics. For the imaging data, we assessed BOLD activation in relation to the task at baseline, followed by analysing any effects of tDCS using a 2 (baseline and post-stimulation) x 2 (anodal and cathodal) ANOVA. Furthermore, we conducted dynamic causal modelling (DCM) analysis of the functional data and employed the parametric empirical Bayes (PEB) framework to investigate polarity specific effective connectivity changes before and after tDCS. We hypothesized that neither anodal nor cathodal stimulation would be able to modulate mind-wandering propensity (based on our behavioural results from Chapter 3). For the imaging analysis, we expected to observe activation of the DMN and ECN during episodes of mind-wandering and being off-task, respectively. We hypothesise anodal tDCS will result in increased activation of right IPL compared to cathodal stimulation. Regarding effective connectivity, we hypothesise anodal tDCS would result in modulation of the connectivity within and between the DMN and ECN, specifically in connections from the site of stimulation (right IPL), in comparison to cathodal.

4.2. Method

4.2.1. Participants

17 right-handed healthy participants from an opportunity sample took part in the study, of which 12 completed both sessions (8 females, 3 males, 1 other; aged 19-29, M = 22.25, SD = 2.77). We removed one participant due to data quality issues, resulting in 11 participant's data being analysed (7 females, 3 males, 1 other; aged 20-29 years, M = 22.55, SD = 2.70). We compensated participants with £60 for completing both parts of the study. The University of Birmingham's Science Technology Engineering and Mathematics Ethical Review Committee provided ethical approval for the study. Before their inclusion in the study, we screened all participants for tDCS and MRI safety.

4.2.2. Materials

4.2.2.1. Brain stimulation

The brain stimulation protocol was identical to that outlined in Chapter 3. We administered tDCS via an MRI compatible NeuroConn DC-Stimulator (neuroCare Group GmbH), using 5 x 5 cm rubber electrodes covered with ten20 conductive gel. We placed one electrode over P4 (according to the standard 10-20 system for electroencephalography electrode placement) and the other over the left cheek, as used in Kajimura et al., (2019) (NOTE: they had 5x7cm electrodes). The position of the electrodes was reversed for the anodal and cathodal conditions (i.e., anodal electrode over P4 or the left cheek respectively). Before applying the electrodes, we cleaned the skin with alcohol wipes. To identify the location of P4 on each participant and session, we used a 64-channel EEG cap, and marked P4 on the participant's scalp using an MRI safe marker. After that, we removed the cap and fixed the electrodes in place using coban tape. Participants received 20 minutes of continuous 1.5mA stimulation at rest with 10 seconds fade-in and fade-out periods. We monitored impedance and made sure it stayed below 15 kΩ.

4.2.2.2. Sustained Attention to Response Task (SART) and Thought-Probes

We administered a sustained attention to response task identical to that used in Chapter 3 and similar to that used by Christoff et al. (2009), with periodic thought-probe sampling. This was delivered using MATLAB 2015b and Psychtoolbox-3 on a Windows 7 computer (processor: Intel Core i5) for the two practice runs and using MATLAB 2011a for the baseline and post stimulation runs in the MRI scanner.

4.2.3. Experimental design & procedure

We adopted a within-subjects design with participants completing both conditions (anodal and cathodal) a minimum of 7 days apart (M = 31.92, SD = 45.79). Both sessions were identical except for the stimulation condition. The order was randomised and counterbalanced with participants blind to the condition on each session.

Participants first completed two practice runs of the task outside of the scanner lasting approximately 40 minutes as done in Christoff et al., (2009) to encourage mind-wandering. Following this, participants entered the scanner and completed a baseline run of the SART, followed by 20 minutes of tDCS at rest ending with a post-tDCS run of the SART. This is in contrast to Kajimura et al., (2019) which only included post-tDCS runs of the SART, with tDCS administered at rest.

4.2.4. fMRI acquisition

We collected data using a 3.0 Tesla Philips Achieva MRI scanner at the Birmingham University Imaging Centre (BUIC). First, we acquired a T1-weighted image (repetition time (TR) = 7.4ms; echo time (TE) = 3.5ms; matrix size = 256 x 256mm; voxel size = 1 x 1 x 1mm; field of view = 256 x 256mm; and flip angle = 7 degrees). For the fMRI, we acquired echo-planar images in ascending interleaved order with the following parameters: 34 slices; TR = 2000ms; TE = 35ms; matrix size = 80 x 80mm; voxel size = 3 x 3 x 3mm; field of view = 240 x 240mm; and flip angle = 79.1 degrees.

Two NAtAtech response boxes were placed into the participant's right and left hands whilst in the scanner (each has five response buttons). The task and instructions were presented using a display back-projected onto a screen mounted at the end of the scanner. A mirror attached to the head coil enabled subjects to view the stimuli and task instructions.

4.2.5. Categorising responses to thought-probes

We first categorised the responses to the thought-probes into three categories: 'mind-wandering'; 'environment'; and 'on-task'. For this, we considered a response of 1 or 2 in the 4-point scale to be high and a response of 3 or 4 to be low. We then classified responses of low internal and high external thoughts as 'environment', those of high internal and low external thoughts as 'mind-wandering', and those of low internal and low external thoughts as 'on-task'. Occurrences of high (1 or 2) to both internal and external were considered 'both high' and were treated as invalid responses for behavioural analysis and disregarded, this appeared for 10/11 participants and accounted for 10% of total responses. Finally, we calculated the frequency/percentage of responses in each of the three categories after these invalid responses were removed.

4.2.6. Performance in the SART task

We recorded reaction time after the presentation of non-target stimuli and accuracy of refraining from pressing to target stimuli. Specifically, we defined errors as a button press in response to a target. We interpreted increased commission errors (to targets) and longer reaction times to non-targets as suggestion of greater levels of mind-wandering.

4.2.7. Behavioural data analyses

We used frequentist and Bayesian equivalent comparisons (with default priors) on JASP (JASP Team, 2020). To test the effect of tDCS on our variables of interest (i.e., probe responses and performance on SART), we conducted repeated measures ANOVAs with stimulation (anodal, cathodal) and session (baseline, post-tDCS) as factors. Finally, to assess any differences in the perception of the sensations generated by stimulation between anodal and cathodal, we performed a Chi-Squared test for the association between received (anodal, cathodal) and perceived (real or sham). We also analysed perception of sensations caused by tDCS (intensity, discomfort, tingling, pain, burning, itching) using paired samples t-tests.

For the frequentist tests, we set the level of significance at $p = 0.05$. For the Bayesian test, we evaluated both the presence and the absence of an effect by comparing how different models explain the data given the factors of interest (Stafford et al., 2019). We used a Jeffrey-Zellner-Siow Bayes factor (JZS-BF10) to contrast the strength of the evidence for models reflecting the null and interactions (Rouder et al., 2012). For ease of interpretation, we include BF10 for those >1 and invert them as BF01 for those <1. We also calculated a Bayes factor for the exclusion of the variable of interest (BFexcl) by comparing all models that exclude the interaction with all models that include it. A JSZ-BF between 0.33 and 3 is considered to be weak/anecdotal evidence for an effect; 3–10: substantial evidence; 10–100: strong evidence; >100: very strong evidence (Jeffreys, 1998).

4.2.8. fMRI pre-processing

We pre-processed the data using SPM12 (www.fil.ion.ucl.ac.uk/spm) on MATLAB version R2014b. Data were first manually AC-PC reoriented. Spatial pre-processing included: realignment to correct subjects' motion using 6-paramter rigid body transformation; slice timing correction; co-registration between the structural images (T1-weighted) and mean functional image; segmentation into grey matter, white matter, cerebrospinal fluid (CSF); normalisation of the structural and functional images to the Montreal Neurological Institute (MNI) stereotactic standard space; and smoothing with an 8 mm full width half maximum Gaussian kernel. For the DCM analysis, to reduce low-frequency drift and high-frequency physiological noise, we applied a bandpass temporal filter between 0.01 - 0.08 Hz to the data using the DPABI toolbox in the DPARSF package (http://rfmri.org/DPARSF).

4.2.9. Univariate GLM task analysis

Condition effects at each voxel were estimated according to the general linear model custom designed on SPM12. Six regressors of interest were constructed. The first four comprised the 10s preceding each probe using subjective responses to thought-probes (categorised as ‘mind-wandering’, ‘both high’, ‘on-task’, and ‘environment’, as mentioned previously). To determine activity related to internal thoughts we compared occasions of high with low internal responses (contrast: high > low internal). For activity related to external thoughts we compared high with low external responses (contrast: high > low external). To determine activity related to on-task thoughts we compared on-task responses with off-task responses (contrast: on-task > off-task) and for off-task we compared off-task with on-task (contrast: off-task > on-task) (see Table 1 for contrasts and weightings). Two further regressors were constructed from the 10s pre-target intervals separated into those preceding a commission error and those before a correct withhold to target (error > correct and correct > error, respectively). A regressor of no interest was used at the time of a response to targets and for each thought-probe with a duration of zero to regress out activity associated with pressing a button to respond. Volumes with motion greater than 2 mm translation and 2° radius were discarded.

For the first level analysis, the four regressors of interest, displayed in **Table *4.1***, were compared in pairwise comparisons for both baseline runs for each participant, and the resulting t maps were subsequently transformed to the unit normal Z-distribution to create a statistical parametric map for each contrast. For the second level analyses, group level baseline activation was calculated and a repeated measure 2 (stimulation: anode, cathode) x 2 (timing: baseline, post) ANOVA was also conducted to ascertain any effects of stimulation. Threshold for significance in the brain was set at a voxel level FWE p < 0.050.

Table 4.1: *Weightings for the four contrasts used in the first level imaging analysis based on the thought-probe responses categories (mind-wandering, both high, on-task and environment).*

	Mind-wandering	Both high	On-task	Environment
High>Low Internal	1.5	0.5	-0.5	-1.5
High>Low External	-1.5	0.5	-0.5	1.5
On Task>Off Task	-0.33	-0.33	1	-0.33
Off Task>On Task	0.33	0.33	-1	0.33

4.2.10. Effective connectivity analysis

4.2.10.1. Selection of regions of interest

To characterise the DMN and ECN we built 12 mm spheres using Marsbar (Brett et al., 2010) for the PCC using coordinates (-5, 49, 40) (based on Fernandez-Espejo et al., (2012) (Fernández-Espejo et al., 2012)) and the left AMFG using coordinates (-33, 44, 24) (based on Kajimura et al., (2019)). We then extracted the time series for the PCC, left AMFG, WM, and CSF for each participant using the fMRI data from their first baseline run of the task. We produced seed-based connectivity maps for each network by running a group level general linear model for the DMN (using the PCC, WM and CSF as masks) and the ECN (using left AMFG, WM and CSF as masks) on the baseline run of the first chronological session. We then found group coordinates for each of the 15 ROIs by taking the peak coordinates from the group level connectivity maps for each area using a searchlight approach based on the coordinates from Kajimura et al., (2019). ROIs for each network were taken from their respective connectivity maps generated earlier (DMN: PCC, MPFC, bilateral IPL, bilateral hippocampus, bilateral MTG and ECN: MCC; bilateral: SMG, AMFG, INS). Group level coordinates can be found in **Table 4.2**. Using these group coordinates we then searched for individual coordinates for each subject by taking the peak activation closest to that of the groups from each participant's baseline run on the first chronological session. For one participant, the coordinates for right and left SMG were greater than 16 mm Euclidean distance from the group, therefore we instead took the nearest suprathreshold voxel from the group mean for these. All other RIOs were within 16 mm Euclidean distance from the group for all participants. Individual coordinates can be found in **Table 4.3.**

4.2.10.2. *Spectral dynamic causal modelling*

We initially ran a separate linear model to extract the time series to be used during dynamic causal modelling. This included the 6 rigid body realignment parameters to account for head motion as well as the cerebral spinal fluid and white matter signals as nuisance regressors. We discarded repetition times with levels of motion above 2 mm translation and 2° radius using a stick regressor. We then performed bilinear, one-state, spectral DCM with the DCM12 routine implemented on SPM12 using MATLAB version R2014b. Spectral DCM operates in the frequency domain (opposed to time) and is therefore suitable for analysis not including task (e.g., considered resting state), see Friston et al., (2014) (Friston et al., 2014). We extracted time series for the 15 aforementioned ROIs, from the GLM generated for DCM, all with 10mm sphere's centred on individual coordinates previously generated. We specified our model space based on a fully and reciprocally connected model, resulting in a total of 225 effective connections (i.e., the A-matrix) produced and estimated for each model, **Figure 3.1** displays the fully connected model based on group level coordinates.

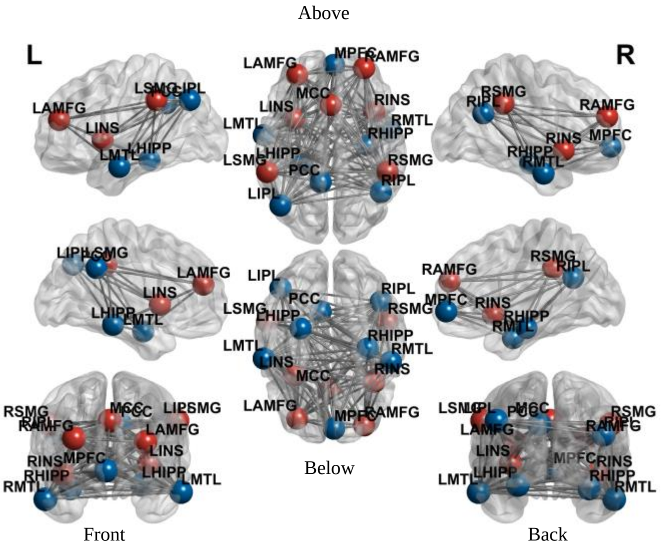

Figure 4.1: ROIs shown in the cortex based on group level coordinates rendered using BrainNet Viewer (https://www.nitrc.org/projects/bnv/) that were used in the fully connected DCM. Blue regions indicate DMN, red indicate ECN.

Table 4.2: *ROIs and group MNI coordinates from seed-based connectivity analysis. All had a sphere radius of 10mm.*

Region	Right / Left	Centre of mass (MNI)		
		x	y	z
Default mode network				
Precuneus (PCC)		-9	-49	35
Medial prefrontal cortex (MPFC)		3	56	-4
Inferior parietal lobe (IPL)	R	45	-58	26
	L	-45	-70	38
Hippocampus (HIPP)	R	33	-16	-19
	L	-27	-34	-16
Medial temporal gyrus (MTG)	R	54	-4	-28
	L	-60	-7	-22
Task-positive network				
Supramarginal gyrus (SMG)	R	51	-40	35
	L	-57	-40	38
Anterior middle frontal gyrus (AMFG)	R	30	53	23
	L	-30	47	20
Anterior insula (INS)	R	39	14	-7
	L	-33	8	2
Middle cingulate cortex (MCC)		0	20	38

Table 4.3: *Individual MNI coordinates for all 15 ROIs (Euclidean distance from group in italics).*

Network	Region	**MNI coordinates (x; y; z)** ***Euclidean distance from group in italics***										
		P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**
DMN	RIPL	49; -63; 29 *3.5*	54; -60; 34 *8.3*	47; -66; 23 *7.4*	50; -66; 26 *5.2*	50; -66; 26 *5.3*	53; -63; 23 *4*	49; -66; 33 *9.1*	54; -58; 24 *4.7*	51; -65; 22 *5.6*	55; -58; 26 *5.3*	53; -63; 17 *9.5*
	LIPL	-39; -67; 35 *10.8*	-48; -61; 29 *7.3*	-45; -67; 17 *8.9*	-42; -64; 20 *7.3*	-45; -70; 29 *4.2*	-51; -64; 20 *9.0*	-45; -67; 20 *5.8*	-36; -64; 35 *12.9*	-45; -67; 23 *3.0*	-50; -67; 26 *5.3*	-48; -64; 29 *5.2*
	PCC	-3; -49; 41 *5.2*	0; -49; 38 *5.2*	0; -49; 38 *7.3*	-3; -49; 38 *7.3*	-3; -49; 38 *7.3*	-3; -49; 38 *4.2*	0; -49; 35 *7.3*	-3; -49; 38 *9.9*	-6; -49; 38 *7.3*	0; -49; 41 *9.9*	-6; -49; 38 *0.0*
	MPFC	0; 53; -1 *7.3*	-6; 53; 11 *11.2*	3; 44; 20 *15.9*	9; 53; 11 *9.0*	3; 56; 5 *6.0*	-3; 56; -4 *12.4*	9; 44; 14 *12.4*	-6; 44; 8 *10.9*	3; 56; 8 *6.7*	12; 50; 8 *9.4*	6; 53; -4 *9.9*
	RHIPP	27; -18; -21 *8.8*	37; -27; -14 *6.6*	27; -35; -15 *14.2*	24; -19; -22 *11.2*	29; -25; -18 *5.2*	34; -23; -16 *1.2*	36; -22; -24 *9.1*	32; -27; -12 *7.1*	27; -25; -19 *7.6*	34; -16; -26 *11.6*	38; -25; -16 *6.2*
	LHIPP	-27; -37; -14 *8.7*	-19; -27; -22 *7.1*	-30; -38; -14 *9.8*	-24; -40; -16 *9.6*	-28; -39; -16 *9.3*	-28; -32; -17 *4.3*	-27; -35; -19 *4.6*	-23; -39; -16 *9.0*	-24; -22; -19 *9.2*	-24; -34; -16 *4.4*	-25; -25; -17 *6.7*
	RMTG	45; 5; -33 *15.1*	60; -5; -18 *15.0*	56; -2; -25 *10.9*	54; -4; -22 *12.0*	39; 15; -25 *17.0*	57; 2; -16 *8.7*	44; 10; -28 *11.7*	57; -10; -22 *18.5*	50; 2; -30 *11.0*	56; -7; -23 *14.8*	42; 11; -27 *13.6*
	LMTG	-53; -2; -25 *6.0*	-48; -3; -31 *11.3*	-53; -7; -19 *3.2*	-58; -13; -13 *11.6*	-52; -10; -20 *4.7*	-56; -10; -22 *3.6*	-56; -10; -22 *3.9*	-50; -9; -25 *5.3*	-45; -1; -34 *15.8*	-58; -9; -25 *5.2*	-51; -1; -24 *7.2*
ECN	RSMG	54; -34; 32 *7.5*	48; -43; 38 *5.3*	56; -37; 36 *6*	46; -39; 32 *6.1*	58; -42; 40 *8.8*	50; -42; 23 *11.9*	59; -54; 27 *18.2*	56; -40; 35 *5*	59; -40; 32 *8.6*	57; -45; 42 *10.4*	57; -40; 39 *7.6*
	LSMG	-36; -43; 41 *10.2*	-51; -42; 41 *12.6*	-44; -44; 36 *5.2*	-33; -45; 35 *10*	-54; -45; 32 *13.1*	-45; -49; 47 *12.4*	-48; -53; 41 *9.4*	-52; -42; 43 *14.3*	-33; -51; 36 *9.2*	-27; -55; 38 *16.2*	-45; -40; 41 *11.3*
	RAMFG	39; 42; 8 *9.4*	27; 47; 17 *10.8*	34; 40; 18 *3*	37; 49; 19 *7.9*	33; 50; 17 *9.4*	36; 44; 20 *4.2*	34; 38; 15 *3.6*	27; 47; 17 *10.8*	30; 47; 26 *12.3*	38; 46; 17 *5.8*	36; 32; 14 *9.5*
	LAMFG	-33; 47; 23 *4.4*	-32; 46; 25 *6.4*	-33; 45; 22 *5*	-35; 46; 17 *5.4*	-32; 43; 26 *8.7*	-33; 44; 23 *6.7*	-30; 47; 20 *4.2*	-32; 43; 22 *7.4*	-35; 46; 22 *5*	-33; 47; 23 *4.4*	-33; 44; 23 *6.9*
	RINS	45; 14; -4 *10.4*	36; 22; -12 *14*	31; 1; -4 *10.9*	39; 17; 2 *9.4*	40; 8; -5 *5.6*	39; 14; -7 *6*	46; 9; 6 *14.7*	42; 11; -4 *7*	37; 14; -6 *4.2*	33; 20; -5 *9.2*	39; 14; 2 *7.6*
	LINS	-42; 13; 2 *8.8*	-39; 14; 2 *7.3*	-34; 8; -9 *6*	-39; 17; 2 *9*	-45; 11; -3 *8.8*	-39; 17; 2 *8.7*	-30; 11; -2 *6.2*	-39; 11; -4 *3*	-39; 7; -1 *5.3*	-43; 10; -3 *7.5*	-47; 11; -1 *11*
	MCC	0; 26; 32 *10.8*	3; 20; 38 *7.3*	11; 15; 29 *6.3*	6; 20; 35 *4.2*	0; 17; 41 *10.8*	6; 23; 29 *6.8*	5; 19; 23 *9.6*	9; 20; 35 *4.9*	0; 20; 23 *11.1*	3; 23; 41 *11.2*	6; 20; 32 *3*

PCC, precuneus/posterior cingulate cortex; MPFC, medial prefrontal cortex; RIPL, right inferior parietal lobe; LIPL, left inferior parietal lobe; RHIPP, right hippocamus; LHIPP, left hippocampus; RMTG, right medial temporal gyrus; LMTG, left medial temporal gyrus; RSMG; right supramarginal gyrus; LSMG, left supramarginal gyrus; RAMFG, right anterior middle frontal gyrus; LAMFG, left anterior middle frontal gyrus; RINS, right insular, LINS, left insular, MCC, middle cingulate cortex.

4.2.10.3. Parameter estimation

After the model specification, we took the first level individual (within-subjects) estimated fully connected DCMs to the second level (between-subjects) analyses using parametric empirical Bayes (PEB) (Friston et al., 2016). PEB is a hierarchical approach to model how individual subject's connections relate to the group level by using the individual DCMs as priors (first level) to constrain the variables in the Bayesian linear regression model (second level) (Zeidman et al., 2019). This method allows individual subject's variability in connection strengths to then influence the group (second level) analysis. After group level connection strengths (parameters) have been estimated, hypotheses are tested by comparing evidence for different variations of these parameters in a process known as Bayesian model comparison.

In order to assess the differences in connectivity strength between stimulation type, we first built a PEB that modelled the interaction (first column all 1s (constant across all sessions), second column [-1 1 1 -1] following the order anodal base, anodal post, cathodal base, cathodal post to model the interaction) for each individual. We then turned this into a hierarchical PEB creating a PEB containing each of the individual PEBs to assess the group-level effects. To test for post-hoc comparisons, we created 2 subsequent PEB models (one for each stimulation). The first column consisted of 1s for the constant (common across both sessions) and the second column had -1 for baseline run and 1 for post-tDCS to compare effective connectivity between baseline and post-tDCS for each individual. We again modelled a PEB for all individual PEBs for anodal and cathodal separately.

For all three of the PEBs, after fitting each PEB model we then used Bayesian model comparison to test the different possible hypotheses (models). This was achieved by repeatedly removing one of the parameters from the full model, therefore producing reduced forms of the full model. With 225 (15 regions x 15 regions) parameters in total, there are a large number of nested models. To overcome this computational issue, we used Bayesian Model Reduction (BMR) which enables an efficient (greedy) search which prunes connections from the full model until there are no more improvements in model-evidence.

Parameters from the best models following BMR were then taken, weighted by their model evidence, and combined using Bayesian model averaging (BMA). To define statistical significance, we applied a threshold of a posterior probability > 0.95 (strong evidence) for each connection. For more information on BMR and BMA, see Friston et al., (2016) and Zeidman et al., (2019) (Friston et al., 2016; Zeidman et al., 2019).

4.3. Results

Note: Due to an error during the baseline SART run of the anodal session for one participant, only 11 thought-probe responses were recorded. Although the post-stimulation run was successful, only the first 11 thought-probe responses of this run were used (in both behavioural and imaging analysis) so that their baseline and post-stimulation runs for their anodal session were balanced.

4.3.1. Behavioural

4.3.1.1. Mind-wandering responses and SART performance

We found no interactions in any of our ANOVA's modelling stimulation and session on percentage of 'mind-wandering', 'environment', and 'on-task' responses to probes nor percentage of commission errors and mean reaction time (s) to correct response to SART. Bayesian analyses provided support for the lack of an effect of tDCS (substantial to strong evidence for the null as compared to the full model for 'mind-wandering', mean reaction time, and commission errors; anecdotal evidence for 'on-task' and 'environment'; strong evidence excluding the interaction for 'mind-wandering' and anecdotal evidence for all other models). See **Table *4.4*** for descriptive statistics and **Table *4.5*** for full results of the statistical analyses. No main effects were found for responses to thought probes. A main effect of session was found for mean reaction time to non-targets, F(1,10) = 14.50, p = 0.003, Partial eta squared = 0.592; BF10 = 1 (BF10inc(session) = 4.415), with reaction times significantly faster post-tDCS (0.630) compared to baseline (0.694). A main effect of session was also found for commission errors, F(1,10) = 8.71, p = 0.014, Partial eta squared = 0.466; BF10 = 1 (BF10inc(session) = 9.416) with significantly more errors post-tDCS (39.98%) compared to baseline (32.27%). We note high variability in in thought probe responses and performance on SART as can be seen in **Table *4.4*** (SD) and in **Figure 4.2**.

Table 4.4: *Percentage of each response type (‘mind-wandering’, ‘on-task’ and ‘environment’) to thought probes and performance on SART. The data are group means (standard deviations in parenthesis).*

	Baseline		Post-stimulation	
	Anodal	Cathodal	Anodal	Cathodal
Mind-wandering (%)	44.184	50.023	39.733	41.90
	(21.07)	(18.57)	(32.65)	(22.46)
On-task (%)	42.357	37.275	55.901	43.003
	(18.44)	(18.09)	(33.68)	(25.27)
Environment (%)	13.459	12.702	4.366	15.097
	(13.80)	(12.84)	(5.52)	(15.68)
Commission errors (%)	33.534	31.012	37.467	42.499
	(16.91)	(13.67)	(17.99)	(18.52)
Mean reaction times (s)	0.682	0.706	0.618	0.643
	(0.13)	(0.13)	(0.13)	(0.10)

Table 4.5: *Bayesian and frequentists repeated measures ANOVA for the interaction of stimulation (anodal and cathodal) and session (baseline and post-stimulation) effects on subjective and objective measures of mind-wandering.*

	JZS-BF_{01} for the null vs full	BFexcl (interact)	F	df	η_p^2	P-value
‘Mind-wandering’ (%)	16.06**	3.31*	0.21	1,10	0.020	0.659
‘On-task’ (%)	2.71	2.13	0.60	1,10	0.057	0.456
‘Environment’ (%)	2.55	0.84	4.06	1,10	0.289	0.072
Commission errors (%)	3.64*	1.14	5.76	1,10	0.366	0.366
Mean reaction time (s)	10.45**	2.66	0.00	1,10	0.000	0.993

*=BF > 3; **=BF > 10

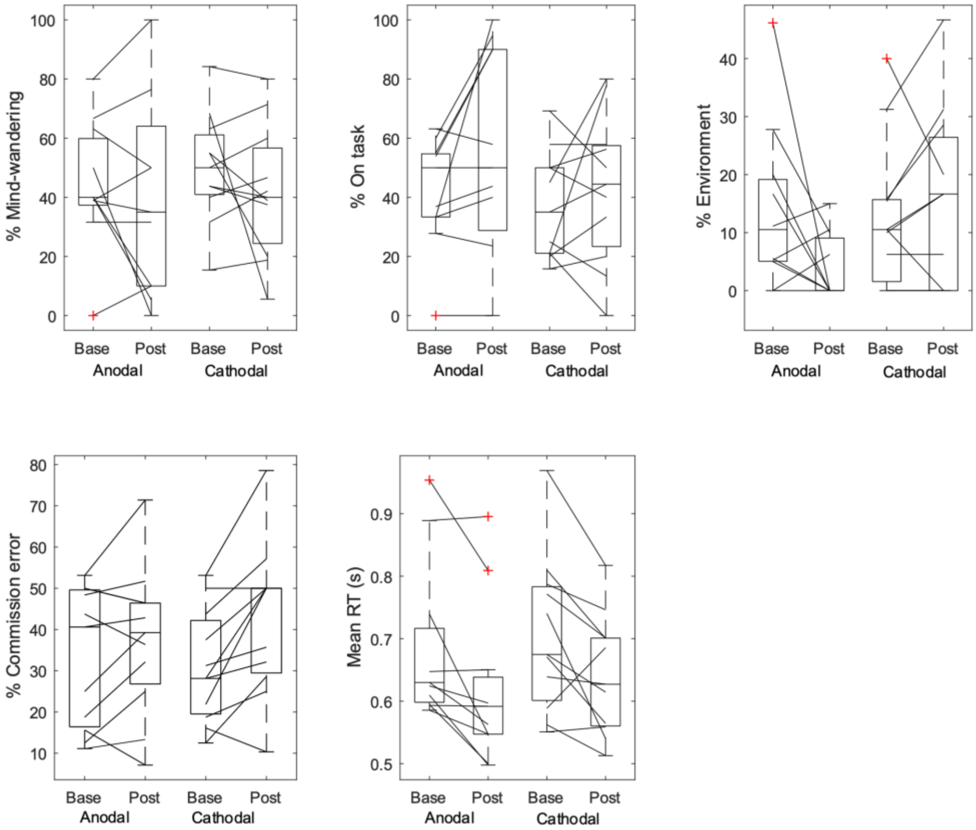

Figure 4.2**:** Line graphs with box plots displaying the variability in subjective responses of A) ‘mind-wandering’, B) ‘On-task’ C) ‘environment’ and variability in task performance D) percent commission error, E) mean reaction time to non-targets before and after tDCS in anodal and cathodal conditions. All measures exhibit large variability both at baseline and in response to tDCS.

4.3.1.2. Post-tDCS questionnaire

Table *4.6* displays the proportion of sessions perceived to have had active stimulation from the post-tDCS perception questionnaire. A Chi-squared test revealed no significant association between stimulation type delivered and perception of receiving real or sham stimulation ($X^2(1) = 0.259$, $p = 0.611$; $BF_{01\ \text{independent multinomial}} = 1.618$, N = 22).

Table *4.7* displays the results of the t-tests for additional perceptual scales. No significant differences were found for itching, burning, pain, tingling and intensity, all with inconclusive Bayesian results except intensity where substantial support the lack of a difference was found. This suggests no difference in perception was perceived between stimulation conditions. However, a significant difference was found for the rating of discomfort (and substantial support from the Bayes results) with cathodal stimulation rated significantly higher (M = 2.67, SD = 2.10) than anodal stimulation (M = 1.75, SD = 1.71). Indicating cathodal stimulation caused more discomfort under this montage.

Table 4.6: *Contingency table displaying the frequency of perceived stimulation type (real or sham) against actual (anodal or cathodal).*

		Stimulation type		Total
		Anodal	Cathodal	
Perceived	Actual	9	8	17
	Sham	2	3	5
Total		11	11	22

Table 4.7: *t-tests for stimulation sensations.*

	t	df	p	BF_{10}	BF_{01}
Intensity	-0.14	11	0.891	0.29	3.45*
Discomfort	2.727	11	0.020*	7.01*	0.143
Tingling	0.761	11	0.463	1.804	0.554
Pain	2.017	11	0.069	0.961	1.04
Burning	-0.983	11	0.347	2.325	0.43
Itching	1.624	11	0.133	1.209	0.827

*=$p < 0.05$, BF > 3

4.3.2. Imaging

4.3.2.1. Univariate task results

When corrected for multiple comparisons (p = 0.05 FWE) we did not observe any significant activation for any of the contrasts at baseline. Furthermore, we did not observe any effect of stimulation on activation. For exploratory purposes we adopted a less conservative threshold of $p < 0.001$ (uncorrected). We found no activation for any of the four contrasts of interests for the baseline run on the first chronological session (using a cut-off of clusters that contained 10 or more voxels). Results for the interaction (anodal > cathodal x baseline < post) for each contrast with clusters of 10 voxels or more can be seen in **Table *4.8***.

4.3.3. Effective connectivity results

The PEB modelling the interaction did not find an effect of stimulation across any of the 225 parameters. **Figure *4.3*** displays the group mean connectivity for the baseline run of the first chronological session in the reduced model (parameters that survived the threshold of 0.95 posterior probability or above). Within the DMN, the PCC and bilateral IPLs display a strong self-inhibitory tone. The PCC and right IPL demonstrate bidirectional excitatory coupling as do the left IPL and left medial temporal gyrus. Both left IPL and right hippocampus show bidirectional excitatory coupling with the PCC and MPFC. The PCC and MPFC demonstrate a largely excitatory coupling between other regions in the DMN. The rest of the network typically exhibits an inhibitory tone over itself. Within the ECN, all except bilateral anterior middle frontal gyrus and MCC display strong self-inhibition. The network largely excerpts an excitatory tone on itself. A bidirectional inhibitory coupling is observed between the left anterior middle frontal gyrus and both left insular and middle cingulate cortex and also between the right supramarginal gyrus and middle cingulate cortex. The right anterior middle frontal gyrus excerpts an inhibitory tone over the left insular. For connections from the DMN to the ECN, the majority are excitatory. Except for connections to the right supramarginal gyrus which are all inhibitory from the DMN bar the right hippocampus. Furthermore, the PCC has an inhibitory tone over the middle cingulate cortex, as does the left hippocampus over the right insular. For connectivity from the ECN to the DMN, most have an excitatory tone. The exceptions being the right supramarginal gyrus (which has an inhibitory tone over all regions bar MPFC, right IPL and right hippocampus) and the right insular (which shows an inhibitory tone over all regions bar PCC, MPFC, and bilateral medial temporal gyrus). Furthermore, the middle cingulate cortex demonstrates inhibitory coupling towards the PCC and MPFC, as does the left supramarginal gyrus towards the PCC and left IPL. Finally, an inhibitory tone is also observed from the right anterior middle frontal gyrus to both PCC and MPFC.

Table 4.8: *Group level uncorrected (p < 0.001) results from contrasts for the interaction (anodal > cathodal x baseline < post). Only clusters of 10 voxels and above are displayed.*

Contrast	Region (using Harvard-Oxford Atlas)	x; y; z	k	z-score	F	P FWE corrected	P uncorrected
Internal > external	Right cerebral white matter	33; -55; -1	38	4.08	26.22	0.267	<0.001
	Right cerebral white matter	33; -37; 23	25	3.77	21.46	0.579	<0.001
	Left cerebral white matter	-21; -79; 8	13	3.49	17.36	0.893	<0.001
External > internal	Right cerebral white matter	36; -55; -1	43	3.84	22.42	0.504	<0.001
	Right cerebral white matter	33; -37; 23	43	3.79	21.78	0.555	<0.001
	Left cerebral white matter	-33; -61; -4	13	3.73	20.9	0.626	<0.001
	Left cerebral white matter	-24; -79; 8	17	3.56	18.68	0.807	<0.001
Commission error > correct withhold	Right cerebral white matter	39; -31; -13	13	3.46	15.95	0.796	<0.001
Correct withhold > commission error	Right cerebral white matter	39; -31; -13	13	3.46	15.95	0.796	<0.001

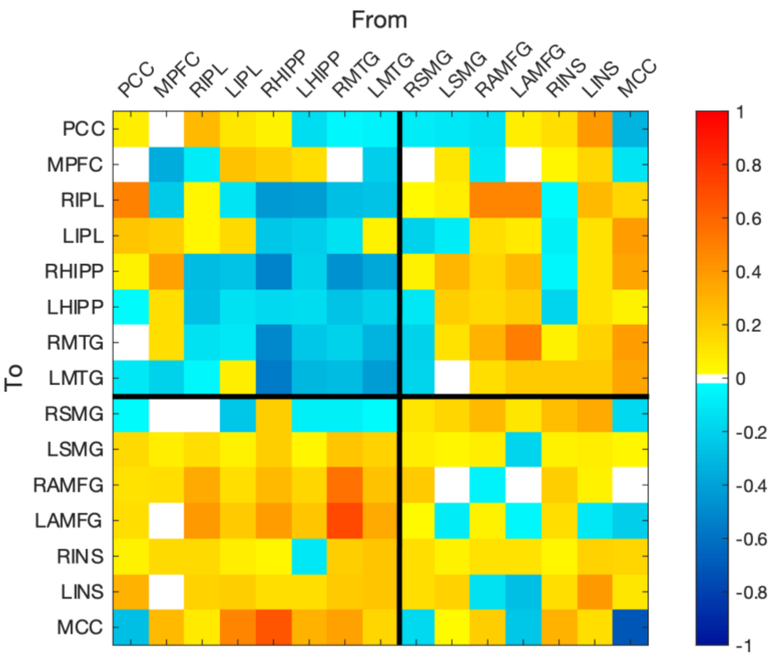

Figure 4.3: Effective connectivity within and between the DMN and ECN for the baseline run on the first chronological session of the task. The colourmap on the right represents connection strength (Ep.A value). Extrinsic connections are represented in Hz and intrinsic self-connections are log scaled. Red indicates excitatory coupling and blue indicates inhibitory coupling for extrinsic connections. PCC, precuneus/posterior cingulate cortex; MPFC, medial prefrontal cortex; RIPL, right inferior parietal lobe; LIPL, left inferior parietal lobe; RHIPP, right hippocampus; LHIPP, left hippocampus; RMTG, right medial temporal gyrus; LMTG, left medial temporal gyrus; RSMG; right supramarginal gyrus; LSMG, left supramarginal gyrus; RAMFG, right anterior middle frontal gyrus; LAMFG, left anterior middle frontal gyrus; RINS, right insular, LINS, left insular, MCC, middle cingulate cortex.

4.4. Discussion

Using a within-subjects design, the current study aimed to investigate the effect of tDCS over the right IPL on behavioural responses of mind-wandering and observe any changes to underlying brain activation and effective connectivity. Supporting our hypothesis, our results suggest that anodal tDCS was unable to modulate mind wandering propensity, as compared to cathodal. Against our hypothesis, we found no brain activation related to the task in our univariate analysis nor an effect of tDCS on this. Furthermore, we found no effect of tDCS on any parameters within or between the DMN and ECN on our effective connectivity analysis.

Overall, our results demonstrate we were unable to modulate mind-wandering propensity or underlying brain activation and effective connectivity.

Specifically, we provide substantial Bayesian evidence for the lack of effect of tDCS on behavioural responses of ‘mind-wandering’ and mean reaction time to SART, substantial evidence for commission errors and anecdotal evidence for ‘on-task’ and ‘environment’ probe responses when comparing the null versus the full model. Additionally, when considering the effect of the interaction itself, we provide substantial evidence for the model excluding the interaction for ‘mind-wandering’ responses; and anecdotal evidence for all other measures (‘on-task’, ‘environment’, mean reaction time and commission errors). Our results contradict the literature, however, are in agreement with our previous research in Chapter 3, highlighting again the lack of effects of tDCS in a different cohort of participants. Previous research reported anodal stimulation of the right IPL reduced mind-wandering propensity compared to sham using a comparable sample size to the current study (13 and 11, respectively) (Kajimura et al., 2019). Notably, although Kajimura et al., (2019) also used a within-subjects design which helps control for inter-subject variability across conditions, they only assessed mind-wandering post-stimulation and therefore did not control for sessions-to-session variability in individual baseline levels of mind-wandering. Here, we included a baseline and post-tDCS run of the task for each session to mitigate this. Indeed, we show large variability in mind-wandering propensity at baseline (0% to 84% across participants), which supports previous research (Unsworth & McMillan, 2014; Vannucci & Chiorri, 2018) and may indicate the findings from Kajimura et al., (2019) reflect subject variability in mind-wandering as opposed to any effects of tDCS.

Additional research from a different lab investigated the effects of HD-tDCS when applied to both IPLs simultaneously (1mA over each) (Chou et al., 2020). This montage would have resulted in more focal stimulation with the current density centred around the parietal lobes due to the use of HD-tDCS. They found no effect of tDCS on overall propensity to mind-wander, which partially supports our findings. However, in addition to asking whether participants were on-/off-task, participants were asked whether the thoughts were about the past, present, or future and if they were positive or negative in mood. Chou et al., (2020) reported an ability to influence the type of mind-wandering with cathodal stimulation reducing the frequency of negative thoughts about the past (Chou et al., 2020). We did not record the type of mind-wandering with our probes and acknowledge that we therefore may have missed any effects of tDCS on this sub-categorisation. Additional research combined stimulation of the right IPL with the left prefrontal cortex as the return electrode (compared to the left cheek in the current study) and would have resulted in a markedly different current density across the brain, specifically over prefrontal regions (Filmer et al., 2021; Kajimura et al., 2016; Kajimura & Nomura, 2015). All three studies found reduced mind-wandering propensity after anodal right IPL stimulation compared to cathodal (Kajimura et al., 2016; Kajimura & Nomura, 2015) and compared to sham (Filmer et al., 2021). The position of the return over the left DLPFC makes it difficult to ascertain what is driving any effects. As the DLPFC is a central node in the ECN, thought to be anticorrelated with the DMN (Fox et al., 2005), the anodal excitation of the DMN coupled with the inhibition of the ECN from the cathode may be necessary to elicit alterations between the networks, thus resulting in changes in behaviour.

In addition to our behavioural results, we observed no effect of stimulation on brain activation or effective connectivity. Previous research found anodal right IPL stimulation resulted in effective connectivity changes within the DMN whilst undertaking the SART (Kajimura et al., 2019). Specifically, enhanced coupling from the MPFC to bilateral medial temporal lobes and right middle temporal gyrus and reduced coupling from bilateral IPLs to both medial temporal lobes (Kajimura et al., 2019). Although the current study was never intended as a direct replication of this research, the 15 ROIs used in our effective connectivity analysis were based on those used by Kajimura et al., (2019), however we failed to replicate these findings. The differences between the current study and Kajimura et al., (2019) potentially contribute to the lack of any effects observed, particularly the use of larger electrodes (7 x 5cm) by Kajimura et al., (2019), which would have resulted in more dispersed current densities across wider brain regions. Additional research from the same lab assessed resting state effective connectivity changes in the DMN before and after concurrent stimulation of the right IPL and left LPFC (Kajimura et al., 2016). They observed anodal-IPL stimulation reduced coupling from the right IPL and MPFC to the PCC, whereas cathodal stimulation increased coupling from the MPFC to the PCC. Contrasting this with their behavioural results it suggests connections from the right IPL and MPFC to the PCC facilitate mind-wandering and these connections were reduced under anodal-IPL stimulation. The inclusion of the left

LPFC electrode may be necessary here to observe such modulations or stimulation of prefrontal cortex alone is enough to modulate network connectivity and behavioural performance.

Separate to this, research suggests neuronal activation of the regions targeted for stimulation by administering a cognitively relevant task during stimulation may be necessary for tDCS to influence the network(s) sufficiently to modulate performance (Kadosh, 2013). Greater improvements in working memory were found when active tDCS was delivered during the n-back task compared to when stimulation was delivered at rest or following dual sham tDCS and task (Andrews et al., 2011). Additional research demonstrated working memory improvements in functional connectivity were observed during stimulation but not after (Nissim et al., 2019). Similarly, from the motor literature, tDCS over M1 had a greater influence on motor learning when it was applied concurrently with the task compared to pre-task only (Karok & Witney, 2013). Therefore, it is appreciated that activation and engagement of the regions being stimulated may be necessary to ensure successful modulation using tDCS and these effects may not last post-stimulation. Considering we administered tDCS as rest, this may have influenced the ability to produce any effects. Future studies could provide concurrent task and stimulation in an effort to activate the DMN throughout tDCS.

Leaving the effects of tDCS aside, contrary to previous research (Christoff et al., 2009) we were unable to demonstrate activation of the DMN to responses of mind-wandering during the baseline chronological session of the task. One of the main differences between the current study and Christoff et al., (2009) was operationalising mind-wandering. Christoff et al., (2009) used a 7-point Likert scale rating TUT which were later categorised as “on-task” (responses 1-3) and “off-task” (responses 4-7). Conversely, we used two 4-point Likert scales to record internal and external attention, to specifically segregate episodes in off-task focus caused by external distraction, and later categorised mind-wandering as high internal/low external responses. Therefore, differences in defining subjective reports of mind-wandering may have resulted in an inability to accurately capture occurrences of mind-wandering and any brain activity associated with it. Another possible explanation may be that the current study was underpowered. Our sample size was slightly smaller (11 compared to 15) than Christoff et al., (2009) and we only included 20 thought-probes per run of the task whereas Christoff et al., (2009) included 80, which we acknowledge is a limitation of the current study. To observe activation outside of stimulation or practice effects, we only included the 20 thought-probes from the baseline run of the first chronological session in the analysis. The relatively small number of probes resulted in some thought-probe categories having no responses for some participants and may have contributed to lack of observed task-related brain activation. Kajimiura et al., (2016) also included 20 probes and reported a similar issue by failing to analyse the task-related fMRI data due to “an insufficient number of trials regarded as mind wandering were obtained in the task-related fMRI analysis”. As exploratory analysis, we combined both baseline runs of the task for the univariate analysis (40 probes) and again failed to observe any task-related brain activation. Subsequent research using the SART and experience sampling similar to Christoff et al., (2009) with a larger sample than ours (27) and slightly more probes (30) was also unable to replicate the initial results and failed to find any task-related brain activation using the same analysis pipeline (Denkova et al., 2019). Replication of the original research by Christoff et al., (2009) is needed to validate the reliability of subjective thought-probes in eliciting the expected brain activation.

For the baseline level of effective connectivity within and between the DMN and ECN, we observed the right IPL, other than from the PCC, receives inhibition from all other regions of the DMN whilst having inhibitory output to all except the PCC and left IPL. The coupling between the right IPL and regions of the ECN was bidirectionally excitatory (excluding an inhibitory coupling from the right insular). The right IPL has been postulated to be involved in regulating attention to behaviourally salient events and may act as a transitory hub between regions of the DMN and ECN during shifts in attention (Singh-Curry & Husain, 2009). The DMN displayed an overall inhibitory coupling between regions, whereas the ECN displayed an excitatory within-network coupling. This may be reflecting the demands of the task, with the DMN inhibiting itself to allow focus on the task. Within the DMN, previous effective connectivity analysis of rs-fMRI found the right IPL had excitatory influence over both the PCC and MPFC (Almgren et al., 2018; Di & Biswal, 2014). Our results support these findings in relation to the PCC, but not the MPFC, where we observed an inhibitory relationship from the right IPL to the MPFC. We found inconclusive evidence for the bidirectional relationship between the PCC and MPFC which is in line with previous research (Almgren et al., 2018). However, several resting state studies have demonstrated an excitatory tone from the MPFC to the PCC (Di & Biswal, 2014; Jiao et al., 2011; Uddin et al., 2009) and has been linked to the generation of self-referential processes (Saverino et al., 2015). The DMN and ECN displayed an overall excitatory coupling with each other. However, the right insular showed an inhibitory tone over several regions of the DMN, specifically bilateral IPLs and bilateral hippocampi. This may reflect the insular mediating internal awareness, particularly given its role in interoceptive awareness of homeostatic emotions (Mayer, 2011). The differences between the previous research and the current study may be attributed to employing DCM over rs-FMRI and during the SART, respectively. Throughout the SART, participants would be fluctuating between focussing on the task and mind-wandering, as demonstrated from the results of the thought-probes, however, during rest participants are free to let their minds wander, unconstrained. Although we see large periods of mind-wandering, this would result in varying mental states across the studies.

To understand the effects of tDCS, researchers often compare active stimulation against a sham condition where stimulation is delivered for a small amount of time (~30s) to mimic the sensations. Recent research suggests that participants may be able to differentiate between active and sham stimulation (Turner et al., 2021). Furthermore, sham-controlled studies have yielded inconsistent results across the field and often fail to confirm whether any effects can be attributed specifically to the brain region being targeted (Fonteneau et al., 2019). A primer on the use of tDCS in cognitive neuroscience suggested a better control would be to change polarity (Parkin et al., 2015). We used polarity as a control condition in the current study without a sham and acknowledge that this may be a limitation. An early meta-analysis found anodal and cathodal stimulation of cognitive areas does not always show a cathodal-inhibitory and anodal-excitatory effect (Jacobson et al., 2012). Furthermore, studies observing anodal and cathodal stimulation can elicit effects in the same direction (Marshall et al., 2005; Sparing et al., 2009). It is therefore possible that the lack of sham condition in the current study could be masking any effects of stimulation overall. However, we do not think this is the case in our paradigm for two reasons. Firstly, we have previously demonstrated evidence for the lack of an effect of right IPL-tDCS on mind-wandering (at the behavioural level) using all three conditions (anodal, cathodal and sham) in a larger sample size (23) (Chapter 3). Secondly, as previously outlined, two of the studies which included the left LPFC as the return site (Kajimura et al., 2016; Kajimura & Nomura, 2015) found anodal and cathodal stimulation modulated mind-wandering in opposing directions, with anodal right IPL reducing mind-wandering and cathodal increasing it and only a significant difference found for polarity, not sham. Therefore, it appears unlikely that the lack of an effect of tDCS in the current study is due to the omission of a sham condition, but we acknowledge further research including a control condition is necessary to fully account for this.

4.4.1. Conclusions

Overall, we found that tDCS over the right IPL was unable to modulate behavioural reports of mind-wandering nor underlying brain activity and effective connectivity. This contradicts previous research and further questions the efficacy of tDCS in modulating self-referential processes.

Chapter 5

Chapter 5 DLPFC-TDCS UNABLE TO MODULATE MIND-WANDERING PROPENSITY NOR UNDERLYING FUNCTIONAL OR EFFECTIVE BRAIN CONNECTIVITY.

5.1. Abstract

Research has shown conflicting evidence over the ability to modulate mind-wandering propensity with anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (DLPFC). Here, twenty participants received 20-minutes of anodal or sham tDCS over the left DLPFC while in the MRI scanner, in two separate sessions (counterbalanced). In each session, they completed two runs of a sustained attention to response task (before and during tDCS), which included probes recording subjective responses of mind-wandering. We assessed behavioural responses and employed dynamic functional network connectivity (dFNC) and dynamic causal modelling over regions of the default mode, salience and executive control networks to observe effects of tDCS on behaviour, as well as functional and effective dynamics. Behavioural results provided substantial evidence in support of no effect of tDCS on task performance nor mind-wandering. We found no effect of tDCS on dFNC analysis of frequency (how often) or dwell time (time spent) in underlying brain states nor any effect of tDCS on effective connectivity. Overall, our results suggest that DLPFC-tDCS is unable to modulate mind-wandering propensity or influence underlying functional and effective connectivity. This expands previous behavioural replication failures in suggesting that DLPFC-tDCS may not lead to even subtle changes in mind-wandering related brain activity.

5.2. Introduction

Research investigating the use of transcranial direct current stimulation (tDCS) as a tool to modulate self-generated cognitive processes, such as mind-wandering, is becoming increasingly popular (Axelrod et al., 2015, 2018; Bertossi et al., 2017; Boayue, Csifcsák, Aslaksen, et al., 2020; Chou et al., 2020; Coulborn et al., 2020; Filmer et al., 2019, 2021; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Mind-wandering is an internally directed process which is typically associated with the activation of the default mode network (DMN) (Fox et al., 2015; Mason et al., 2007). This is a network found to be more active at rest and when engaged in decisions about oneself, with core regions including the posterior cingulate cortex / precuneus (PCC) and the medial prefrontal cortex (MPFC) (Buckner, 2012). Conversely, the dorsolateral prefrontal cortex (DLPFC), is an area associated with high order cognitive functions (Duncan & Owen, 2000) and working memory (Curtis & D'Esposito, 2003) and forms part of the executive control network (ECN). Engagement of the ECN has been observed during tasks which require externally-directed attention, such as response inhibition (Aron, 2007), working-memory (Curtis & D'Esposito, 2003), and task-set switching (Dreher & Berman, 2002). Although the DMN and ECN have previously been thought to be anti-correlated (Fox et al., 2005), recruitment of the DLPFC has also been implicated in mind-wandering (Christoff et al., 2009; Dumontheil et al., 2010). Based on this, several studies have targeted the DLFPC with non-invasive brain stimulation to try to modulate mind-wandering. Specifically, anodal left DLPFC-tDCS (return over the right supraorbital area) has increased self-reported mind-wandering propensity during a sustained attention to response task (SART) with interspersed thought probes (Axelrod et al., 2015, 2018), providing causative evidence for the role of DLPFC in mind-wandering. However, a pre-registered large-scale replication of the original study was unable to show the same effects and instead reported Bayesian support for the lack of an effect of tDCS stimulation (Boayue, Csifcsák, Aslaksen, et al., 2020). Further research stimulating the DLPFC has reported modulation of mind-wandering propensity but in an inconsistent manner. For example, one study found cathodal (not anodal) stimulation of the DLPFC increased mind-wandering compared to sham (Filmer et al., 2019), while a further study showed that anodal tDCS (this time with a high definition montage) over the DLPFC reduced mind-wandering propensity, opposing the direction previously reported (Boayue, Csifcsák, Kreis, et al., 2020). In line with the original findings, subsequent research reported increased mind-wandering propensity during anodal stimulation of the left DLPFC, but crucially, when the cathode was placed over the right inferior parietal lobule (Filmer et al., 2021; Kajimura et al., 2016; Kajimura & Nomura, 2015). This leaves it unclear as to whether the DLPFC or the right inferior parietal lobule was driving these effects. This lack of congruous effect of tDCS therefore questions the role of the DLPFC in mind-wandering and the efficacy of tDCS in modulating it.

One way in which we could garner more information about the effects of tDCS would be to look at any changes in brain activation and connectivity, for example through the use of functional MRI. Understanding these effects may help explain some of the inconsistent results found at the behavioural level. The SART is currently the most commonly used task in the literature measuring mind-wandering propensity and the potential of tDCS in modulate it (Axelrod et al., 2015, 2018; Filmer et al., 2019, 2021; Kajimura et al., 2019). Previous fMRI studies have confirmed that subjective episodes of mind-wandering during the SART elicit activation in the DMN, while occasions when the participant reports being on-task are related to activation of the ECN (Christoff et al., 2009; Stawarczyk, Majerus, Maquet, et al., 2011). To our knowledge, there is no research investigating the effect of tDCS on brain activation during this task.

In addition to standard task-related activation, time-varying functional and effective connectivity analysis may reveal more subtle underlying effects of stimulation on network connectivity. One such method is dynamic causal modelling (DCM); a technique that maps the causal influence brain regions have over each other (i.e., effective connectivity). Previous research found modulations to the effective connectivity within the DMN following tDCS over the inferior parietal lobule during the SART (Kajimura et al., 2016). To our knowledge, no research to date has investigated the effect of DLPFC-tDCS on causal dynamics during this task.

In turn, dynamic functional network connectivity (dFNC) allows one to observe reoccurring ‘brain states’ and provides the frequency and the dwell time for each state. Evidence using an array of different tasks has indicated a strong relationship between functional states and ongoing cognitive processes allowing for a convergence between functional states and mental states (Gonzalez-Castillo et al., 2015). Denkova et al., (2019) employed this technique on functional MRI data collected whilst participants undertook the SART (without tDCS stimulation). They observed five reoccurring ‘brain states’ over three key intrinsic brain networks (DMN, ECN and the salience network (SN)) (Denkova et al., 2019). No study to date has investigated the potential effects of tDCS on the frequency or dwell time of these reoccurring brain states. If tDCS indeed modulates underlying neural activity, observing whether this impacts the likelihood of certain states and the length of time spent in them would provide further insight into the casual role of tDCS on brain dynamics and how this translates into behavioural changes.

In this study, we used the SART with interspersed thought-probes before and during tDCS over the left DLPFC concurrently during functional MRI acquisition to investigate whether tDCS could indeed modulate mind-wandering propensity and brain activation and connectivity. We expect to see increased activation of the DMN during episodes of mind-wandering and activation of the ECN when focussed on-task. If the left DLPFC is indeed causally involved in mind-wandering, we predict anodal stimulation will result in increased reports of mind-wandering and increased activation of this region during off-task responses. As exploratory analysis, we also investigate the effects of tDCS on typically occurring brain states during the task using dynamic functional network connectivity and the effective connectivity within and between intrinsic brain networks. We hypothesise that tDCS will result in an increased frequency and dwell time in states reflecting overall positive connectivity within and between networks which would allow for increased rumination without affecting task performance, as previously posited (Axelrod et al., 2015). Regarding effective connectivity changes, we hypothesise anodal stimulation will result in modulation of effective connectivity within and between DMN and ECN, specifically to and from the DLPFC.

5.3. Method

5.3.1. Pre-registration

We pre-registered this study at https://osf.io/8um5s/ on 16th July 2019. Specifically, we pre-registered the design of the task, the stopping criteria for data collection, and the behavioural and GLM analysis. For the GLM analysis we deviated away from the pre-registered pre-processing steps to instead use the increasingly more standard fMRIprep pipeline to allow for easier replicability. However, we performed the statistical analysis (GLM) as described in the pre-registration. All further dynamic and effective connectivity analyses were exploratory.

5.3.2. Participants

27 right-handed healthy participants from an opportunity sample took part in the study, of whom 26 completed both sessions (16 females, 10 males) aged 19-35 years (M = 24.50, SD = 3.56). We removed 6 participants who failed to respond to either 10% or more of the task or thought probes as specified in our pre-registration as this indicates they were not following task

instructions. This resulted in 20 participant's data being analysed (13 females, 7 males) aged 19-35 (M = 24.85, SD = 3.92). We compensated participants with £30 for completing both parts of the study. The University of Birmingham's Science Technology Engineering and Mathematics Ethical Review Committee provided ethical approval for the study. Before their inclusion in the study, we screened all participants for tDCS and MRI safety. All participants provided informed consent prior to their participation.

5.3.3. Materials

5.3.3.1. Brain stimulation

We administered tDCS via an MRI compatible NeuroConn DC-Stimulator (neuroCare Group GmbH), using 5 x 5 cm rubber electrodes covered with ten20 conductive gel. We placed the anode electrode over the left DLPFC and the cathode electrode over the right supraorbital area. The position of the electrodes was counterbalanced for the sham conditions. Before applying the electrodes, we cleaned the skin with alcohol wipes. To identify the location of left DLPFC on each participant and session, we used a 64-channel EEG cap, and marked F3 with a pen on the participants scalp. After that, we marked Fp2 to indicate the right supraorbital area. We removed the cap and fixed the electrodes in place using self-adhesive tape. Participants received 20 minutes of continuous 1.8mA stimulation with 10 seconds fade-in and fade-out periods. We monitored impedance and made sure it stayed below 15 kΩ. **Figure 5.1** shows a simulation of the current through the brain in standard MNI space.

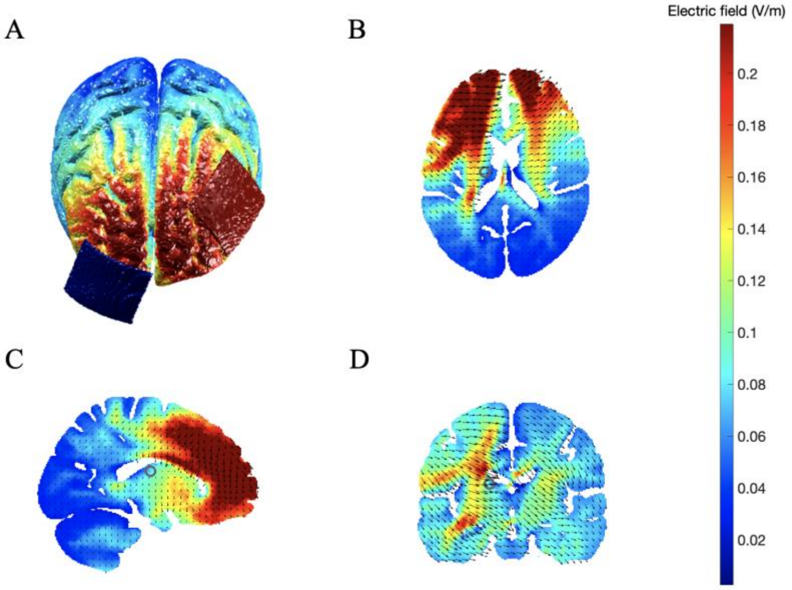

Figure 5.1: Example of a computational model produced with the open-source tool ROAST for the simulation of transcranial direct current stimulation (tDCS). The current magnitude and distribution was simulated using the default 'MNI152_T1_1mm' template based on delivering 1.8mA current from the anode electrode (left DLPFC, F3) with cathode placed over right supraorbital area (Fp2). A) Illustration of the montage for left DLPFC (anode, red patch) and right supraorbital area (cathode, blue patch) and electric field distribution on the cortical surface. B) C) and D) show electric field strength and current flow in black arrows for axial, sagittal and coronal views, respectively. Colour chart on the right represents the magnitude of the electric field in Volts per meter. The default conductivities were used for the simulation (white matter 0.126 S/m; gray matter 0.276 S/m; cerebral spinal fluid 1.65 S/m; bone 0.01 S/m; skin 0.465 S/m; air 2.5e-14 S/m; gel 0.3 S/m; electrode 5.9e7 S/m).

5.3.3.2. Sustained Attention to Response Task (SART) and Thought-Probes

We used the SART, similar to Axelrod et al., (2015), as displayed in **Figure 5.2**. Here participants responded with a button press to the visual presentation of a digit (from 0 to 9) as quickly and accurately as possible, except from the instances where the digit '3' was presented (target) and the participant must refrain from responding. Failure to do so would result in a commission error. Overall, the task included 535 non-targets (95.4%) and 26 targets (4.6%), which never appeared in the final 10s prior to a thought-probe. All stimuli were displayed for 1 second, followed by a fixation cross, also displayed for 1s. Participants needed to respond as quickly and accurately as possible. Throughout the task, we presented 32 thought-probes at pseudo-random intervals (20, 30, 40 and 50s; average 35s). These read ‘Where was your attention focused just before the probe?’. The participants responded by indicating whether they were ‘on-task’ or ‘off-task’. They had 4s to make a response before the SART began again. The task lasted for 20 minutes and 14 seconds.

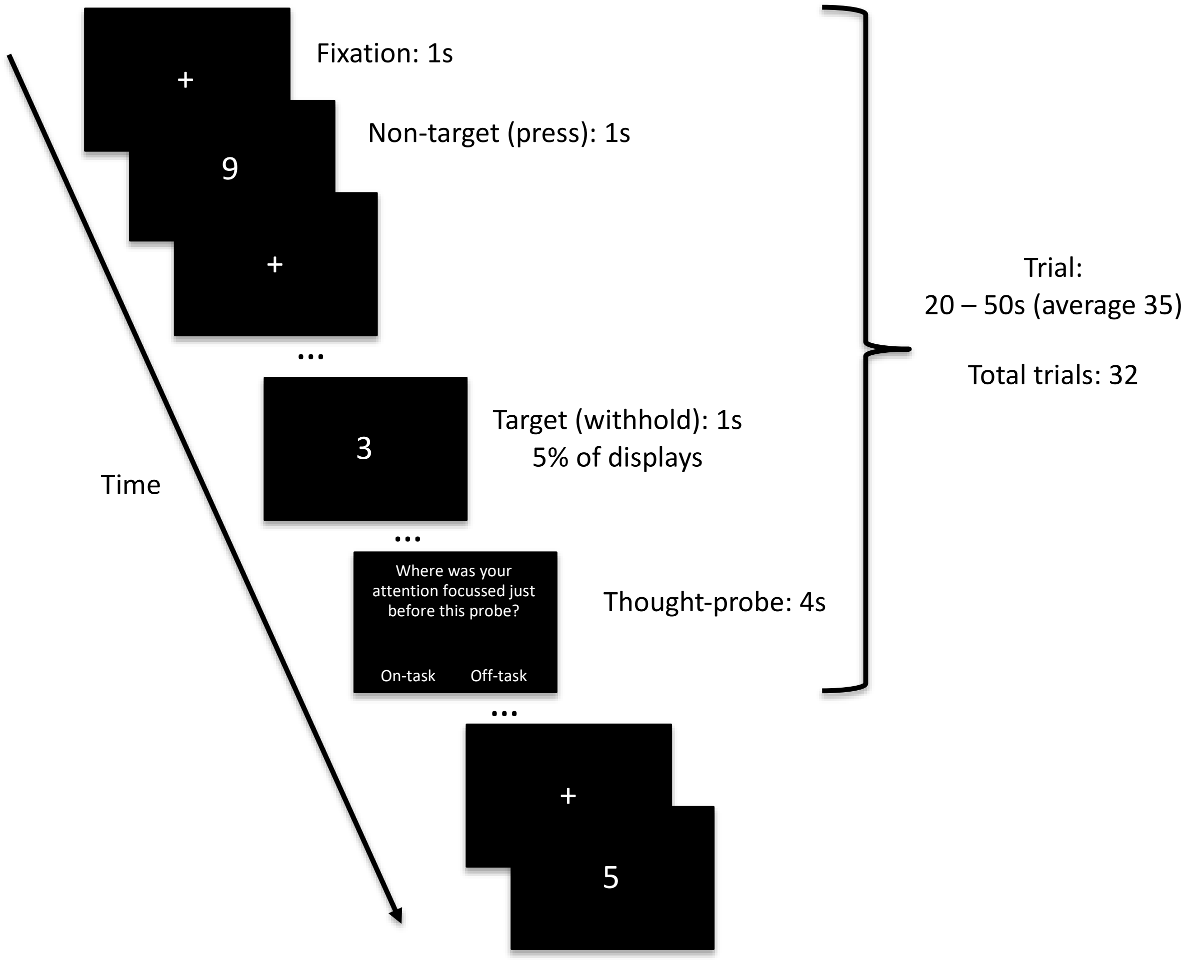

Figure 5.2: Flow diagram of the SART and thought-probe experimental design

5.3.4. Experimental design & procedure

We adopted a within-subjects design with participants completing both conditions (anodal and sham) a minimum of 7 days apart (M = 10, SD = 3.87). Both sessions were identical except for the stimulation condition. The order of the anodal and sham sessions was counterbalanced, and participants were blind to the condition on each session.

Participants first completed three practice probes of the task outside of the scanner lasting approximately 30 seconds to become familiar with the task. They then completed the Karolinska sleepiness scale. Following this, participants entered the scanner and completed an offline (no tDCS) run of the SART, followed by an online (tDCS) run, which took place alongside 20 minutes of tDCS. The task was delivered using MATLAB 2017b and Psychtoolbox-3 on a Macbook Air (processor: Intel Core i7) for the practice run outside the MRI room and using MATLAB 2018a and Psychtoolbox-3 on a Windows 10 computer (processor: Intel Core i7) for the offline and online runs in the MRI scanner. At the end of each session, participants completed a post-tDCS questionnaire to assess their perceptions of the stimulation and again completed the Karolinska sleepiness scale.

5.3.5. fMRI acquisition

We collected data using a 3.0 Tesla Siemens PRISMA MRI scanner, using a 32-channel head-coil at the Centre for Human Brain Health (CHBH), University of Birmingham. First, we acquired a T1-weighted image (repetition time (TR) = 2 ms; echo time (TE) = 2.03 ms; matrix size = 256 x 256 mm; voxel size = 1 x 1 x 1 mm; field of view = 210 x 210 mm; and flip angle = 8 degrees). Echo-planar images were obtained with the following parameters: 57 slices (interleaved with multiband); TR = 1500 ms; TE = 35 ms; matrix size = 84 x 84 mm; voxel size = 2.5 x 2.5 x 2.5 mm; field of view = 210 x 210 mm; and flip angle = 71 degrees. This resulted in 812 volumes collected per run of the task.

We placed a NAtAtech response box (3 response buttons) into the participant’s right hand whilst in the scanner. The task and instructions were presented using a display back-projected onto a screen mounted at the end of the scanner. A mirror attached to the head coil enabled subjects to view the stimuli.

5.3.6. Behavioural variables

We categorised responses to thought-probes as on-task and off-task and converted them into percentages per run of the task for analysis. We also recorded reaction time after the presentation of non-target stimuli and calculated the mean reaction time per run of the task for the analysis. We defined commission errors as a button press in response to a target and recorded the number of commissions errors per run of the task for analysis. We interpreted increased commission errors (to targets) and longer reaction times to non-targets as suggestion of greater levels of mind-wandering.

5.3.7. fMRI pre-processing

We pre-processed the data using fMRIPrep (version 20.2.0) (Esteban et al., 2019), based on Nipype (Gorgolewski et al., 2011). We used the standard pre-processing pipeline: anatomical T1 images were corrected for intensity and nonuniformity using N4BiasFieldCorrection (Tustison et al., 2010) distributed on ANTs 2.3.2 (Avants et al., 2008) and then skull-stripped using antsBrainExtraction.sh workflow; we then segmented the brain tissue into cerebrospinal fluid (CSF), white-matter (WM) and grey matter (GM) using FAST on FSL v5.0.11 and finally spatially normalised to the ICBM 152 Nonlinear Asymmetrical template 2009c (Fonov et al., 2009). We pre-processed functional images by first generating a reference volume (BOLD reference) and its skull-stripped version using the standard pipeline of fMRIPrep; then, we co-registered the BOLD reference to the T1w with boundary-based registration cost function (Greve & Fischl, 2009) configured with nine degrees of freedom accounting for the remaining distortion in BOLD images; following this, head motion parameters (transformation matrices and six corresponding rotation and translation parameters) were estimated before spatio-temporal filtering using *mcflirt* (Jenkinson et al., 2002)*;* slice timing correction was performed alongside motion-correction with additional ‘fieldmap-less’ distortion correction (Wang et al., 2017); the functional images were then normalised into MNI space (MNI152NLin2009cAsym (Fonov et al., 2009)); finally, framewise displacement (Power et al., 2014) and DVARS (Power et al., 2012) were implemented on Nipype for each functional run.

We performed spatial smoothing of the functional images in SPM12 (www.fil.ion.ucl.ac.uk/spm) on MATLAB version R2019b using an 8mm FWHM Gaussian kernel. To reduce low-frequency drift and high-frequency physiological noise for the dFNC and DCM analysis, we applied a bandpass temporal filter between 0.01 - 0.1 Hz to the data using the DPABI toolbox in the DPARSF package (http://rfmri.org/DPARSF).

5.3.8. Univariate analysis of fMRI data

One participant was removed from all subsequent imaging analysis due to excessive head-movement across the scans (>15% of scans had > 0.9mm framewise displacement in any given run of the task). A further participant was removed from the univariate analysis as they had no responses of ‘off-task’ in one of the runs of the task, and therefore this dataset wouldn’t allow for a valid comparison between ‘on-task’ and ‘off-task’ activity. The final sample for the univariate analysis was a total of 18 participants and 19 for the dynamic and effective connectivity analysis.

We estimated condition effects at each voxel according to a general linear model custom designed on SPM12 similar to that used by Christoff et al., (2009). We used four regressors of interest. The first two comprised the 10s preceding each type of thought-probe response (‘on-task’ and ‘off-task’). We then created two further regressors from the 10s pre-target intervals separated into those preceding a commission error and those before a correct withhold to target to represent occasions of being focussed on the task and being off task, respectively. We also included regressors of no interest to model incorrect response to targets, correct response to targets and correct responses to non-targets, for the occurrence of each thought-probe and the response to a thought-probe, all with a duration of zero. This was to regress out activity associated with pressing a button to respond. Finally, we included seven additional regressors capturing the six motion parameters estimated in the realignment step and the framewise displacement. Furthermore, frames that exceed the threshold of >0.9mm framewise displacement were treated as outliers and marked using a stick regressor (as per (Botvinik-Nezer et al., 2019)).

For the first level analysis, we estimated pairwise contrasts between regressors of interest for each participant independently for offline and online runs. Specifically, we compared self-reported on-task and off-task responses. To obtain brain activity associated with performance in the task (as an indirect measure of mind-wandering) we compared commission errors and correct withholds to targets.

For the second level analyses, first we calculated a group level baseline activation using a 1-sample t-test for the offline run of the task taken during participants first session, in order to generate the canonical patterns of activation associated with our task and contrasts (on-task > off-task, off-task > on-task, commission errors > correct withholds and correct withhold > commission error). We also tested for the effects of stimulation using 2 (stimulation: anodal left-DLPFC, sham) x 2 (run: online, offline) repeated measure ANOVAs on each contrast above.

5.3.9. Selection of regions of interest

We used a total of nine regions of interest (ROIs) for the functional connectivity analysis: two for the DMN (MPFC, PCC), four for ECN (bilateral DLPFC, bilateral PPC), and three for the SN (bilateral FIC and the ACC). To define these, we used the MNI coordinates used by Denkova et al., (2019) to center a sphere of 6mm radius (see Table 1). We then used these ROIs for the dynamic functional network connectivity and dynamic causal modelling analysis.

5.3.10. Dynamic functional network connectivity

After the functional images were smoothed, we regressed the six rigid body motion parameters and framewise displacement calculated during pre-processing and frames that exceed the threshold of >0.9mm framewise displacement were treated as outliers and marked using a stick regressor (as per (Botvinik-Nezer et al., 2019)). We followed the same pipeline and parameters at Denkova et al., (2019). Specifically, time series for the nine ROIs were extracted and then submitted for DFC analysis with a sliding window approach using the GIFT toolbox (https://trendscenter.org/software/gift/). We employed a window length of 44s and step size of 1 TR (1.5s) and did not isolate or delete probe periods as these are an integral part of the task (and as per Denkova et al., (2019)), therefore the sliding windows focussed on an uninterrupted continuous temporal dynamic. This produced a correlation matrix which was 768 (sliding windows) x 36 (paired connections) per run per subject. We set number of clusters (k) to 5 (as per Denkova et al., (2019)). We then calculated dFNC metrics for each run of the task per subject. These consisted of frequency of occurrence (percentage a brain state occurred) and dwell time (average time in sliding windows) spent in each of those 5 states. We also recorded the number of transitions (changes from one state to another).

5.3.11. Effective connectivity analysis

5.3.11.1. Spectral dynamic causal modelling

To assess effective connectivity, we employed a similar pipeline to that used by Kajimura et al., (2019). We initially ran a separate linear model to extract the time series to be used during dynamic causal modelling. This included the 6 rigid body parameters, framewise displacement as well as the cerebral spinal fluid and white matter signals as nuisance regressors. We removed volumes with motion > 0.9mm framewise displacement using a stick regressor.

We then performed bilinear, one-state spectral DCM with the DCM12 routine on SPM12 using MATLAB version R2019b (see Friston et al., (2014) for more details). We extracted time series from the same 9 ROIs as used in the dynamic functional connectivity analysis (see **Table *5.1***). We used a fully and reciprocally connected model resulting in a total of 81 effective connections (the A-matrix) produced and estimated for each model.

Table 5.1: *ROIs and MNI coordinates used in dFNC and DCM analyses. All had sphere radius of 6mm.*

Network	Region	Right / Left	MNI coordinates (x, y, z)
DMN	MPFC	L	−2, 36, −10
DMN	PCC	L	−7, −43, 33
SN	FIC	R	37, 25, −4
SN	FIC	L	−32, 24, −6
SN	ACC	R	4, 30, 30
ECN	DLPFC	R	45, 16, 45
ECN	DLPFC	L	−45, 16, 45
ECN	PPC	R	54, −50, 50
ECN	PPC	L	−38, −53, 45

DMN, default mode network; SN, salience network; CEN, executive control network; MPFC, medial prefrontal cortex; PCC, precuneus / posterior cingulate cortex; FIC, frontoinsular cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex.

5.3.11.2. Parameter estimation and effects of tDCS on effective connectivity

Following model specification and estimation, we took the first level individual DCMs to the second level (between-subjects) using parametric empirical Bayes (PEB) (K. J. Friston et al., 2016). PEB uses a hierarchical Bayesian framework to model individual subject's effective connectivity relative to the group level by using individual DCMs (first level) as priors to constrain the variables in the Bayesian linear regression model (second level) (Zeidman et al., 2019). Following this, we used Bayesian model reduction (BMR) to prune away any parameters not contributing to the evidence from the full model until no more improvements could be made. We then applied Bayesian model averaging (BMA) (K. J. Friston et al., 2016; Zeidman et al., 2019) to take the remaining parameters, weigh them by their model evidence, and combine them into the final group model. We defined statistical significance by applying a threshold of posterior probability > 0.95 (strong evidence) for free energy.

To capture the typical group mean connectivity elicited whilst undertaking the task, we performed a group level PEB for participants' first offline run. To test the effects of tDCS on the model parameters, we first created a PEB model in each participant which captured the pairwise interaction for greater increases during anodal stimulation as compared to sham (offline run < online run x anodal > sham condition). We then entered each subject's PEB into a subsequent PEB that encoded the commonalities at the group level (mean).

5.3.12. Statistical analyses of behavioural, dynamic functional connectivity

We used frequentist and Bayesian equivalent comparisons (with default priors) on JASP (JASP Team, 2020) to test the effect of tDCS on behavioural data and frequency and dwell time in the dynamic functional states. For our behavioural variables of interest (i.e., on task responses and performance on SART), we conducted repeated measures ANOVAs with stimulation (anodal, sham) and run (offline, online) as factors.

To test the effects of tDCS on each brain state we performed a 2 (stimulation: anodal left-DLPFC, sham) x 2 (run: online, offline) repeated measure ANOVA for each of the states for frequency of occurrence, dwell time and number of transitions.

We used a repeated measures ANOVA to model the main effects of stimulation (anodal and sham) and time (before and after), as well as the interaction between them, for the score from the Karolinska sleepiness scale.

To assess any potential differences in the perception of the sensations generated by stimulation between anodal and sham, we performed a Chi-Squared test for the association between received and perceived (real or sham) stimulation. We also analysed perception of sensations caused by tDCS (intensity, discomfort, tingling, pain, burning, itching) using paired samples t-tests.

For the frequentist tests, we set the level of significance at p = 0.05. For the Bayesian test, we evaluated both the presence and the absence of an effect by comparing how different models explain the data given the factors of interest (Stafford et al., 2019). We used a Jeffrey-Zellner-Siow Bayes factor (JZS-BF10) to contrast the strength of the evidence for models reflecting the null and interactions (Rouder et al., 2012). For ease of interpretation, we include BF10 for those >1 and invert them as BF01 for those <1. In addition, for all ANOVAS, we also calculated a Bayes factor for the exclusion of the variable of interest (BFexcl) by comparing all models that exclude the interaction with all models that include it. A JSZ-BF between 0.33 and 3 is considered to be weak/anecdotal evidence for an effect; 3–10: substantial evidence; 10–100: strong evidence; >100: very strong evidence (Jeffreys, 1998).

5.4. Results

5.4.1. Behavioural

5.4.1.1. Mind-wandering responses and SART performance

While the data for percentage of ‘on-task’ responses, number of commission errors, and mean reaction time to non-targets violated tests for normality, we still employed ANOVAs as this has previously been shown to be robust enough even when all assumptions are not met (Schmider et al., 2010).

Frequentist analyses revealed no interaction between stimulation (anodal and sham) and run (offline / online) for any of the measures studied. Bayesian analyses provided further support for the lack of an effect of tDCS (substantial to strong evidence for the null as compared to the full model for ‘on-task’ responses, mean reaction time, and commission errors; strong evidence in support of excluding the interaction for ‘on-task’ responses and mean reaction time; and anecdotal evidence in support of excluding the interaction for commission error). see **Table *5.2*** for descriptive statistics and **Table *5.3*** for statistical analyses.

Similarly, we found no main effects for on task-responses. However, we found a main effect of run for commission errors, F(1,19) = 22.06, p < 0.001, Partial eta squared = 0.537; BF10 = 1 (BF10inc(run) = 108.124), with commission errors significantly higher in the online (second) run of the task. We also found a main effect of run for reaction times to non-targets, F(1,19) = 66.92, p < 0.001, Partial eta squared = 0.779; BF10 = 1 (BF10inc(run) = 399.692), with reaction times significantly faster during online runs.

As it can be appreciated in **Figure 5.3**, there was large variability across participants and sessions for both probe-responses and performance on the task.

Table 5.2: *Percentage of ‘on-task’ responses to thought-probes and performance on SART. The data are group means (standard deviations in parenthesis).*

	Offline		Online	
	Anodal	Sham	Anodal	Sham
On-task (%)	69.53	70.76	71.85	71.59
	(19.60)	(18.48)	(14.87)	(16.65)
Commission errors (out of a total of 32 trials)	8.60	7.25	10.4	10.1
	(4.67)	(3.78)	(4.85)	(5.05)
Mean reaction times (s)	0.370	0.379	0.348	0.354
	(0.069)	(0.056)	(0.067)	(0.050)

Table 5.3: *Bayesian and frequentists repeated measures ANOVA for the interaction of stimulation (anodal and sham) and run (offline and online) effects on subjective and objective measures of mind-wandering.*

	JZS-BF_{01} for the null vs full	BFexcl (interact)	F	df	η_p^2	P-value
On-task (%)	49.21**	3.56*	0.152	1,19	0.008	0.701
Commission errors (%)	4.42*	2.31	0.929	1,19	0.929	0.347
Mean reaction time (s)	6.33*	3.28*	0.093	1.19	0.005	0.763

*=BF > 3; **=BF > 10

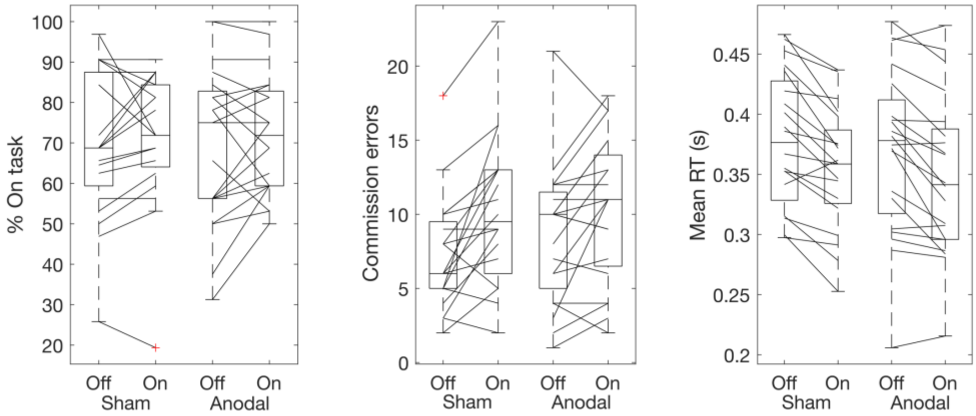

Figure 5.3: Line graphs with box plots displaying the variability in subjective responses (on-task) and variability in task performance (commission error and mean reaction time to non-targets) before (off) and during (on) tDCS in sham (left) and anodal (right) conditions. All measures exhibit large variability both at baseline and in response to tDCS.

5.4.1.2. Post-tDCS questionnaire

Table 5.4 displays the proportion of sessions where participants perceived to have had active stimulation from the post-tDCS perception questionnaire. A Chi-squared test revealed no significant association between stimulation type delivered and perception of receiving real or sham stimulation-($X^2(1) = 3.584$ $p = 0.058$, $BF_{10\ \text{independent multinomial}} = 2.379$, $N = 40$), however this does seem to be trending towards significant and may simply be underpowered.

Table 5.5 displays the results of the t-tests for additional perceptual scales. We found no significant differences for intensity, discomfort, tingling, pain, burning, and itching with substantial Bayesian support for lack of a difference for discomfort, pain, and itching (the rest were inconclusive). This suggests participants did not perceive a difference in sensations between stimulation conditions.

Table 5.4: *Contingency table displaying the frequency of perceived stimulation type (real or sham) against actual (anodal or sham).*

		Stimulation type		Total
		Anodal	Sham	
Perceived	Real	18	13	31
	Sham	2	7	9
Total		20	20	40

Table 5.5: *t-tests for stimulation sensations from the post-tDCS questionnaire.*

	t	df	p	BF_{10}	BF_{01}
Intensity	-1.894	19	0.074	1.031	0.97
Discomfort	-0.358	19	0.724	0.246	4.061*
Tingling	-1.631	19	0.119	0.718	1.392
Pain	-0.533	19	0.587	0.267	3.752*
Burning	-1.351	19	0.192	0.512	1.953
Itching	-0.73	19	0.474	0.295	3.392*

*=BF > 3

5.4.1.3. Karolinska sleepiness scale

Both Bayesian and frequentist analyses revealed no interaction, with Bayesian analyses providing substantial support for the lack of an effect of tDCS for the null as compared to the full model and also for all models excluding the interaction (F(1,19) = 0.053, p = 0.821, Partial eta squared = 0.003; BF01 = 19.99, BF01excl(interaction) = 3.07). We found no main effect of stimulation but did observe a main effect of time (F(1,19) = 24.06, p < 0.001, Partial eta squared = 0.559; BF10 = 1 BF10inc(time) = 4431.12) with sleepiness scores significantly higher after the MRI sessions. See Figure 3 for summary statistics.

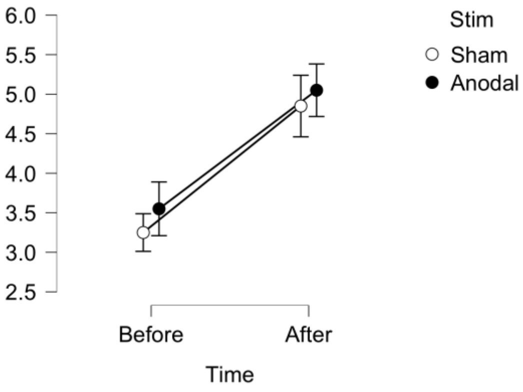

Figure 5.4: Mean scores for the Karolinska sleepiness scale (y-axis) before and after completion of the MRI session for both sham and anodal stimulation conditions. Bars represent standard error.

5.4.2. Imaging

5.4.2.1. Univariate results

When corrected for multiple comparisons (p = 0.05 FWE) we did not observe significant activations in the one-sample t-test capturing canonical activity on the offline run of the task corresponding to the first chronological session for any of our contrasts ('off-task' vs 'on-task', 'on-task' vs 'off-task', 'commission error' vs 'correct withhold', 'correct withhold' vs 'commission error'). We also did not observe any effects of tDCS (interaction), or a practice effect (main effect of run) on BOLD activation in the ANOVA. For exploratory purposes, we adopted a less conservative threshold of p < 0.001 (uncorrected); the results for which can be found in **Table** ***5.6***.

Table 5.6: *Group level uncorrected ($p < 0.001$) results from the offline first session run of the SART for off-task > on-task, commission errors > correct withhold, the interaction for off-task > on-task (online > offline x anodal > sham) and effect of run for the interaction of commission errors > correct withhold (online > offline x anodal > sham). Only clusters of 10 and above are displayed.*

Contrast	Region (using AAL atlas)	x; y; z	k	z-score	F/t
Offline session 1 off-task > on-task	Postcentral Gyrus	-41.5; -30.0; 54.0	571	4.377	6.089
	Extra-Nuclear	-29.0; -27.5; -3.5	27	3.945	5.151
	Outside BA	1.0; -67.5; -46.0	138	3.899	5.060
	Outside BA	1.0; -30.0; 1.5	60	3.894	5.051
	Cingulate Gyrus	-14.0; -27.5; 34.0	19	3.892	5.046
	Cuneus	8.5; -87.5; 4.0	755	3.886	5.035
	Inferior Occipital Gyrus	-41.5; -90.0; -8.5	185	3.875	5.014
	Culmen	-29.0; -47.5; -28.5	14	3.651	4.590
	Thalamus	-16.5; -15.0; 4.0	90	3.626	4.544
	Outside BA	-29.0; -52.5; 69.0	67	3.589	4.476
	Fusiform Gyrus	28.5; -87.5; -23.5	52	3.576	4.453
	Middle Temporal Gyrus	51.0; -52.5; 6.5	71	3.479	4.282
	Cerebellar Tonsil	-41.5; -50.0; -48.5	38	3.366	4.090
	Cingulate Gyrus	-4.0; 22.5; 29.0	20	3.321	4.015
Offline session1 commission error > correct withhold	Precentral Gyrus	-11.5; -25.0; 69.0	364	4.103	5.479
	Sub-Gyral	31.0; -42.5; -3.5	308	4.067	5.403
	Precentral Gyrus	26.0; -20.0; 61.5	79	3.876	5.015
	Insula	-44.0; -5.0; 14.0	35	3.873	5.008
	Medial Frontal Gyrus	8.5; -15.0; 61.5	42	3.694	4.668
	Sub-Gyral	-34.0; -62.5; -1.0	82	3.649	4.585
	Precentral Gyrus	11.0; -22.5; 74.0	33	3.624	4.540
	Middle Temporal Gyrus	48.5; -75.0; 19.0	13	3.549	4.405
	Postcentral Gyrus	28.5; -37.5; 51.5	18	3.488	4.298
	Sub-Gyral	13.5; -30.0; 56.5	22	3.392	4.134
Interaction: online > offline x anodal > sham	Sub-Gyral	-41.5; -5.0; -18.5	19	3.780	17.669
	Middle Occipital Gyrus	38.5; -85.0; -1.0	44	3.505	15.154
	Superior Temporal Gyrus	43.5; 2.5; -13.5	15	3.494	15.058
	Declive	8.5; -70.0; -21.0	37	3.424	14.463
	Cuneus	-26.5; -87.5; 19.0	11	3.256	13.096
	Middle Occipital Gyrus	31.0; -90.0; 11.5	13	3.252	13.061
	Sub-Gyral	-26.5; -75.0; 21.5	10	3.185	12.541
#	Insula	46.0; 5.0; 6.5	28	3.596	15.863

[#] Effect of run commission error > correct withhold

5.4.3. Dynamic functional connectivity analysis

5.4.3.1. Time-varying fMRI results

Figure 5.5 displays the 5 brain states that dynamically reoccurred during each run (i.e., when all sessions were pooled together regardless of stimulation and run). State 1 was characterised by slightly negative connectivity from DMN to both ECN and SN and a slight positive connectivity within networks. State 2 was characterised by slightly negative connectivity between DMN and SN, and DMN and ECN, specifically for the MPFC, with strong positive connectivity found between SN and ECN. State 3 and 4 were characterised by overall positive connectivity between and within networks which was particularly stronger for state 4. State 5 was characterised by slight positive connectivity within and between networks with the MPFC showing particularly weak connectivity with the rest of the regions.

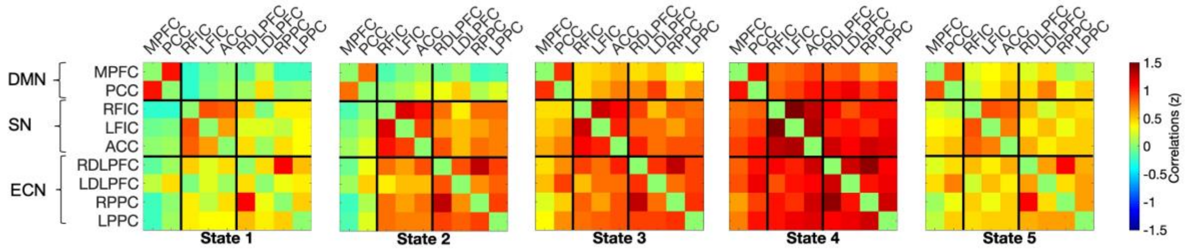

Figure 5.5: Five brain states which reoccurred during each session of the task. Colour bar on the right depicts the correlation strength (as z-score). MPFC, medial prefrontal cortex; PCC, precuneus / posterior cingulate cortex; FIC, frontoinsular cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex.

5.4.3.2. Frequency of occurrence, dwell time and number of transitions

Both and Bayesian frequentist analyses revealed no interaction for any of the measures studied. Bayesian analyses indeed provided support for the lack of an interaction, suggesting no effect of tDCS. Specifically, we found strong evidence for the null as compared to the full model for frequency of states 1, 2 and 4 and dwell time in states 1-3, and found substantial evidence for all other measures (frequency of states 3 and 5 and dwell time for states 4-5).

Furthermore, we found substantial evidence excluding the interaction for frequency of states 1, 2, 4 and 5**,** dwell time in states 1 and 2 and for the number of transitions, as well as anecdotal evidence for all other measures (frequency of state 3 and dwell time in states 3-5). **Table *5.7*** shows the results of the statistical analysis for the interactions. **Figure 5.6** displays the descriptive statistics for frequency of occurrence and dwell time. We found no main effects of stimulation (see **Table *5.8***). A significant main effect of run was found for frequency of state 2 with increased occurrence in the online run compared to offline. No other main effects were found for run (see **Table *5.9***).

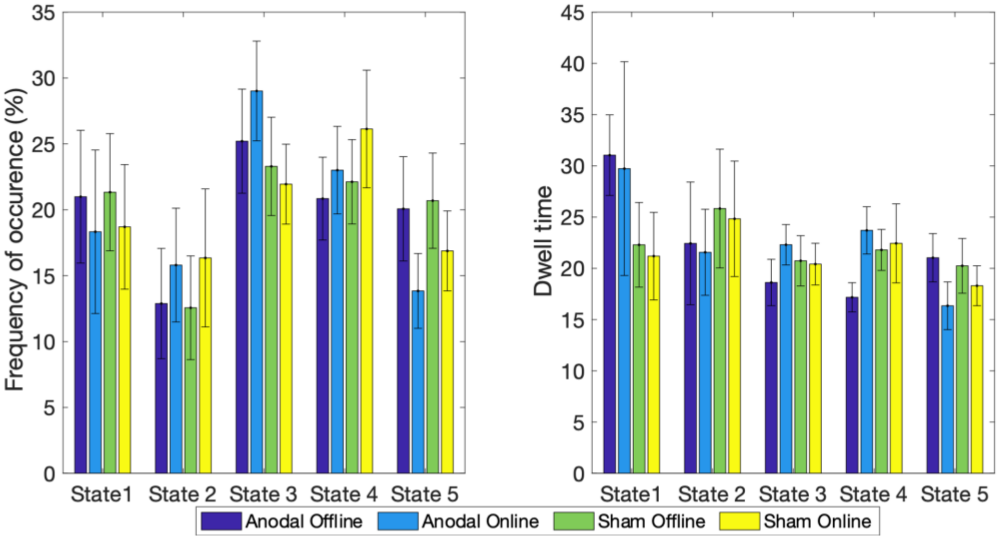

Figure 5.6: Frequency of occurrence and dwell time for each state for each session (anodal offline, anodal online, sham offline and sham online). No significant interactions or main effects were found. Bayesian results support the lack of an effect of tDCS. Error bars represent standard error of the mean.

Table 5.7: *Bayesian and frequentists repeated measures ANOVA for the interaction of stimulation (anodal and sham) and session (offline and online) effects on frequency and dwell time and number of transitions.*

	JZS-BF_{01} for the null vs full	BFexcl (interact)	F	df	η_p^2	P-value
Frequency						
State 1	30.601**	3.118*	0	(1,18)	0	0.992
State 2	17.562**	3.259*	0.05	(1,18)	0.003	0.825
State 3	5.889*	1.545	1.685	(1,18)	0.086	0.211
State 4	21.805**	3.217*	0.182	(1,18)	0.01	0.675
State 5	9.468*	3.060*	0.286	(1,18)	0.016	0.6
Dwell Time						
State 1	13.641**	3.304*	0	(1,18)	0	0.979
State 2	34.013**	3.182*	0	(1,18)	0	0.981
State 3	22.821**	1.891	0.963	(1,18)	0.051	0.34
State 4	6.705*	1.469	1.638	(1,18)	0.071	0.257
State 5	9.508*	2.435	0.632	(1,18)	0.034	0.437
Number of transitions						
All	37.092**	3.201*	0.061	(1,18)	0.003	0.808

*=BF > 3; **=BF > 10

Table 5.8: *Bayesian and frequentists repeated measures ANOVA for the main effect of stimulation on frequency and dwell time and number of transitions.*

	JZS-BF_{01} for the null vs full	BFexcl (stim)	F	df	η_p^2	P-value
Frequency						
State 1	4.283*	4.265*	0.020	(1,18)	0.001	0.889
State 2	4.233*	3.176*	0.002	(1,18)	0.000	0.966
State 3	1.000	3.176*	2.824	(1,18)	0.136	0.110
State 4	3.174*	3.176*	0.575	(1,18)	0.031	0.458
State 5	6.203*	3.110*	1.034	(1,18)	0.054	0.323
Dwell Time						
State 1	1.000	3.347*	4.291	(1,18)	0.192	0.053
State 2	2.479	3.347*	1.060	(1,18)	0.056	0.317
State 3	4.265*	3.347*	0.006	(1,18)	0.000	0.937
State 4	3.369*	3.347*	0.638	(1,18)	0.034	0.435
State 5	4.563*	3.959*	0.140	(1,18)	0.008	0.713
Number of transitions						
All	3.956*	3.904*	0.236	(1,18)	0.013	0.633

*BF01 > 3

Table 5.9: *Bayesian and frequentists repeated measures ANOVA for the main effect of stimulation on frequency and dwell time and number of transitions.*

	JZS-BF_{01} for the null vs full	BFexcl (run)	F	df	η_p^2	P-value
Frequency						
State 1	2.238*	1.267	1.153	(1,18)	0.060	0.297
State 2	1.263	2.25	5.025	(1,18)	0.218	$0.038^{\#}$
State 3	4.644*	2.25	0.343	(1,18)	0.019	0.566
State 4	2.249	2.249	1.254	(1,18)	0.065	0.278
State 5	1.000	0.505 (BF10=1.981)	3.690	(1,18)	0.016	0.600
Dwell Time						
State 1	7.851*	1.405	0.089	(1,18)	0.005	0.769
State 2	4.118*	1.405	0.085	(1,18)	0.005	0.774
State 3	2.921	1.405	0.818	(1,18)	0.043	0.387
State 4	1.410	1.405	2.783	(1,18)	0.134	0.113
State 5	1.000	0.876 (BF10=1.141)	0.632	(1,18)	0.034	0.437
Number of transitions						
All	3.089*	3.056*	0.894	(1,18)	0.047	0.357

*BF01 > 3, $^{\#}p < 0.050$

5.4.4. Effective connectivity

The PEB modelling the interaction did not find evidence for an effect of tDCS across any of the parameters. **Figure 5.7** shows the effective connectivity matrix depicting the group mean for the first session offline run of the task in the reduced model (only parameters with evidence above the threshold of 0.95 posterior probability). The DMN midline regions have an excitatory role over each other, and the PCC is strongly self-inhibitory. From the DMN to the SN, we observe excitatory coupling from the MPFC to both right frontoinsular cortex and anterior cingulate cortex with inhibitory coupling from the PCC to left frontoinsular cortex. From the DMN to ECN the PCC exerted excitatory coupling towards bilateral DLPFC, MPFC showed excitatory coupling with the left DLPFC and inhibitory towards right DLPFC and left posterior parietal cortex. The SN did not show any self-inhibitory connections but otherwise was largely excitatory within and between the networks. The ECN displayed excitatory coupling from both DLPFCs to PCC and left DLPFC to MPFC with both the posterior parietal cortices inhibitory towards MPFC. For the ECN to SN we show mixed communication with a combination of inhibitory and excitatory tones. For the ECN towards itself, we found strong self-inhibitory connections and an overall excitatory coupling within the network, except from left to right DLPFC which was inhibitory.

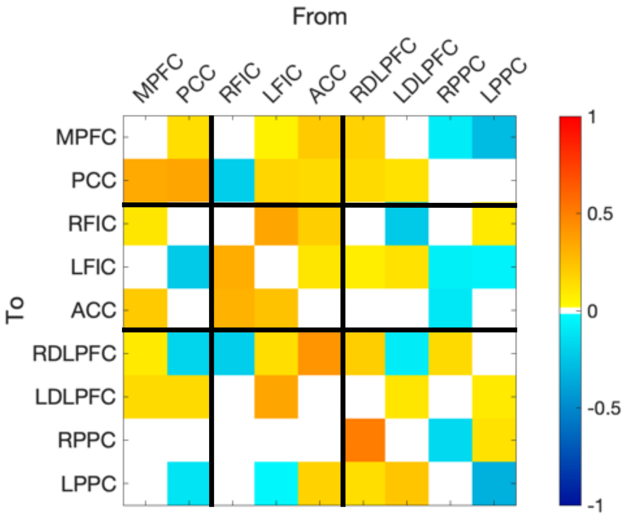

Figure 5.7: Group mean effective connectivity for session one offline run of the task. Connections present in the reduced model (>95% posterior probability for free energy) are displayed. Extrinsic connections are represented in Hz and intrinsic self-connections are log scaled. Colour bar on right indicates mean parameter strength (Ep.A). MPFC, medial prefrontal cortex; PCC, precuneus / posterior cingulate cortex; FIC, frontoinsular cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; L, left; R, right.

5.5. Discussion

Using a within-subjects design on a comparable sample size to previous research (Axelrod et al., 2018; Kajimura et al., 2016; Kajimura & Nomura, 2015), we aimed to investigate the efficacy of left DLPFC-tDCS in modulating mind-wandering propensity. Furthermore, we aimed to assess the effects of tDCS on intrinsic brain activity and any influences of tDCS on functional and effective connectivity. Our results suggest DLPFC-tDCS is unable to modulate any of these measures. Specifically, Bayesian results for behavioural measures showed strong evidence for the lack of an effect of stimulation on subjective reports of on-task responses, and substantial evidence for the lack of an effect on commission errors and mean reaction time to SART, all when comparing the null versus full models. Furthermore, when considering the effect of the interaction itself, we found substantial evidence for the models excluding the interaction for on-task responses and mean reaction time (with anecdotal evidence for commission errors). Similarly, the dynamic function network connectivity analysis revealed substantial to strong evidence for the null versus the full model across all states for frequency and dwell, as well as for number of transitions across states. Additionally, we found substantial evidence for models excluding the interaction for the frequency of 4 states, dwell time of 2 states, as well as the number of transitions across states (all others showed anecdotal evidence). Finally, we found no effect on brain activity nor on any parameters within or between the networks on our effective connectivity analysis. Overall, our results therefore suggest, against our hypothesis, that left DLPFC-tDCS was unable to modulate mind-wandering propensity or underlying brain activity, functional, and effective connectivity.

Our behavioural results contradict the early reports of successful modulation using this montage (Axelrod et al., 2015, 2018) and support the recent multi-centre failed replication of the initial study (Boayue, Csifcsák, Aslaksen, et al., 2020). However, there are a few differences between our study and previously successful ones that should be acknowledged. We used an increased number of thought probes per run (32 compared to 12 (Axelrod et al., 2015) and 18 (Axelrod et al., 2018)). However, recent research which varied the probe rate found no effect on probe responses caught by online sampling, therefore the additional thought probes unlikely explains any differences between ours and previous studies (Schubert et al., 2020). Additionally, we used a higher intensity of stimulation (1.8mA compared to 1mA). However, while increasing current has sometimes been related to contradictory effects for cathodal stimulation (Batsikadze et al., 2013), it is typically acknowledged that it should enhance the effects for anodal stimulation. In fact, some previous studies failed to elicit increased mind-wandering at 1mA anodal stimulation but did observe this for 2mA cathodal stimulation as compared to sham (Filmer et al., 2019). Furthermore, additional research observed both 1mA and 2mA anodal stimulation of the DLPFC resulted in increased mind-wandering as compared to sham, however it should be noted the return was placed over the right inferior parietal lobule therefore it is unclear which region is driving the effects (Filmer et al., 2021). Indeed, anodal stimulation (1.5mA) of the right inferior parietal lobule (with the return over left cheek) reduced mind-wandering propensity (Kajimura et al., 2019), although to our knowledge there is only one study showing this and therefore the effect is yet to be replicated. Therefore, it is clear there is a lack of consistency in the effect of tDCS, specifically regarding polarity, stimulation site and current intensity, and our results add up to this. Future research is needed to delineate these differences to understand the impact of each element (current intensity, polarity and stimulation site) to help explain the observed discrepancies across the literature.

One possible explanation for the disparity of effects could relate to the effects depending on the brain state during stimulation (Li, Violante, Leech, Ross, et al., 2019). As participants were completing the SART during stimulation, it is expected that their thoughts would have been drifting between internally (mind-wandering) and externally directed attention (as observed in the subjective reports to thought probes). These drifts would have been accompanied by changes in the underlying brain activity and networks involved. As we display here in **Figure 5.3**, a large inter-subject variability was observed for baseline levels of being on-task. This individual preference for being more on or off-task may affect the extent to which each participant is in the most optimal state to be influenced by tDCS. This could account for the differences between studies, particularly those which used a between subjects' design, as some cohorts may have contained more participants likely to mind-wander. Furthermore, as we are delivering a constant current throughout both periods, perhaps any effects of stimulation are ultimately cancelled out.

In addition to the lack of behavioural responses to tDCS, we were unable to observe any modulation to brain activation at the level of BOLD response, functional dynamic connectivity over time (in the form of frequency and dwell time of brain states, as well as number of transitions across states) or to effective connectivity within and between the DMN, EC and SN. A systematic review found that tDCS was unable to produce reliable neurophysiological effects beyond that of motor evoked potentials (Horvath et al., 2015a). Although this study has been highly criticised as being overly pessimistic (Filmer et al., 2020), it highlights the difficulty in obtaining consistent results from tDCS beyond that of motor evoked potentials. Currently, there are only a small number of studies investigating the effects of DLPFC tDCS on brain activation. Two of which observed modulations in brain activation and functional connectivity, specifically concerning the DLPFC, interestingly without any effects of tDCS on behaviour (Nissim et al., 2019; Weber et al., 2014). It should be noted that both of these studies were not monitoring mind-wandering, moreover their focus was task performance. An important difference between our study and these however is the task participants completed while in the scanner. The previously successful modulations were observed in studies that employed the Balloon Analogue Risk Task (a reward versus loss, risk-behaviour task) and the N-back task which have both been found to consistently recruit activation of the DLPFC. Given that these tasks repeatedly engage the target area (N-back (Owen et al., 2005) and Balloon Analogue Risk Task (Rao et al., 2008)), observing any subtle changes during and post stimulation by may be more likely.

Previously, the SART with interspersed thought-probes reportedly activated the DMN during episodes of ‘off-task’ and the ECN for ‘on-task’ responses (Christoff et al., 2009; Stawarczyk, Majerus, Maquet, et al., 2011). However, our study and subsequent research using the same design has been unable to replicate this (Denkova et al., 2019). An additional study which also used the SART during fMRI did not directly report the results of the task-based imaging analysis, instead using independent component analysis (ICA) to identify networks of interests, thus suggesting they too were unable to show activation at the level of the GLM (Zhou & Lei, 2018). This lack of replication suggests the task is unable to reliably activate the regions of interest. Furthermore, the subjective nature of the probes and requiring participants to identify between the dichotomy of being on- or off-task is problematic (Robison et al., 2019), particularly given the all-encompassing classification of ‘mind-wandering’ (Seli, Kane, Smallwood, et al., 2018). This lack of baseline activation to the task may also help explain the lack of an effect of tDCS on brain states given we are not reliably evoking a response from the required regions of interest. Despite the SART being a popular task when investigating mind wandering (Christoff et al., 2009; Denkova et al., 2019; Smallwood, Beach, et al., 2008; Smilek et al., 2010), in particular in conjunction with tDCS (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020; Coulborn et al., 2020; Filmer et al., 2019, 2021; Kajimura et al., 2019), perhaps a task that actively elicits mind-wandering and does not rely on thought-probes (for example, measured by pupillometry) is needed in order to accurately measure and influence the desired cognitive functions with such stimulation montages.

Mind-wandering is a self-generated, internally directed process with propensity and characteristics unique to each individual. An ability to modulate this multifaceted self-referential process with an external medium, such as tDCS, would be an invaluable tool to researchers and clinicians. Manipulating participants propensity to mind-wander with such a technique via electrode placement over specific brain areas would help unveil the underlying neural processes involved in this complex phenomenon and reveal more about the causal influences of tDCS on brain activation. Mind-wandering, particularly an excessive propensity to do so, has been associated with poor task performance (Unsworth & McMillan, 2014) and with a number of neurological disorders (including: schizophrenia (Iglesias-Parro et al., 2020), and depression (Hoffmann et al., 2016)). Moreover, DLPFC-tDCS has been posed as a potential therapeutic tool in both of these patient groups (Bennabi & Haffen, 2018; Palm et al., 2016). Our results, however, displaying lack of effects on mind-wandering propensity, but more specifically, lack of effects on brain activity and connectivity, call into question its ability to modulate this self-generated process and its use in clinical settings. Further research is needed, perhaps with multimodal techniques which are more sensitive to subtle changes in neuronal function (for example the use of the more temporally sensitive EEG), to fully understand the efficacy of tDCS in modulating these processes.

An overarching concern surrounding the tDCS research, and another possible explanation for the lack of an effect, could be that we are not delivering large enough currents to the brain to elicit any effects. Research in mice has suggested that an E-field of 1 V/m gradient is required to garner online effects on neuronal spiking (Vöröslakos et al., 2018). Given that in the current study we used 1.8mA stimulation on the surface which translated into a predicted maximum cortical intensity of 0.235 V/m (based on the ROAST simulation, see **Figure 5.1**), perhaps this was insufficient to perturb neuronal firing, hence why we do not observe any behavioural effects, but more importantly supported by the lack of an effect on functional and effective connectivity. Future research may benefit from implementing higher currents (e.g., 4-6mA), or more specifically tailored current dosage dependent upon individual anatomy and tissue properties, in order to reach the required current at the cortical level to elicit the desired neuronal changes.

Regarding the perception of active or sham stimulation, our results suggest participants were unable to discriminate between the two. Furthermore, we did not observe any differences in physical sensations resulting from the stimulation. To ensure any effects of tDCS were not being driven by fatigue, we also measured sleepiness using the Karolinska Sleepiness Scale. Here, we also found no effect of TDCS on how tired the participants felt after completing the scan. We did find a very strong effect of time, with sleepiness being significantly greater post completing the session (with very strong Bayesian evidence). This is expected given the monotonous nature of the task and time spent lay down in the scanner. stimulation. This increase in fatigue may also help explain the main effect of run (offline / online) where we observed reduced reaction times and increased errors. Overall, this suggests that any effect, or lack thereof was not produced by tiredness or sensations from the stimulation.

Leaving the effects of tDCS aside, we failed to observe any task-related brain activation during the offline run of the first chronological session. However, we were able to characterise typically occurring brain states with the dynamic functional networks connectivity analysis. Here we replicate the brain states previously observed between these networks in research which compared connectivity during resting state fMRI and throughout the SART (Denkova et al., 2019). State 1 showed the weakest overall connectivity within and between states and may be associated with transitioning between states of focus and unfocussed attention (Hellyer et al., 2015; Tognoli & Kelso, 2014). State 2 showed negative DMN to SN and ECN (more prominent for MPFC) and positive SN to ECN which may reflect the role of the SN in switching between task-positive and task-negative networks as attention shifts (Goulden et al., 2014; Menon & Uddin, 2010; Sridharan et al., 2008). States 3 and 4 were characterised by overall strong positive connectivity within and between networks and were the most frequent states throughout the task. State 5 displays a small but overall positive connectivity within and between networks (slightly less for the MPFC to SN and ECN) and appears to be the transitory phase between states 3 and states 1 and 2. Throughout all of the states we observe a stronger connectivity between the PCC and the DLPFC (specifically the left) compared with other regions outside the DMN. This supports research detailing the importance of this connection in mind-wandering and goal-directed cognition (Inman et al., 2018; Spreng et al., 2010) and could be reflecting the important role of the PCC being a major hub in switching between intrinsic networks (Deshpande et al., 2011; Hagmann et al., 2008; van den Heuvel & Sporns, 2011). Interestingly, we did not observe one of the states previously reported (state 2 in Denkova et al., (2019)). This state was characterised by negative connectivity between SN and ECN, specifically for bilateral frontoinsular cortex, with connectivity being negative between the PCC and SN being and positive between PCC and ECN. This discrepancy between our findings is not unexpected given that they report this brain state being most common during resting state (which we do not have in the current study) as compared to throughout the SART, suggesting that this state is something more specifically characteristic at rest.

Regarding the baseline level of effective connectivity during the offline run of the task, we observed an overall excitatory coupling between regions within each network supporting previous research (Li et al., 2020). Within the DMN we observe excitatory coupling in both directions between the PCC and MPFC which supports previous research observing this relationship at rest (Sharaev et al., 2016) and contradicts the bi-directional inhibitory relationship observed during the more cognitively demanding N-back task (Zhou et al., 2018). This may indicate the SART indeed elicits more self-referential thought processes resulting in the network acting similar to when at rest. However, the literature here is inconsistent with healthy controls previously showing an inhibitory role of the PCC towards the MPFC at rest (Crone et al., 2015; Li et al., 2012) and excitatory coupling during a gender judgement task (Li et al., 2012). From the DMN we see an inhibitory role of the PCC and an excitatory role of the MPFC towards both the SN and ECN. The excitatory coupling between the MPFC and the SN has been noted before, particularly towards the anterior cingulate cortex (Li et al., 2020). The DMN and ECN / SN have previously been reported to be anti-correlated (Fox et al., 2005). Therefore, the excitatory coupling from the PCC to the MPFC in conjunction with the inhibitory coupling from the PCC to both ECN and SN may signify the PCC acting as a switch between internally and externally directed thoughts. This again supports research indicating the PCC is a major hub between networks (Deshpande et al., 2011; Hagmann et al., 2008; van den Heuvel & Sporns, 2011), particularly regarding task switching (Araña-Oiarbide et al., 2020). This may also help explain the inconsistent results previously mentioned regarding the role of the PCC at rest and during tasks. If the role of the PCC is to shift between internally and externally directed thoughts, its coupling with each network will differ depending on the task at hand. We provided the session one offline effective connectivity here as reference for future studies, however, further research is needed to delineate the relationship of the networks in healthy controls, both at rest and during cognitive tasks, before predictions can be made regarding any expected changes from tDCS.

5.5.1. Conclusions

We provide evidence for the lack of an effect of anodal tDCS over the left DLPFC in modulating mind-wandering propensity, which challenges previous research. Furthermore, we demonstrate a lack of an effect on brain connectivity (both functional and effective) in three intrinsic brain networks thought to be associated with internal and externally directed thought processes. The study highlights the need to replicate findings, particularly concerning tDCS, and employ well constrained methods.

Chapter 6

DISRUPTIONS IN EFFECTIVE CONNECTIVITY WITHIN AND BETWEEN DEFAULT MODE NETWORK AND ANTERIOR FOREBRAIN MESOCIRCUIT IN PROLONGED DISORDERS OF CONSCIOUSNESS[3]

6.1. Abstract

Recent research indicates prolonged disorders of consciousness (PDOC) result from structural and functional impairments to key cortical and subcortical networks, including the default mode network (DMN) and the anterior forebrain mesocircuit (AFM). However, the specific mechanisms which underpin such impairments remain unknown. It is known that disruptions in the striatal-pallidal pathway can result in the over inhibition of the thalamus and lack of excitation to the cortex that characterizes PDOC. Here, we used spectral dynamic causal modelling and parametric empirical Bayes on rs-fMRI data to assess whether DMN changes in PDOC are caused by disruptions in the AFM. PDOC patients displayed overall reduced coupling within the AFM, and specifically, decreased self-inhibition of the striatum, paired with reduced coupling from striatum to thalamus. This led to loss of inhibition from AFM to DMN, mostly driven by posterior areas including the precuneus and inferior parietal cortex. In turn, the DMN showed disruptions in self-inhibition of the precuneus and medial prefrontal cortex. Our results provide support for the anterior mesocircuit model at the subcortical level but highlight an inhibitory role for the AFM over the DMN, which is disrupted in PDOC.

6.2. Introduction

Recent years have seen an increasing interest in characterizing the neural bases underlying the (full or partial) lack of awareness in prolonged disorders of consciousness (PDOC) with neuroimaging techniques (Stender et al., 2014). Alongside contributing to advancing our understanding of the neural correlates of consciousness (Di Perri et al., 2016), the outcomes of this research can provide biomarkers to improve diagnosis and prognostication accuracy, as well as assist with the development of potential therapies. Much of the work to

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date has focused on structural and (resting-state) functional connectivity (Snider & Edlow, 2020). This has identified disconnections in long-range fronto-parietal networks, and particularly the default mode network (DMN) (Amico et al., 2017; Boly et al., 2008, 2009; Cauda et al., 2009; Crone et al., 2015; Fernández-Espejo, Junque, Cruse, et al., 2010; Fernández-Espejo et al., 2012; Lant et al., 2016; Soddu et al., 2011; Vanhaudenhuyse et al., 2010), as a key contributor to the lack of awareness in PDOC. The DMN is an intrinsic brain network encompassing the posterior cingulate cortex/precuneus (PCC), bilateral inferior parietal lobules (IPL), and the medial prefrontal cortex (MPFC), which show synchronic activity in individuals at rest (Gusnard & Raichle, 2001). There is increasing evidence of structural (Fernández-Espejo, Junque, Cruse, et al., 2010; Fernández-Espejo et al., 2012; Lant et al., 2016) and functional disconnections (Amico et al., 2017; Boly et al., 2009; Cauda et al., 2009; Soddu et al., 2011; Vanhaudenhuyse et al., 2010) as well as metabolic impairments in the DMN in PDOC (Fridman et al., 2014; Laureys et al., 1999), the severity of which correlates with clinical severity (Amico et al., 2017; Boly et al., 2009; Fernández-Espejo, Junque, Cruse, et al., 2010; Fridman et al., 2014; Lant et al., 2016; Soddu et al., 2011; Vanhaudenhuyse et al., 2010) and prognosis (Fernández-Espejo, Junque, Cruse, et al., 2010; Norton et al., 2012). For example, recently, intact functional connectivity of the DMN was associated with later recovery (observed through command following) in a patient who became unresponsive after contracting COVID-19 (Fischer et al., 2020). The DMN has a key role in the generation of self-referential processes and awareness (Boly et al., 2008; Buckner & Carroll, 2007), suggesting its deficits could specifically explain the lack of self-awareness in PDOC.

In parallel, the so called mesocircuit hypothesis (Schiff, 2010) proposes that the lack of awareness in PDOC is caused by disbalances in the anterior forebrain mesocircuit (AFM) that result in an excess of thalamic inhibition and lack of excitation to the cortex. In support of this model, positron emission topography (PET) studies have confirmed reduced metabolic uptake in the striatum, thalamus, and fronto-parietal regions, coupled with increased metabolism of the globus pallidus in PDOC (Fridman et al., 2014). According to the mesocircuit model, the striatum fails to inhibit the globus pallidus, which becomes hyperreactive and excessively inhibits the thalamus. This excess of inhibition in an already damaged and hypoactive thalamus (Fernández-Espejo et al., 2011) in turn leads to severely reduced excitatory output to high order frontoparietal regions. The mesocircuit model provides a framework to interpret causal mechanisms explaining the, sometimes paradoxical, positive effect of pharmacological agents such as zolpidem or amantadine on the basis of their effects on striatal and thalamic populations (Brown et al., 2010; Chatelle et al., 2014; Fridman & Schiff, 2014; Williams et al., 2013).

We have previously demonstrated that these models are not mutually exclusive. In fact, the DMN and AFM are highly interconnected via well-established thalamo-cortical and corticostriatal white matter paths, and these show specific damage that correlates with severity in PDOC (Lant et al., 2016). In line with earlier work focusing on the DMN alone (Fernández-Espejo et al., 2012), we identified a key role for the PCC in the relationship between DMN and AFM. Specifically, we confirmed structural damage to the white matter fibers connecting the PCC with all major nodes in the DMN, as well as with key subcortical structures including the thalamus and striatum (Lant et al., 2016). The PCC is known to be highly structurally connected to other high order regions in the brain and is considered to be one of the major hubs for the functional integration across networks (Deshpande et al., 2011; Hagmann et al., 2008; van den Heuvel & Sporns, 2011). In line with our structural findings, dynamic causal modelling (DCM) provided support to the PCC's role in mediating functional disconnections in the DMN in PDOC (Crone et al., 2015). Similarly, a recent study demonstrated abnormal effective connectivity in anterior forebrain regions in PDOC (Chen et al., 2018). Here, we expand these results by using DCM to investigate causal dynamics within and between regions of the DMN and AFM in a group of PDOC patients, including both diagnoses of vegetative and minimally conscious state. We aim to confirm previously reported disconnections and disbalances in both networks but also to establish whether (1) cortical changes in the DMN are caused by lack of excitation from the thalamus (as predicted by the mesocircuit model) and (2) this is modulated by the PCC specifically (as earlier structural and functional research suggests).

6.3. Materials and Methods

6.3.1. Participants

We recruited a convenience sample of 18 PDOC patients, in a vegetative or minimally conscious state, at the University of Western Ontario (UWO) between 2012 and 2015. Exclusion criteria included age under 18 years, and lack of eligibility to enter the MRI environment. Two patients were discarded due to poor data quality (excessive movement in the scanner > 3 mm translation and 3° radius for more the 15% of the acquired scans) leaving a final sample of 16 patients (7 female, aged 20–56, M = 35.94, SD = 11.91). Patients were behaviorally assessed repeatedly through administrations of the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) over a 5-day period during the week they were scanned (Median number of CRS-R assessments = 3, range = 1–5). Independent functional (Beukema et al., 2016; Fiacconi & Owen, 2016; Gibson et al., 2014, 2016; Naci & Owen, 2013) and structural (Fernández-Espejo et al., 2015; Lant et al., 2016) subsets of this dataset have previously been reported. Table 1 contains clinical details of each patient. We also recruited 16 right-handed healthy volunteers (7 female, aged 19–29, M = 25.43, SD = 2.53), with no history of psychiatric or neurological disorders, between 2013 and 2014.

The UWO's Health Sciences Research Ethics Board (London, Ontario, Canada) provided ethical approval for the study. All healthy volunteers provided informed written consent. For each patient, a surrogate decision maker provided informed written consent to participate in the study.

Table 6.1: *Clinical information.*

Patient No.	Sex	Age (y)	Interval Since Ictus (Months)	Etiology	Diagnosis	CRS-R on Day of Scan	Max CRS-R on Week of Scan	Auditory Function	Visual Function	Motor Function	Oromotor/ Verbal	Communication	Arousal	Number of CRS-R Scores Taken on Week of Scan
1	Male	38	150	Traumatic	VS	6	6	1	0	2	1	0	2	1
2	Male	33	176	Non-Traumatic	MCS	9	10	1	3	2	1	0	2–3	5
3	Male	27	88	Traumatic	VS	7	7	1–2	0–1	2	1	0	1–2	5
4	Female	44	245	Traumatic	VS	3	5	0–1	0–1	0–2	0–1	0	0–2	4
5	Female	46	230	Non-Traumatic	MCS	-	10	1–2	3	2	1	0	1–2	2
6	Male	57	37	Non-Traumatic	VS	-	6	1	0–1	0–2	1	0	1–2	3
7	Male	27	36	Non-Traumatic	MCS	-	13	3	3	0–2	2	0	3	3
8	Female	20	67	Non-Traumatic	VS	6	8	1–2	0–1	1–2	1	0	2	4
9	Female	35	24	Non-Traumatic	VS	5	5	0–1	0	0–2	1	0	1–2	3
10	Male	19	2	Non-Traumatic	VS	6–7	7	2	1	1	0–1	0	2	3
11	Female	25	68	Traumatic	MCS	8	9	1–2	3	1	1	0	2	5
12	Female	43	55	Non-Traumatic	VS	5	7	1	0–1	2	1	0	1–2	3
13	Male	20	48	Non-Traumatic	VS	5	6	1	0–1	0–2	1	0	1–2	3

14	Female	51	11	Non-Traumatic	VS	4	4	3–4	1	0–1	0–1	0	1	5
15	Female	52	78	Non-Traumatic	VS	6	6	1	0	1–2	1	0	1–2	4
16	Male	40	38	Traumatic	MCS	7	7	1	0–3	0–1	0–1	0	1–2	5

CRS-R, coma recovery scale-revised; VS, vegetative state; MCS, minimally conscious state.

6.3.2. MRI Acquisition

We acquired MRI data with a 3T Siemens scanner (Siemens, Erlangen, Germany) and a 32-channel head-coil at the Centre for Functional and Metabolic Mapping at Robarts Research Institute (London, Canada). The patients were recruited over a 3-year period, during which time the 3T scanner was upgraded. Seven patients and 7 healthy volunteers were scanned before the upgrade, in a Magnetom Trio system, and the remaining 9 patients and 9 healthy volunteers were scanned in the new Magnetom Prisma system. This resulted in a balanced distribution of patients and healthy controls across the two scanners. The fMRI acquisition consisted of functional echo-planar images of 36 slices covering the whole brain with the following parameters: TR = 2000 ms, TE = 30 ms, matrix size = 70 × 70, slice thickness = 3 mm, in-plane resolution = 3 × 3 mm, flip angle = 78°, 245 volumes (9 healthy controls and 10 patients), and TR = 2000 ms, TE = 30 ms, matrix size = 64 × 64, slice thickness = 3 mm, in-plane resolution = 3 × 3 mm, flip angle = 75°, 150 volumes (7 healthy controls and 6 patients).

In addition to the fMRI data, we acquired a high-resolution, T1-weighted, 3-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) image during the same session (Trio system: TR = 2300 ms, TE = 2.98 ms, inversion time = 900 ms, matrix size = 256 × 240, voxel size = 1 × 1 × 1 mm, flip angle = 9°; Prisma system: TR = 2300 ms, TE = 2.32 ms, inversion time = 900 ms, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm, flip angle = 8°; for five patients matrix size = 240 × 256 and flip angle = 9°).

6.3.3. Preprocessing

We reprocessed all data using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) running on MATLAB version R2014b. We first reoriented the data according to the AC-PC. Spatial pre-processing included: realignment to correct subjects' motion, co-registration between the functional and structural data sets, and smoothing with an 8 mm full width half maximum Gaussian kernel. Finally, to reduce noise, we applied a bandpass temporal filtering between 0.009–0.08 to the data using the DPABI toolbox in the DPARSF package (http://rfmri.org/DPARSF) (Yan et al., 2016).

Note that we conducted all analysis in native space for both patients and healthy volunteers in order to avoid misalignment errors related to the gross brain abnormalities that characterize our patient group.

6.3.4. Selection of ROIs

We used four regions of interest (ROIs) to characterize the DMN (medial frontal cortex; PCC; bilateral inferior parietal lobules), in line with previous DCM reports focusing on this network (Bastos-Leite et al., 2015; Crone et al., 2015; Di & Biswal, 2014; B. Li et al., 2012). In addition, we included four ROIs to represent the anterior forebrain mesocircuit (bilateral thalamus; bilateral striatum). To functionally localize each region in each participant, we conducted a seed-based connectivity for each network using the PCC and the striatum as seeds for the DMN and the AFM, respectively. For this, first we identified coordinates for the PCC and bilateral striatum manually for each individual by visual inspection of the T1. To locate the PCC, we moved 6mm left in the x-axis from the AC-PC and located the space between the marginal sulcus and the parieto-occipital sulcus in sagittal view. From here, to identify the center of our sphere in the z plane, we used a reference line crossing the upper boundary of the corpus callosum. This resulted in centring the sphere in the same anatomical subregion that was reported by Fox et al. (2005) (Fox et al., 2015). For the striatum, we made note of the coordinates 5 mm above the AC-PC line on the coronal plane, as well as the coordinates of the point at which the superior edge of the dorsal striatum ends, bordered by the lateral ventricle, as recommended elsewhere (Di Martino et al., 2008). After finding the coordinates halfway between these two points, we used the sagittal and axial axes to find the center of the dorsal striatum by inspection, checking that the sphere was going to fully remain within the anatomical boundaries of the region. In addition, we identified coordinates for two spheres to be located in the cerebrospinal fluid (CSF) and white matter (WM) for their time series to be used later as regressors of no interest. We used the posterior horn of the right lateral ventricle for the CSF, and the area anterior to the anterior horn of the right lateral ventricle for WM, ensuring 5 mm spheres would fit within their respective anatomical boundaries.

After this, we used the MarsBaR SPM toolbox (Brett et al., 2010) to generate spheres centered on the above coordinates for each individual: we set the radius at 8mm for the PCC, 3 mm for right and left striatum, and 5 mm for CSF and WM, to accommodate for anatomical differences in the size of each structure. We then ran seed-based connectivity analysis on SPM independently for the PCC and bilateral striatum using CSF and WM as nuisance regressors. For each individual, we then located each region of interest (MPFC, and IPL for the DMN and thalamus for the AFM) visually and saved the coordinates of the nearest local maxima to use in the extraction of time series for the DCM. Note that we used connectivity with PCC to identify the DMN regions, and connectivity with striatum to identify the AFM. As visual reference, for the medial prefrontal cortex, we placed the cursor in the middle of the frontal medial cortex in the area between the paracingulate gyrus and the frontal pole (as per Harvard-Oxford Cortical Structural Atlas); to locate the IPL, we placed the cursor in the middle of the angular gyrus, located between the lateral occipital cortex and the supramarginal gyrus. Finally, to locate the coordinates for the left and right thalamus, we simply placed the crosshairs in the center of each before selecting the nearest local maximum. Note that, due to the level of subcortical damage that characterizes PDOC patients, and the spatial resolution of our data, it was not possible to accurately identify the globus pallidus in most patients and we will not include this region in our analyses.

For all regions, we visually inspected the location of the nearest local maxima selected in the above step to ensure the area was still appropriate anatomically. If no local maxima was present in the appropriate anatomical region, we used anatomical coordinates (based on our visual inspection as described above) to extract the timeseries for the DCM. **Figure *6.1*** displays the ROIs used in the DCM for a representative healthy volunteer overlaid onto their T1 image.

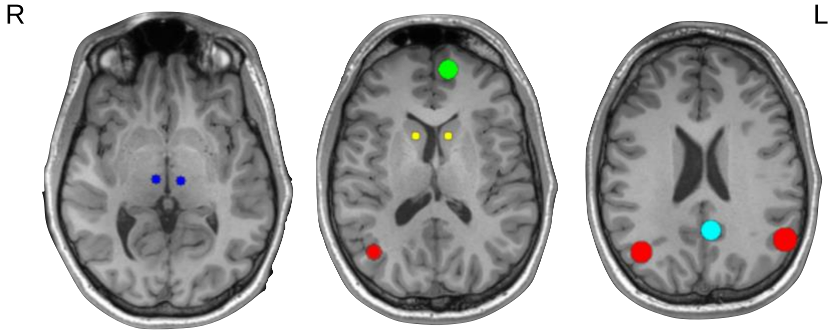


Figure 6.1: Regions of interest for DCM analyses, on the T1 of a representative healthy control and. Red, IPL; green, MPFC; light blue, PCC; dark blue, thalamus; yellow, striatum; L, left hemisphere; R, right hemisphere; HC, healthy control.

6.3.5. General Linear Model

Note that the above ROI selection was done independently of the analyses used to draw inferences about effective connectivity. For this, we ran a second linear model to extract the time series to be used during dynamic causal modelling. This included 6 rigid body realignment parameters to account for head motion in our general linear model, as well as white matter and cerebral spinal fluid mean signals as nuisance regressors. We discarded volumes with levels of motion above 3 mm and 3 degrees for patients. No volumes were above 2 mm translation and 2° radius for any of the healthy volunteers.

6.3.6. Dynamic Causal Modelling

We performed bilinear, one-state spectral DCM with the DCM12 routine implemented on SPM12 on MATLAB version R2014b. Spectral DCM operates in the frequency domain rather than time and is therefore better suited to resting state data analysis (see (Friston et al., 2014) for more details). We first extracted the time series using the ROIs with spheres centred on the individual coordinates previously generated for PCC, MPFC, left and right IPL (all 8 mm radius), bilateral striatum and thalamus (all 3 mm radius). The difference in radius-reflected differences in anatomical size for cortical vs subcortical regions. We specified our model space based on a fully and reciprocally connected model, resulting in a total of 64 effective connections (i.e., the A-matrix) produced and estimated for each model.

6.3.7. Parameter Estimations—Parametric Empirical Bayes (PEB), Bayesian Model Reduction (BMR) and Bayesian Model Averaging (BMA)

After the model specification, we took the first level individual (within-subjects) estimated fully connected DCMs to a second level (between-subjects) analysis using parametric empirical Bayes (PEB) (K. J. Friston et al., 2016). PEB is a hierarchical approach to model how individual subjects' connections relate to the group level by using the individual DCMs as priors (first level) to constrain the variables in the Bayesian linear regression model (second level) (Zeidman et al., 2019). This method allows individual variability in connection strengths to then influence the group (second level) analysis. After group level connection strengths (parameters) have been estimated, hypotheses are tested by comparing evidence for different variations of these parameters in a process known as Bayesian model comparison.

In order to assess the differences in connectivity strength between patients and healthy controls we first built a PEB model including the average connectivity in the healthy group (as baseline), the intercept of differences between healthy controls (0) and patients (1), and the mean centered age as non-interest regressor (to account for the effect of differences in age between the groups, $p = 0.002$).

We subsequently ran a second PEB model including only PDOC patients to assess the canonical connectivity in this group, also using mean centered age as covariate. This was used to extract connectivity parameters to conduct correlations with clinical variables (see CRS-R below).

For both PEBs, after fitting each model we used Bayesian model comparison to prune away parameters that are not contributing to the model evidence. This was achieved by performing a search over nested models where parameters are removed from the full model hierarchically. We then used Bayesian Model Reduction (BMR) to prune connections from the full model until there are no more improvements in model-evidence. This approach uses the group parameters as empirical priors to re-estimate the individual parameters, and in doing so, limits the effects of outliers (Litvak et al., 2015). Parameters from the best models following BMR were then taken, weighted by their model evidence, and combined using Bayesian model averaging (BMA). To define statistical significance, we applied a threshold of a posterior probability > 0.95 (strong evidence) for free energy for each connection (i.e., comparing the evidence for all models in which the particular connection is on with those where the connection is switched off). For more information on BMR and BMA, see Friston et al., 2016 and Zeidman et al., 2019 (K. J. Friston et al., 2016; Zeidman et al., 2019).

6.3.8. Correlations with CRS-R

To investigate any relationship between the effective connectivity and level of consciousness in the PDOC group, we extracted re-estimated parameters (Ep.A values) from the PDOC PEB for each connection that was significantly different in the comparison between PDOC and HC and correlated them with CRS-R on the day of scan and maximum CRS-R on the week of scan using the Kendall's Rank Correlation Coefficient (both frequentist and Bayesian implementations) in JASP (JASP Team, 2020). It should be noted that CRS-R score on the day of scan was unavailable for 3 of the patients (see Table 1). We will define outliers as any data point equal or greater than 2 standard deviations from the mean. For this analysis, we converted self-connection parameters to Hz using $y = -0.5 * \exp(x)$, where x is the log scaling parameter (Ep.A value), −0.5 Hz is the prior, and y is the self-connections strength in Hz. We set statistical significance at two-tailed $p < 0.05$. For the Bayesian analysis, we used a Jeffrey-Zellner-Siow Bayes factor (JZS-BF10) to contrast the strength of the evidence for models supporting a relationship between the variables versus the null. A JZS-BF10 between 0.33 and 3 is considered to be weak/anecdotal evidence for an effect; 3–10: substantial evidence; 10–100: strong evidence; >100: very strong evidence. To consider any support for the null we also calculated JZS-BF01.

6.4. Results

6.4.1. Effective Connectivity

Figure 6.2 shows the effective connectivity matrix depicting the mean for healthy controls (A) as well as the differences between healthy controls and patients (B) in the reduced model: i.e., only for those parameters with evidence above our threshold of 0.95 posterior probability; the lower half of the figure displays the differences between groups as a schematic for DMN (C) and AFM (D) separately, and well as for the connections between both networks (E).

As our main focus is the difference between groups, we will only make a few remarks regarding the pattern of effective connectivity observed in healthy controls: the PCC has a clear excitatory role over all other regions of the DMN; each striatum excites the ipsilateral thalamus; the AFM is mostly inhibitory towards the DMN, with a marked lateral component (left thalamus and right striatum); and the DMN seem to modulate the AFM mostly through frontal (MPFC) rather than parietal (PCC) medial areas.

In terms of group differences, within the DMN we observe disruptions only in self-connections of medial areas, with PDOC patients having decreased self-inhibition of the PCC and increased self-inhibition of the MPFC compared to healthy controls. Note that parameters for self-connections are log scale parameters and thus negative differences (blue cells in Figure 2B) reflect less self-inhibition in patients. In contrast, parameters for the between region connections reflect differences in the connection strength across groups, and thus negative values (blue cells) represent reduced coupling in PDOC. In the AFM, PDOC patients show less self-inhibition in both striata, as well as the left thalamus. In turn, most connections between AFM regions also show reduced coupling in PDOC, resulting in overall reductions in connectivity. We did not identify any connection with increased coupling in PDOC for the AFM. Crucially, PDOC patients showed decreased coupling from both striata to the ipsilateral thalamus, which would result in an increased inhibitory tone. The reduced thalamic self-inhibition in the left hemisphere would in turn suggest that the left thalamus is more readily affected by the inhibitory striatal input.

In terms of extrinsic (between networks) connections, PDOC patients showed increased coupling, reflecting an overall reduction in inhibition from the AFM to the DMN. Specifically, this affected afferent connections from left thalamus to PCC and right IPL, left striatum to MPFC, and right striatum to both IPLs. In contrast, the connection from right striatum to MPFC showed a very weak negative value. However, upon further investigation, its 95% confidence interval included zero values (

Supplementary Figure 6-1) and therefore it is not possible to determine the sign of this effect (even when this connection contributes to the model evidence, albeit weakly).

Finally, for the connections from DMN to AFM, PDOC patients showed a decoupling of afferent connections from midline regions. This had a laterality effect, with the PCC showing reduced coupling with both right thalamus and right striatum, and MPFC showing reduced coupling with the equivalent regions (thalamus and striatum) in the left hemisphere. Similarly, the lateral parietal areas significantly lost their natural inhibitory tone to the right thalamus (displaying an increased coupling) in PDOC. In addition, the left and right IPL showed increased and decreased coupling with the left thalamus respectively, but we did not find these connections to contribute to the healthy controls model (Figure 2A) and therefore the differences in PDOC are not straightforward to interpret. For clarity, **Figure 6.3** shows the strengths of the connections that showed differences between groups.

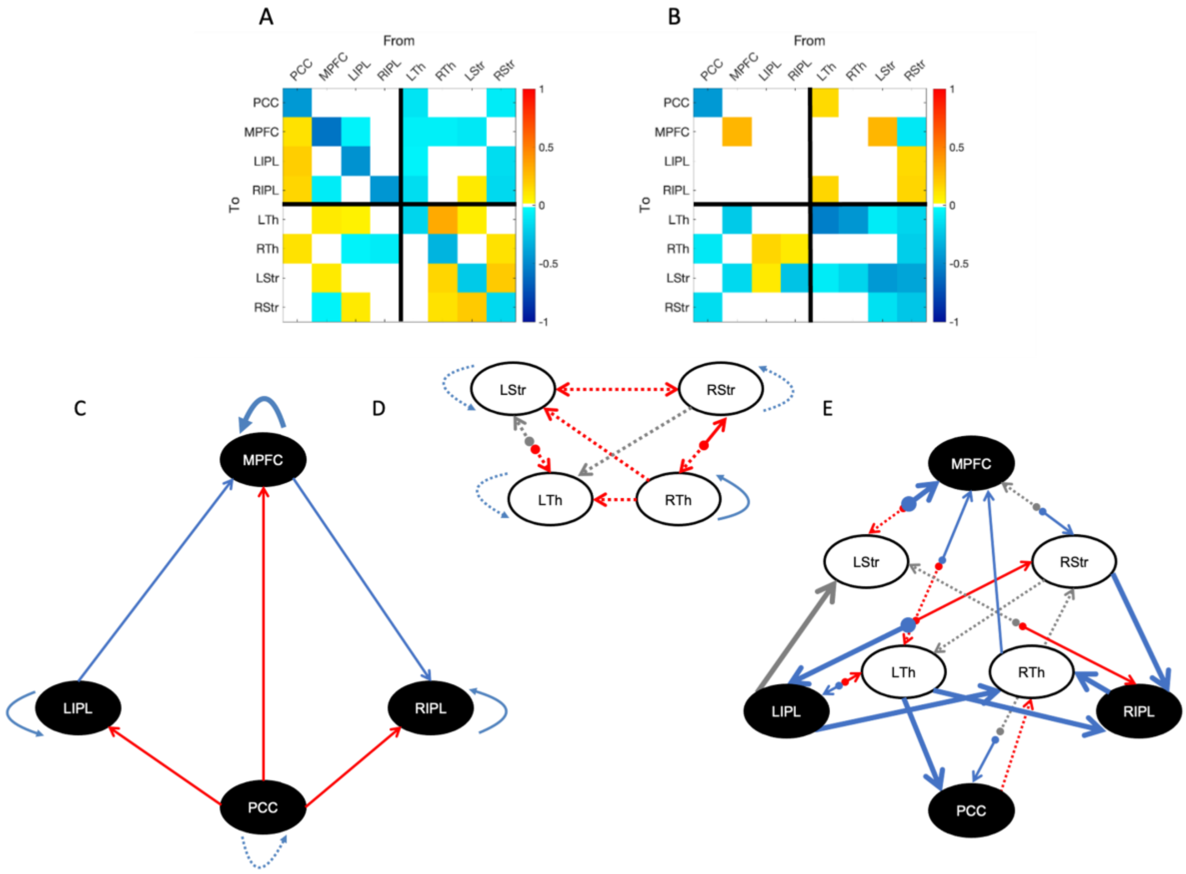


Figure 6.2: Group mean effective connectivity in healthy controls (**A**,**C**–**E**) and differences with PDOC patients (**B**–**E**). We only display connections present in the reduced model (>95% posterior probability for free energy). The top two panels, **A** and **B**, show the mean parameter strength (Ep.A) for the healthy controls mean and the difference between them and PDOC, respectively. Note that self-connections are always inhibitory meaning a positive self-connection parameter in B indicates that PDOC have stronger self-inhibition compared to healthy controls (negative being the opposite). (**C**,**D**) show schematic representations of the results in the matrix in **B** separately for the DMN (**C**), the anterior forebrain mesocircuit (AFM) (**D**), and the extrinsic connections between them (**E**). Note that this is only to facilitate visualization, but all regions were part of the model space in our analysis. The colour of the line refers to its tone in the healthy control mean: red lines represent excitatory connections, and blue represent inhibitory. Grey lines show connections that did not contribute to the healthy control mean model but showed differences between them and PDOC. The format of the line represents the differences between groups: a dashed line represents reduced coupling in PDOC and a thick line shows stronger coupling in PDOC. For self-connections, dashed lines represent reduced self-inhibition and thicker lines increased self-inhibition. PCC, posterior cingulate cortex/precuneus; MPFC, medial prefrontal cortex; LIPL, left inferior parietal lobule; RIPL, right inferior parietal lobule; LTh, left thalamus; RTh, right thalamus; LStr, left striatum; RStr, right striatum.

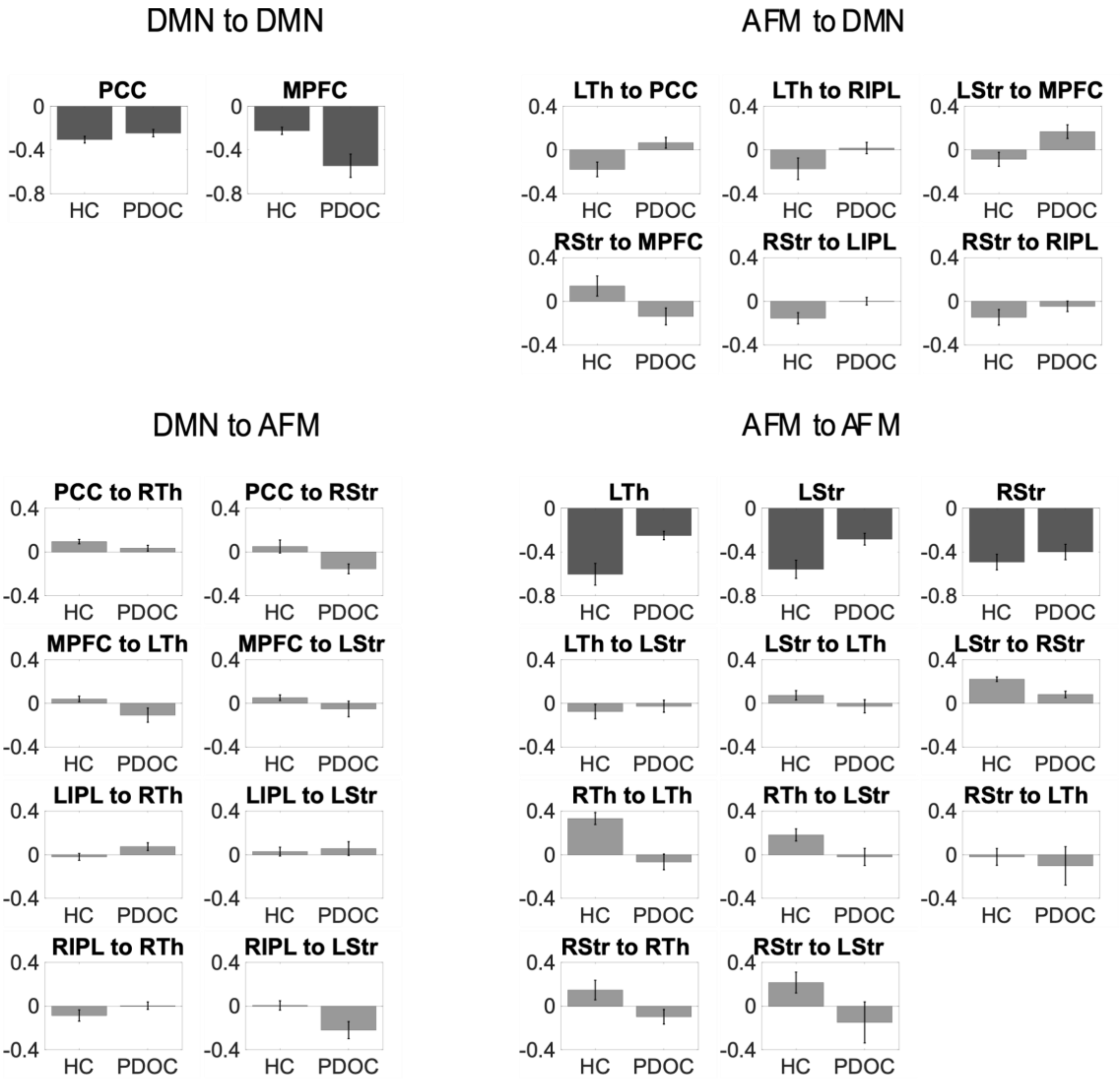


Figure 6.3: Mean connection strength (Ep.A) for the connections contributing to the difference between groups. Error bars represent standard error. Self-connections appear in darker grey and have been converted into Hz. PCC, posterior cingulate cortex/precuneus; MPFC, medial prefrontal cortex; LIPL, left inferior parietal lobule; RIPL, right inferior parietal lobule; LTh, left thalamus; RTh, right thalamus; LStr, left striatum; RStr, right striatum.

6.4.2. CRS-R and Effective Connectivity

We found significant correlations with CRS-R score on the day of scan (n = 13) for the left thalamus self-connection (r = −0.477, *p* = 0.029, JZS-BF10 = 3.630) and the connection between right thalamus to left thalamus (r = −0.450, *p* = 0.040, JZS-BF10 = 2.804). Both were, however, driven by outliers, and when these were removed, they both were no longer significant (left thalamus: n = 12, r = 0.375, *p* = 0.105, JZS-BF10 = 1.331; right thalamus to left thalamus: n = 11, r = −0.350, *p* = 0.150, JZS-BF10 = 1.032). See

Supplementary Figure 6-2 We found no significant correlations for the maximum CRS-R on the week of scan. In addition, when outliers were removed, we found evidence for the lack of a relationship between maximum CRS-R and four connections: MPFC to left thalamus (JZS-BF01 = 3.045), RIPL to right thalamus (JZS-BF01 = 3.154); left thalamus to left striatum (JZS-BF01 = 3.14), and left striatum to MPFC (JZS-BF01 = 3.1). See **Supplementary Table 6-1**

6.5. Discussion

In this study, we provide the first report of disruptions in effective connectivity within and between the DMN and AFM in PDOC patients using spectral DCM of fMRI. We show marked disruptions in coupling mostly affecting the AFM and key connections from and to the DMN.

6.5.1. The AFM and Extrinsic Connections to the DMN

PDOC patients showed extensive decoupling between most regions of the AFM, alongside reduced self-inhibition across all but the right thalamus (no differences) compared to healthy controls. As expected, healthy controls showed bi-directional excitation between the striatum and the thalamus, in line with the well-known canonical interactions between these regions at the neuronal level (Schiff, 2010). The mesocircuit hypothesis posits that, in PDOC, the striatum fails to inhibit the globus pallidus, which in turn becomes hyperactive and excessively inhibits the thalamus. This catalyzes a widespread downregulation of the anterior forebrain and its cortical projections (Schiff, 2010). In the current study, we did not have the spatial resolution to reliably identify the globus pallidus as a region of interest to include in our DCM models, and we included a direct connection between striatum and thalamus instead. However, DCM does not assume direct anatomo-functional connections between the regions and thus our effects for the connection from striatum to thalamus are likely to be mediated by the globus pallidus. As predicted, PDOC patients showed reduced coupling from each striatum to the ipsilateral thalamus as compared to controls. The left thalamus was also less self-inhibited, which made it more vulnerable to this reduced excitation from the striatum (or increased inhibition from the globus pallidus). In turn, the left thalamus showed reduced coupling with the striatum, which was also more responsive to external inputs, further contributing to a reduced excitatory output back to thalamus. Overall, our results are in line with previous research showing a reversal in the resting metabolic profiles of the globus pallidus and thalamus in PDOC patients compared to controls using PET (specifically, an increase in globus pallidus metabolism alongside a reduction in central thalamus metabolism in patients) (Fridman et al., 2014). Therefore, we provide further support for the mesocircuit hypothesis to explain forebrain disfunctions in PDOC (Schiff, 2010). In addition, our results suggest a hemispheric asymmetry, with the left hemisphere more strongly contributing to the differences between PDOC and controls.

Although the aim of our study was to investigate the neural mechanisms underlying PDOC, our results may also contribute to understanding the success (or otherwise) of pharmacological and stimulation therapies. For example, a number of studies have observed clinical improvements in PDOC following administration of amantadine (Thibaut et al., 2019). The proposed mechanism of action is an excitatory modulation of the mesocircuit (and its cortical projections) via targeting the striatum (Thibaut et al., 2019). Our findings confirmed a reduced excitatory coupling from striatum to thalamus in PDOC, providing further support to the use of pharmacological agents that can restore this coupling.

Against our prediction, the AFM showed a widespread inhibitory tone towards the DMN in healthy controls, and a reduction of this inhibition in PDOC. The AFM typically exerts an excitatory role over fronto-parietal networks, which is thought to be reduced in PDOC (Schiff, 2012). While the specific cortical networks involved in this subcortico-cortical disbalance in PDOC are not fully defined, we have previously argued that the DMN is likely to have a central role, on the basis of its strong structural connectivity with the AFM and its widely reported functional and metabolic impairments in this patient group (Lant et al., 2016). Our current results confirm an important relationship between both networks but, interestingly, this was in an unexpected direction. It is well known that the DMN is typically deactivated during tasks (Fox et al., 2005), and anti-correlates with dorsal fronto-parietal networks associated with external awareness and high order cognitive functions and executive control (Vanhaudenhuyse et al., 2011). It is thus possible that the AFM exerts a different tone over the

DMN as compared to its anti-correlated dorsal networks. The study of such dorsal networks was beyond our scope and therefore this conclusion remains necessarily speculative, but our findings could be suggesting a role for the thalamus, and the rest of the AFM, in the modulation of excitation and inhibition between anticorrelated networks, which would be altered in PDOC and might result in an inability to filter internal and external stimuli. In either case, our results suggest that the lack of awareness in PDOC may be underpinned by lack of inhibition to the DMN rather than lack of excitation. Interestingly, previous research in severe traumatic brain injury has revealed increased functional connectivity in the DMN compared to controls. While this study focused on patients who had recovered consciousness, their findings highlight the complex relationship between brain injury and observed disruptions to brain function, which can be translated in both hypo- and hyper-connectivity (Sharp et al., 2011).

The relationship between AFM and DMN once again showed a hemispheric asymmetry, with the left thalamus and the right striatum driving the effects for their respective hemisphere. Specifically, patients had increased coupling from the left thalamus to the PCC and right IPL, as well as from the right striatum to both IPLs. In addition, the left striatum showed increased coupling with MPFC. Previous research suggests that structural differences are more prominent in the left hemisphere in PDOC (Fernández-Espejo, Junque, Bernabeu, et al., 2010; Lutkenhoff et al., 2015), and atrophy in the left thalamus predicts functional outcome in post-traumatic brain injury survivors (Lutkenhoff et al., 2020). Furthermore, the metabolic integrity of the left hemisphere better predicts clinical diagnosis (vegetative versus minimally conscious state) (Rosazza et al., 2016). In a recent ultrasound stimulation study on three chronic PDOC patients, stimulation of the left thalamus elicited some promising improvements in CRS-R scores (Cain et al., 2021). Together, these studies provide evidence for a laterality effect in the neural bases of PDOC, although the reasons behind the higher vulnerability of structures in the left hemisphere remains unclear.

6.5.2. The DMN and Extrinsic Connections to the AFM

PDOC patients were characterized by differences in the self-inhibitory tone of the two midline regions of the DMN (PCC and MPFC), but no differences in any intrinsic (region to region) connections. Specifically, they showed reduced self-inhibition of the PCC and increased self-inhibition in MPFC.

The observed reduced PCC self-inhibition would leave this region more susceptible to afferent inputs from other regions, which in our case were limited to the above discussed increased coupling from the left thalamus. Therefore, PCC self-inhibition would make the DMN more vulnerable to the effects of the AFM modulations. This result is in line with an earlier report investigating effective connectivity changes in the DMN of PDOC patients (Crone et al., 2015). They observed reduced self-inhibition of the PCC in vegetative state compared with minimally conscious state patients, which correlated with level of consciousness (Crone et al., 2015). Similarly, a PET study reported reduced effective connectivity (based on reduced glucose metabolism) of the PCC in vegetative state patients compared with controls (Laureys et al., 1999). The PCC is widely regarded as a central hub for functional integration of information within the DMN and across networks (Deshpande et al., 2011; Hagmann et al., 2008; van den Heuvel & Sporns, 2011), and it has been noted this pathway could play a central role in consciousness (Fernández-Espejo et al., 2012; Schiff, 2012). We have previously reported specific structural damage to all white matter connections, connecting the PCC with the rest of the DMN and the AFM in PDOC (Fernández-Espejo et al., 2012; Lant et al., 2016) and more broadly, damage to the PCC area consistently appears as crucial to understanding the neural basis of PDOC (Boly et al., 2017). Interestingly, two recent transcranial direct current stimulation (tDCS) studies attempted to target the PCC with high definition-tDCS and both found clinical improvements in minimally conscious and vegetative state patients (Guo et al., 2019; R. Zhang et al., 2020).

Leaving differences between PDOC and controls aside, previous research from healthy populations reported inconsistent results on the role and tone of the influence of the PCC to the rest of the DMN at rest. Some studies observed all driving influences from the PCC were negative (Crone et al., 2015; B. Li et al., 2012), whilst others found the PCC exerts an excitatory tone over the network (G. Li et al., 2020; Sharaev et al., 2016). In our sample, we found support for the latter, with the PCC displaying excitatory output to all remaining regions of the DMN. This tone did not appear to differ in PDOC.

In contrast, we observed a marked increase in the self-inhibition of the MPFC in patients. This would lead to the MPFC being less influenced by inputs from within the DMN (specifically the PCC and LIPL) and the AFM (bilateral thalamus and left striatum). This is in line with previous research using graph theory on functional connectivity that found enhanced MPFC connectivity in PDOC (Liu et al., 2017). Interestingly, their effects were driven specifically by minimally conscious patients, with no changes between vegetative state and controls. While our sample size does not allow for disaggregated comparisons across diagnostic categories, our cohort includes a large proportion of vegetative state patients (11/16), suggesting that our differences are not likely to be driven by minimally conscious patients alone. In either case, our results agree in suggesting more marked disruptions in posterior regions of the DMN in PDOC (Boly et al., 2017).

Beyond the above discussed changes in self-inhibition, we did not identify any differences in the region-to-region connections of the DMN in PDOC. This is in contrast with previous studies reporting differences in functional connectivity between PDOC and healthy controls, many of which consistently reported disconnections between midline DMN regions (Demertzi et al., 2014; Di Perri et al., 2016; Rosazza et al., 2016; Silva et al., 2015). These typically correlate with level of consciousness (based on CRS-R score) and outcome (Wu et al., 2015). It is worth highlighting here that functional and effective connectivity tap into very different underlying mechanisms. While functional connectivity analyses identify areas with correlated activity (time series) across time, effective connectivity investigates the causal influence one region exerts over another (K. J. Friston, 2011). Our findings thus suggest that previously reported disruptions in functional connectivity across the DMN in PDOC do not necessarily translate into changes in how they influence or depend on each other.

To our knowledge, only one previous study has looked at effective connectivity within the DMN in PDOC (Crone et al., 2015). The authors reported reduced inhibitory coupling from PCC to MPFC and LIPL in both vegetative and minimally conscious patients (Crone et al., 2015), which we did not see in our study. It is possible our inclusion of the AFM in our model is explaining this discrepancy and some of the effects in (Crone et al., 2015) were driven by indirect connections to subcortical regions. Additionally, contrary to Crone and colleagues, we found no differences between healthy controls and PDOC for connectivity from MPFC to either IPL. Interestingly, the authors reported reduced excitation in both connections in vegetative state patients only, while minimally conscious patients did not significantly differ from controls. It is therefore possible that the discrepancy with our results may be due to our minimally conscious patients masking potential differences existing in the vegetative state group. As discussed above, our sample size did not allow for disaggregation of diagnostic categories in our analyses. Future research with larger samples is needed to disentangle these potential differences. We also note that we conducted our analyses in native space with manually defined masks. While Crone and colleagues embedded robust steps in their analyses to account for potential confounds due to brain abnormalities, we cannot rule out that differences in the pipeline are explaining the discrepancy in our results. This highlights the need for further research to investigate these discrepancies.

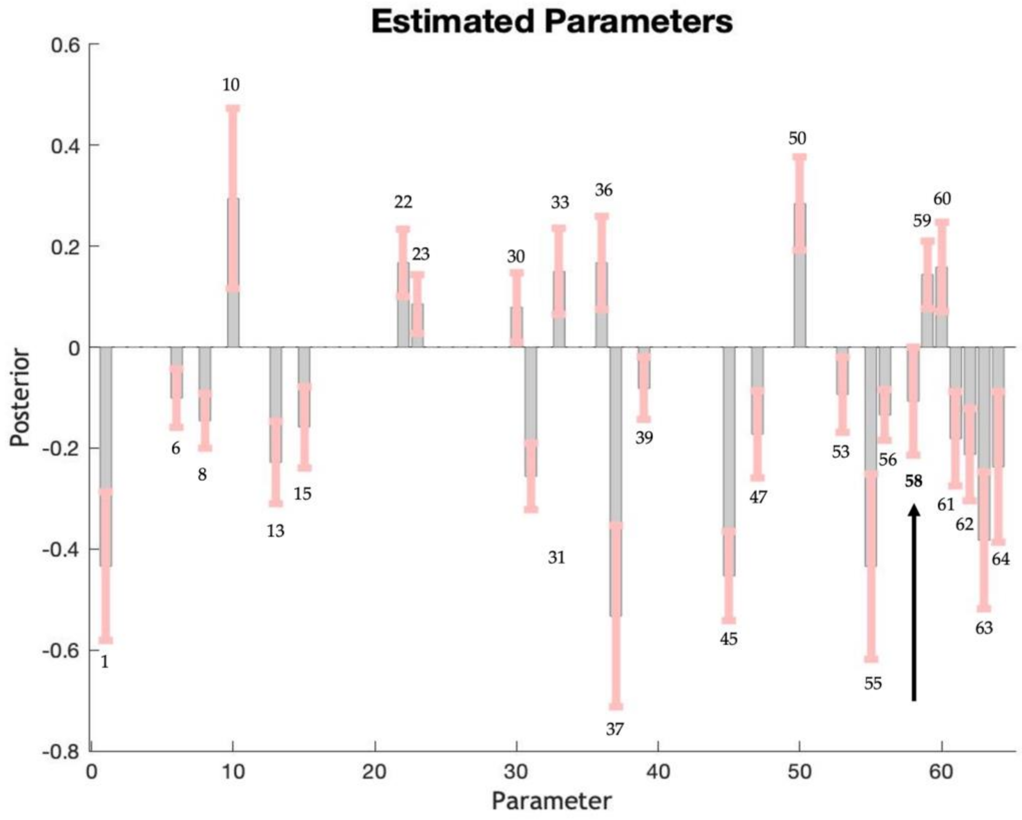
The influence of cortical networks on the AFM is much less understood. Here, we saw a decoupling from the PCC to right thalamus and right striatum in PDOC, as well as from the MPFC to left thalamus and left striatum. This suggests a lack of excitation, which would further contribute to the downregulation of the AFM. Interestingly, we also identified a laterality effect with PCC and MPFC modulating the right and left hemispheres, respectively.

6.5.3. Clinical Severity

We were unable to identify a relationship between the differences in effective connectivity observed between healthy controls and PDOC and clinical severity as indexed by CRS-R. We note that our sample size was small and thus our correlations may be underpowered, specifically for CRS-R on the day of scan where the scores for three patients were unavailable. Indeed, our Bayesian analyses confirmed lack of support for a relationship or a lack of for most connections. Our small sample size also precluded us from undertaking comparisons between vegetative state and minimally conscious state. Therefore, while we can conclude that the above discussed differences in effective connectivity contribute to explaining the neural bases of disorders of consciousness, we cannot make strong arguments about the specific relationship between these two different levels of awareness in PDOC.

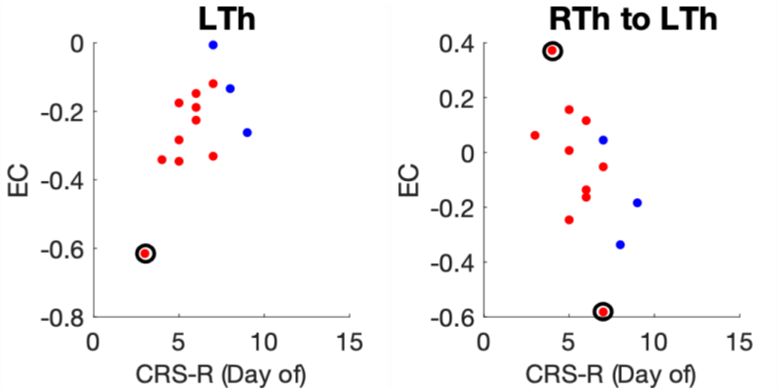
6.5.4. Conclusions

In summary, the current study aimed to establish whether previously reported changes in the DMN in PDOC are caused by lack of excitation from the AFM and the role of the PCC in modulating these effects. PDOC patients showed an overall downregulation of the AFM, likely caused by an increased inhibitory tone of the striatum over the thalamus, providing support for the anterior mesocircuit model. Moreover, in PDOC, the AFM modulated the DMN mostly through posterior areas, including the PCC and IPL. However, instead of identifying a loss of excitation from AFM to DMN in PDOC, we found the AFM has an inhibitory tone over the DMN in the healthy brain at rest and this is disrupted in PDOC. Overall, our results suggest that complex disruptions in the interplay between DMN and AFM characterize PDOC.



Parameter	From	To	Parameter	From	To
1	PCC	PCC	45	RTh	LTh
6	PCC	RTh	47	RTh	LStr
8	PCC	RStr	50	LStr	MPFC
10	MPFC	MPFC	53	LStr	LTh
13	MPFC	LTh	55	LStr	LStr
15	MPFC	LStr	56	LStr	RStr
22	LIPL	RTh	**58**	**RStr**	**MPFC**
23	LIPL	LStr	59	RStr	LIPL
30	RIPL	RTh	60	RStr	RIPL
31	RIPL	LStr	61	RStr	LTh
33	LTh	PCC	62	RStr	RTh
36	LTh	RIPL	63	RStr	LStr
37	LTh	LTh	64	RStr	RStr
39	LTh	LStr			

Supplementary Figure 6-1: Posterior estimates after Bayesian model reduction (grey bars) and 95% Bayesian confidence intervals (pink lines). The parameters along the horizontal axis represent the connection number. The problematic parameter between the right striatum (RStr) and medial prefrontal cortex (MPFC) is indicated with an arrow (parameter 58).



Supplementary Figure 6-2: Correlations between effective connectivity (y-axis) in the Left thalamus (left) and the connection from right to left thalamus (right) and CRS-R (x-axis) on the day of the scan (N = 13). Note that these correlations are no longer significant when the outliers (circled red dot) are removed from the analysis. Red dots indicate vegetative state patients and blue show minimally conscious state. All connections (including self-connections) are displayed in Hz. EC, effective connectivity; CRS-R, coma recovery scale-revised; LTh, left thalamus; RTh, right thalamus.

Supplementary Table 6-1: *Correlation between CRS-R and effective connectivity in the regions and connections showing differences between PDOC and healthy controls.*

		CRS-R on day of scan					Max CRS-R on week of scan				
		Kendall's Tau B	p-value	JZS-BF10	JZS-BF01	N	Kendall's Tau B	p-value	JZS-BF10	JZS-BF01	N
DMN	PCC to PCC	0.259	0.237	0.699	1.432	13	0.301	0.118	1.088	0.92	16
	PCC to RTh	-0.014	0.95	0.35	2.86	13	-0.177	0.358	0.486	2.058	16
	PCC to RStr	-0.423	0.053	2.199	0.455	13	-0.319	0.098	1.262	0.792	16
	MPFC	-0.123	0.575	0.408	2.452	13	-0.124	0.52	0.391	2.558	16
DMN to AFM		*-0.276*	*0.365*	*0.642*	*1.558*	*8*	*0.048*	*0.853*	*0.4*	*2.503*	*10*
	MPFC to LTh	0.095	0.663	0.384	2.607	13	0.071	0.713	0.34	2.945	16
		0.016	*0.944*	*0.363*	*2.756*	*12*	*0.02*	*0.92*	*0.328*	*3.045**	*15*
	MPFC to LStr	0.123	0.575	0.408	2.452	13	0.177	0.358	0.486	2.058	16
		0.048	*0.834*	*0.37*	*2.704*	*12*	*0.141*	*0.481*	*0.419*	*2.388*	*15*
	LIPL to RTh	0.041	0.852	0.355	2.816	13	-0.071	0.713	0.34	2.945	16
		0.048	*0.834*	*0.37*	*2.704*	*12*	*-0.153*	*0.447*	*0.439*	*2.28*	*15*
	LIPL to LStr	0.068	0.755	0.366	2.731	13	0.124	0.52	0.391	2.558	16
	RIPL to RTh	0.014	0.95	0.35	2.86	13	0	1	0.317	3.154*	16

	RIPL to LStr	-0.286	0.191	0.814	1.228	13	-0.106	0.582	0.37	2.704	16
	LTh to PCC	-0.204	0.35	0.538	1.859	13	-0.142	0.462	0.417	2.399	16
							-0.101	*0.614*	*0.371*	*2.696*	*15*
	LTh to RIPL	-0.204	0.35	0.538	1.859	13	-0.053	0.783	0.329	3.035*	16
		-0.463	*0.123*	*1.3*	*0.769*	*8*	*-0.327*	*0.176*	*0.909*	*1.1*	*11*
	LTh	**0.477**	**0.029***	**3.63**	**0.275**	**13**	0.266	0.168	0.828	1.207	16
		0.375	***0.105***	***1.331***	***0.751***	***12***	*0.183*	*0.362*	*0.497*	*2.012*	*15*
	LTh to LStr	-0.095	0.663	0.384	2.607	13	-0.018	0.927	0.318	3.14*	16
	RTh to LTh	**-0.45**	**0.04***	**2.804**	**0.357**	**13**	-0.337	0.081	1.477	0.677	16
		-0.35	***0.15***	***1.032***	***0.969***	***11***	*-0.258*	*0.218*	*0.72*	*1.388*	*14*
	RTh to LStr	-0.041	0.852	0.355	2.816	13	0.018	0.927	0.318	3.14*	16
		0.048	*0.834*	*0.37*	*2.704*	*12*	*0.04*	*0.84*	*0.333*	*2.999*	15
	LStr to MPFC	0.232	0.29	0.608	1.644	13	0.035	0.854	0.323	3.1*	16
							-0.02	*0.92*	*0.328*	*3.045**	*15*
AFM to DMN	LStr to LTh	0.041	0.852	0.355	2.816	13	0.124	0.52	0.391	2.558	16
		0.145	*0.596*	*0.469*	*2.133*	*9*	*0.176*	*0.442*	*0.483*	*2.07*	*12*
	LStr	0.068	0.755	0.366	2.731	13	0.106	0.582	0.37	2.704	16
		-0.016	*0.944*	*0.363*	*2.756*	*12*	*0.06*	*0.762*	*0.342*	*2.924*	*15*
	LStr to RStr	-0.014	0.95	0.35	2.86	13	0.071	0.713	0.34	2.945	16
	RStr to MPFC	0.095	0.663	0.384	2.607	13	0.089	0.646	0.353	2.834	16

	RStr to LIPL	0.259	0.237	0.699	1.432	13	0.213	0.27	0.586	1.705	16
		0.272	*0.263*	*0.694*	*1.442*	*11*	*0.117*	*0.576*	*0.395*	*2.534*	*14*
	RStr to RIPL	0.204	0.35	0.538	1.859	13	0.177	0.358	0.486	2.058	16
AFM	RStr to LTh	-0.041	0.852	0.355	2.816	13	-0.213	0.27	0.586	1.705	16
		-0.242	*0.355*	*0.598*	*1.671*	*10*	*-0.357*	*0.104*	*1.301*	*0.768*	*13*
	RStr to RTh	0.204	0.35	0.538	1.859	13	0.089	0.646	0.353	2.834	16
							0.04	*0.84*	*0.333*	*2.999*	*15*
	RStr to LStr	0.314	0.152	0.964	1.037	13	0.355	0.066	1.743	0.574	16
		0.229	*0.342*	*0.58*	*1.726*	*11*	*0.38*	*0.067*	*1.742*	*0.574*	*14*
	RStr to RStr	0.259	0.237	0.699	1.432	13	0.124	0.52	0.391	2.558	16
		0.304	*0.184*	*0.855*	*1.169*	*12*	*0.081*	*0.687*	*0.354*	*2.822*	*15*

* $p < 0.05$, JSZ-BF10 > 3, JSZ-BF01 > 3; Italics represent results after removing outliers for each comparison. We highlight in bold the comparisons that indicated a significant correlation prior to removal of outliers, and in grey those that provided evidence for a lack of a correlation after removing outliers. PCC, posterior cingulate cortex / precuneus; MPFC, medial prefrontal cortex; LIPL, left inferior parietal lobule; RIPL, right inferior parietal lobule; LTh, left thalamus; RTh, right thalamus; LStr, left striatum; RStr, right striatum.

Chapter 7

7.1. Summary of aims

This thesis aimed to investigate the behavioural and neural effects of an external modulator, tDCS, on the self-referential process of mind-wandering and underlying networks. Previous research has suggested an ability to modulate the propensity of mind-wandering, as subjectively reported (Axelrod et al., 2015, 2018; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Furthermore, multimodal imaging studies suggested that tDCS-induced changes in mind-wandering propensity were mediated by modulation of underlying brain connectivity, specifically within the DMN (Kajimura et al., 2016, 2019). However, these findings were highly inconsistent, with failed replications and a lack of standardised methodologies (Boayue, Csifcsák, Aslaksen, et al., 2020; T. Chou et al., 2020; Filmer et al., 2014). Collectively, this has resulted in a limited understanding of the neural mechanisms behind the possible effects of tDCS on mind-wandering. To address some of these issues, we conducted a series of experiments to assess the effects of tDCS on behavioural reports of mind-wandering and underlying neural activity.

7.2. Summary of results and discussion

Chapter 3 provides evidence that neither anodal nor cathodal 1.5mA tDCS (at rest) over the right IPL (return over left cheek) modulated subjective reports of mind-wandering during the SART compared to sham. Using Bayesian statistical methods, we provide strong to very strong support for the lack of an effect of tDCS in the null compared to the full model (main effects of stimulation (anodal, cathodal, and sham) and session (baseline, post-tDCS), as well as the interaction between them), and substantial evidence for the model excluding the interaction on behavioural reports of mind-wandering. Our results oppose the previous literature, which implemented the same stimulation montage and intensity but observed reduced mind-wandering propensity for anodal right IPL stimulation compared to sham using the same task (Kajimura et al., 2019). For the objective measures based on task performance (reaction time to task and errors), we also observe no effect of stimulation (again providing support against it), which corroborates the previous research (Kajimura et al., 2019).

Chapter 4 used the same task design as Chapter 3 (without a sham condition) on a separate cohort of participants. We implemented the task concurrently during fMRI to investigate the neural basis of mind-wandering and any effects of tDCS on the brain that may be too subtle to result in changes in behaviour. Here, we replicated our initial findings by demonstrating no effect of tDCS on behavioural reports of mind-wandering and provide strong evidence for the null compared to the full model alongside substantial evidence for the model excluding the interaction. Furthermore, we again show no effect of stimulation on task performance. For the effects of tDCS on brain activity, we report no effect on BOLD activation and no effect on effective connectivity within or between regions of the DMN and ECN. Although we failed to replicate the task-related brain activation in our univariate analysis, we provide the typical effective connectivity observed in the baseline run of the first chronological session of the task for regions of the DMN and ECN.

In Chapter 5, we found that 1.8mA anodal tDCS (online, during SART) over the left DLPFC (return over the right supraorbital cortex) could not modulate mind-wandering propensity as compared to sham. Bayesian analysis provided strong support for the null compared to the full model and substantial evidence for the models excluding the interaction. These results oppose the initial research that observed anodal stimulation of the left DLPFC increased mind-wandering propensity (Axelrod et al., 2015, 2018). However, our findings support the recent large-scale failed replication of this initial research (Boayue, Csifcsák, Aslaksen, et al., 2020). We also found no effect of stimulation on task performance, supporting the previous literature (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020). Using concurrent fMRI during task completion, we investigated the effect of tDCS on underlying brain activity and connectivity. We provide evidence suggesting no effect of stimulation on BOLD, dynamic functional network connectivity, nor effective connectivity within and between regions of the DMN, ECN and SN.

Together, the results across our three studies, using two of the most prominent montages adopted in this field, consistently demonstrate tDCS was unable to modulate mind-wandering propensity nor underlying brain function. Our results suggest the previously reported modulations by Kajimura et al., (2019) and Axelrod et al., (2015, 2018) may have been false positives or driven by inadvertent exogenous factors. For example, the samples used in previous research may have coincidentally contained participants responsive to tDCS. Reinforcing the latter claim, evidence from computational modelling of electric field distribution demonstrated large variability in individual responses to tDCS due to anatomical differences (Boayue et al., 2018). The current thesis used enhanced and more robust research designs than the previous studies, which may account for the disagreement between findings and supports the claim that the previous research may have been false positives. Specifically, all three studies in the current thesis used a within-subjects design on larger samples with baseline levels of mind-wandering recorded on each session to control for inter- and intra-subject variability. Kajimura et al., (2019) contained 13 subjects in their right IPL condition (compared to 23 in Chapter 3) and only recorded post-stimulation mind-wandering. Axelrod et al., (2015) used 10-14 participants per group (compared to 20 in Chapter 5) and recorded mind-wandering during and post-stimulation only. Overall, our results indicate tDCS is unable to modulate mind-wandering propensity using these montages.

Our negative results could be attributed to several reasons. Perhaps neither the DMN nor the DLPFC contribute to mind-wandering in the way we thought and stimulating either would therefore have no influence on modulating it. This seems unlikely given the previous literature demonstrating the DMN involvement with mind-wandering, increased activity during rest, and the recruitment of the ECN during mind-wandering in previous studies, however, it is worth noting these results were based on correlational analysis (Christoff et al., 2009; Greicius et al., 2003; Stawarczyk, Majerus, Maquet, et al., 2011). Alternatively, perhaps the intrinsic process of mind-wandering cannot be modulated externally and can only be modulated intrinsically. On the other hand, tDCS may be unable to stimulate the targeted regions to induce changes in behaviour. This holds true, given our imaging analysis revealed no effects on brain activity and connectivity. On the other hand, the bipolar montages used in the current thesis may have resulted in stimulation of various regions (as demonstrated in **Figure 1 A) & C)**) with the effects ultimately cancelling out. For example, stimulation reaching both the MPFC and DLPFC would interfere with internal and external awareness via the DMN and ECN, respectively. Overall, the current literature investigating modulating mind-wandering via tDCS is highly heterogenous, with inconsistent findings based on various montages (different current and electrode placement) and a lack of polarity-specific effects.

The studies conducted as part of this thesis add to this body of literature, and our null results highlight the lack of replicability within the field.

Another possible explanation for the lack of observed effects of tDCS could be attributed to the combined large inter-subject variability across both tools being used in our research: tDCS and self-reported mind-wandering. Large variability in the responsivity to tDCS has widely been noted for a number of reasons including, but not limited to, arousal, cortical morphology and baseline performance levels (Esposito et al., 2020; Filmer et al., 2019; Rudroff et al., 2020; Wiethoff et al., 2014). In addition, throughout the current thesis, we observed large inter- and intra-subject variability in both the subjective and objective levels of mind-wandering across all studies. This is consistent with previous research demonstrating individuals on average mind-wander between 30% and 50% of their daily lives (Killingsworth & Gilbert, 2010; Klinger & Cox, 1987; Song & Wang, 2012) and is also consistent with the large variability observed in the mind-wandering and tDCS literature (Axelrod et al., 2018; Filmer et al., 2019, 2021). Combining both of these highly variable elements (responsivity to tDCS and baseline levels of mind-wandering) makes controlling for the inter- and intra-subject differences particularly difficult. Throughout the thesis, we attempted to reduce the impact of inter-subject variability by using within-subjects designs, however the identified variability across sessions of the same participant remains a problem. This is an important issue to address for the field of tDCS and mind-wandering, particularly when attempting to investigate the effects of tDCS on brain networks, such as the DMN. Although research is currently attempting to understand the differences in the responsivity to tDCS, the tasks used to accurately capture individuals thought processes are also a poignant issue. Going forward, studies may wish to include participants who are particularly sensitive to changes in one’s thoughts (such as, people that regularly practice meditation) in order to reduce the influence of variability in self-reported levels of mind-wandering.

Leaving the effects of tDCS aside, in both of our imaging studies, we observed no task-related brain activation from the general linear model in either Chapter 4 or 5. Contrary to previous research, episodes of mind-wandering during the baseline chronological session of the task did not elicit activation from DMN or ECN regions (Christoff et al., 2009). In Chapter 4, the lack of activation may be attributed to the more complicated operationalisation of mind-wandering. Here, participants responded to each probe with how internally and externally directed their thoughts were both on a scale of 1-4 (max to min). We then categorised episodes of mind-wandering as occasions where participants responded with 1 or 2 on internal and 3 or 4 on external. As there were a total of four response outcomes from this method ("mind-wandering", "high external", "on-task", and "other"), this often resulted in a very low number of mind-wandering episodes for some individuals. Because of this, we acknowledge that we may have been underpowered to capture the desired brain activation accurately.

For Chapter 5, we amended the protocol to include more thought probes (32) and used a binary choice ("on-task" and "off-task"). Again, however, we showed no brain activation at the group level in our contrasts. Our research mirrors that of subsequent research, which used a comparable number of thought probes (30) to ours (32) and failed to observe group-level task-related activation (Denkova et al., 2019). The original research by Christoff et al., (2009) included 80 probes across 15 subjects. Large inter-subjective variability in the propensity and duration of mind-wandering may have contributed to the lack of group-level activation observed in the current thesis. To accurately replicate the group-level findings from Christoff and colleagues and reduce variability, studies need to capture a large number of thought probes from a small participant sample. This, however, would be difficult to implement within the field of tDCS as larger sample sizes are needed to control for inter-subject variability in response to tDCS. Furthermore, the large number of probes would make each session in the scanner very long when controlling for baseline levels of mind-wandering (>1.5 hours per scan). Overall, our results (and those from Denkova et al., (2019)) suggest that the thought-probe experience sampling technique is an unreliable method of capturing brain activation related to mind-wandering and suggests the initial results from Christoff et al., (2009) may have been a false-positive or been driven by exogenous factors. For example, the sample used by Christoff and colleagues may have been particularly sensitive to characterising and accurately reporting episodes of mind-wandering. This highlights the inherently subjective nature of experience sampling, which relies on participants' self-awareness to accurately report the content of their thoughts. This, therefore, leaves the blocks for the thought-probe GLM analysis vulnerable to high levels of noise and interference, often contaminating episodes of mind-wandering with other types of thoughts.

In addition to the thought-probes, we also investigated the conditions of commission errors compared to correct responses. This was used as an objective measure of mind-wandering, with errors on the task thought to reflect participants' attention being off-task. We again demonstrated no group-level brain activation, in contrast to Christoff et al., (2009) who observed activation in the DMN, specifically dorsomedial PFC and ventromedial PFC. As the SART is specifically designed to promote mind-wandering via low cognitive demand, the task may be so easy it allows participants to complete the task and mind-wander comfortably. Therefore, performance based on errors is not related to mind-wandering but is caused by other factors. This would explain why we do not see any activation for the contrast between correct responses and errors. Corroborating this, Axelrod et al., (2015, 2018) observed increased mind-wandering propensity without changes in task performance, suggesting performance is not an indicator of mind-wandering propensity.

Although we observed no stimulation effect on the effective connectivity, we were able to report the typical connectivity while undertaking the SART across intrinsic networks. We did observe several commonalities across the studies. In particular, strong self-inhibition in the PCC and bi-directional excitatory coupling between the PCC and left DLPFC. Furthermore, bi-hemispheric inhibitory coupling was found from the supramarginal gyrus and the PCC. Although we found inconclusive evidence for the relationship from the MPFC to the PCC in Chapter 4, Chapter 5 demonstrated a strong excitatory tone. This is in line with several resting-state studies (Di & Biswal, 2014; Jiao et al., 2011; Uddin et al., 2009) and supports the involvement of this connection with the generation of self-referential processes (Saverino et al., 2015). A direct comparison between Chapter 4 and 5 is not possible due to the different methodological designs (lack of practice runs in Chapter 5) and inclusion of different regions in the DCM analysis (fifteen ROIs from the DMN and ECN in Chapter 4, nine ROIs from the DMN, ECN and SN in Chapter 5). The different ROIs employed in each were both informed by previous research. We based our pipeline for Chapter 4 on Kajimura et al., (2019) who also stimulated the right IPL and included effective connectivity analysis. In Chapter 5, we used the ROIs from the dFNC analysis based on Denkova et al., (2019) as exploratory analysis beyond that described in our preregistration (https://osf.io/8um5s/). Our results offer further insight into the interplay between these intrinsic networks during the SART, which promotes mind-wandering, and provide a baseline level of effective connectivity in healthy controls for future research using DCM to compare with.

Our exploratory analysis investigating dFNC in Chapter 5 did not reveal any effects of tDCS on the frequency or dwell time of the observed brain states. Despite this, our results corroborate previous research which also employed this method on fMRI data during the SART (without tDCS) (Denkova et al., 2019). These brain states seemingly represented a continuum of positively- to negatively-correlated connectivity between networks which may reflect the switching between internally or externally focussed thoughts throughout the task. Our research helps validate the use of dFNC on task-based fMRI data to help characterise dynamic brain states. Furthermore, this technique offers an interesting insight into continuous changes in brain states over time. Considering tDCS is typically applied for 20 minutes, this method allows researchers to investigate subtle changes in the frequency and time spent in reoccurring brain states throughout this period. More research is needed in this area to delineate the dynamic properties of mind-wandering and explore the effects of an external modulator on these brain states.

7.3. Limitations of the research

7.3.1. Task and thought probes

Baseline cognitive abilities have been shown to influence the efficacy of tDCS in modulating performance which also may result in ceiling effects on neuronal and behavioural modulation (Li et al., 2015). For example, performance gains on a visual short-term memory task following tDCS over the posterior parietal cortex were only found for participants who performed poorly at baseline with no improvement in those with high performance at baseline (Tseng et al., 2012). The SART was adopted throughout this thesis as its monotonous nature induces high levels of mind-wandering. A small degree of executive control is required, and the number of target trials was purposely kept to a minimum (5%) to facilitate mind-wandering. This may have resulted in such weak executive demands that TUTs, as assessed by thought probes, were already at or near ceiling. In the current thesis, average mind-wandering throughout chapters 3-5 ranged between 30-50%, which corroborates previous research that found mind-wandering typically consumes between a third and a half of people’s daily lives (Killingsworth & Gilbert, 2010; Klinger & Cox, 1987; Song & Wang, 2012). Participants may, therefore, be performing at a ceiling level of mind-wandering (or an optimum amount) as they have the cognitive resources to both mind-wandering and perform the SART, which requires minimal executive input due to its simplicity.

As mentioned in the previous section, how we operationalised mind-wandering episodes may have influenced our ability to accurately capture brain activation related to the task. However, this may also have impacted our ability to assess the effects of tDCS. As we grouped mind-wandering episodes as TUTs this would have undeniably captured a wide range of self-referential thought processes beyond those that are simply task-unrelated. Mind-wandering is a multifaceted phenomenon (Seli, Kane, Smallwood, et al., 2018), and these self-referential thoughts have various dissociable features, including relating to the past, present or future, being negative or positive in mood, and arising spontaneously or deliberately. We acknowledge that the way mind-wandering was operationalised throughout this thesis could have been oversimplistic and resulted in an inability to capture more subtle changes in the effects of tDCS on these sub-divisions of mind-wandering. Indeed, dual HD-tDCS over the parietal lobules found no effect on mind-wandering propensity but did observe a reduced frequency of negative mind-wandering episodes about the past (T. Chou et al., 2020). Therefore, the true effect of tDCS may be to influence the type of mind-wandering participants experience and would rely on the ability of participants to distinguish between them. This may help explain the variability in responsiveness to tDCS observed across the literature, and future studies should investigate this further by dissociating between these different forms of self-referential thoughts when using experience sampling to measure TUTs.

Throughout this thesis and across the literature, we rely on the participants’ ability to be meta-aware of and accurately recall where their thoughts were during probes. Although the gold standard method of capturing mind-wandering episodes is currently through self-reports to thought-probes, the most prevalent issue is its inherent subjectivity (Konishi & Smallwood, 2016). The use of covert objective measures of mind-wandering would mitigate this issue by relying on physiological responses to indicate participants’ thought processes. Numerous measures have been investigated, including pupil-dilation (Mittner et al., 2014; Smallwood et al., 2011; Wainstein et al., 2017), galvanic skin response (Smallwood, O’Connor, et al., 2007), fingertip pressure during responses, and respiratory signals (Zheng et al., 2019). However, large variability exists, and given that mind-wandering is by definition an intrinsic process, it is unlikely ever to be understood by a single objective measure and remains an inherent, unavoidable problem. Combining these measures with subjective experience sampling may help triangulate the physiological indicators of mind-wandering and minimise the subjectivity of probe sampling.

7.3.2. fMRI and data analysis

The imaging modality, fMRI, used in this thesis relies on an indirect measure of brain activity, the BOLD response, which is the ratio of oxygenated to deoxygenated haemoglobin. As neuronal firing increases, the metabolic demand for oxygen also increases, resulting in increased cerebral blood flow in specific brain areas and increased oxygenated blood. As neuronal firing stops, a decrease is observed to the point of an undershoot, after which the region normalises to baseline levels. fMRI looks at this haemodynamic response function by measuring the levels of paramagnetic deoxygenated haemoglobin. Therefore, this method is susceptible to many factors that affect the neurovascular response. Several different factors have been noted to influence the BOLD signal, including caffeine, alcohol, nicotine, medication, level of psychical exercise, body weight, respiration, and perhaps most notably, head motion (Weinberger & Radulescu, 2016, 2021). A study of resting-state networks in healthy controls found functional connectivity within the DNM and frontoparietal control network was reduced in those who displayed the highest head motion levels compared to those with the lowest (Van Dijk et al., 2012). Although we used a within-subjects design that helped mitigate some of these confounds, session-to-session differences remain a problem. Overall, we cannot rule out that head motion, along with other vascular factors affecting MRI signal, could have influenced our ability to observe network activity in our studies, particularly given the long length of task and stimulation runs used (3 x 20 minutes in Chapter 4 and 2 x 20 minutes in Chapter 5). We attempted to mitigate these issues by instructing participants to remain as still as possible, corrected for rigid body motion by regressing out the six dimensional motion parameters, and excluded excessive motion and removed participants above a threshold of excessive head motion. Recently, pre-processing pipelines, such as fMRIprep (as used in Chapter 5), offer standardised protocols and generate comprehensive confound factors that can be used as regressors of no interest in second-level analysis (including the motion parameters that were regressed in Chapter 4). The use of such pipelines (although not always appropriate, such as for patients with lesions) allows increased validity, reproducibility and generalisation across the field (Esteban et al., 2019).

DCM also relies upon the hemodynamic response signals, which can be sluggish, providing low-pass filtered information of previous neural events, and is also susceptible to the aforementioned influences on MRI signals. Until recently, the number of nodes that could be successfully modelled within a given DCM was limited (3-4 nodes with full connectivity) due to the computational time required to invert the models (K. J. Friston, 2011; Hartwigsen et al., 2015). Thanks to advances in statistical methods, including the computationally efficient PEB approach (K. Friston et al., 2015; K. J. Friston et al., 2016), models can now include a larger number of nodes to assess connectivity across a wider network. Although we made use of these advances, we only investigated the effects of tDCS on a limited network of brain regions based on previous research. The regions used in the current studies are not a comprehensive list of those that may play a role in mind-wandering or be influenced by tDCS. Specifically, large current spread using bipolar montages will likely stimulate a number of regions beyond the targeted area, which may not have been included in the analyses. Therefore, future research should include additional nodes to understand further the neural base of mind-wandering and the effects of tDCS. Additionally, these techniques are still relatively new, and further methodological optimisation is needed to fully utilise the potential of DCM (Hartwigsen et al., 2015).

For the effective connectivity analysis in Chapters 4 and 5, we analysed the data independently of the task state. This decision was partly founded on the lack of brain activation for the task GLM, particularly given the thought-probes were not reliable at establishing network activation, and is also in line with previous research employing this technique during the SART (Kajimura et al., 2019). Throughout the task, participants experience being focused on the task and mind-wandering, as captured in the subjective reports. Although we did not observe task-related brain activation in relation to thought-probes or SART performance, we aimed to investigate how tDCS affects the intrinsic connectivity within and between core networks independently of the task, which DCM captures. This allows for comparisons between changes in effective connectivity with probe-response frequency and task performance. Together, this helps establish a causal relationship between the external modulation of neural processes and resulting behavioural changes. We observed no effect of tDCS on effective connectivity, which suggests stimulation was unable to modulate underlying brain connectivity and corroborates our behavioural results. Despite this, we acknowledge analysing the data independently of the task may be a limitation, and future research should incorporate this where possible.

7.3.3. tDCS

One of the prevailing issues in the field of psychological research is the “crisis in confidence” (Pashler & Wagenmakers, 2012), largely due to the lack of replicability (Open Science Collaboration, 2015). This issue is exacerbated in the field of tDCS further with claims of a lack of strong evidence for cognitive effects of single-session tDCS (Horvath et al., 2015b). As is widely appreciated, inter-subject variability in response to tDCS is a significant issue for the field (Li et al., 2015), with underpowered studies from small sample sizes overestimating the effect sizes (Gelman & Carlin, 2014; Schäfer & Schwarz, 2019). Throughout Chapters 3-5, we used a within-subjects design with Bayesian results suggesting we had enough power to support evidence for no effect of stimulation on our behavioural measures and the frequency and dwell time of states for dFNC in Chapter 5. Despite this, the sample sizes used did not allow us to investigate the inter-subject variability in depth. Therefore, we are unable to ascertain whether this lack of effect was driven by population samples that were inherently unresponsive to tDCS and acknowledge this as a limitation. Despite this, sample sizes used in the current study are comparable to those reporting successful modulation of mind-wandering (and often using a between-subjects design) (Axelrod et al., 2015; Bertossi & Ciaramelli, 2016; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Therefore, if the lack of effects is due to sample, it would indicate that a large portion of the population are non-responders to tDCS. It is currently unknown what characterises a tDCS “responder” and, therefore, much larger samples are needed to understand the reliability and generalisability of tDCS in evoking behavioural responses in healthy populations.

A possible explanation for the lack of effects might be attributed to the small current intensity used (1.5mA and 1.8mA). It is worth noting here that we could not use current intensity above 2mA due to ethical restrictions. Research on mice suggests larger currents are needed to modulate neuronal resting potentials (Vöröslakos et al., 2018). Specifically, an E-field of 1 V/m gradient was required to garner online effects on neuronal spiking (Vöröslakos et al., 2018). In the current thesis we used up to 1.8mA stimulation which translates into a predicted maximum cortical intensity of 0.235 V/m (based on the ROAST simulation, see **Figure 1** and **Figure 5.1**). Such low cortical intensity may have been insufficient to perturb neuronal firing and may explain the lack of any behavioural effects and is further supported by the lack of any effects on functional and effective connectivity in Chapters 4 and 5. Research on a cadaver found currents applied to the scalp needed to exceed 4-5mA in order to achieve 1mV/mm voltage gradient in brain tissue and the authors note that this may need to be larger in vivo due to the increased shunting of better hydrated vivo tissue (Vöröslakos et al., 2018). Despite this, most of the studies in the tDCS literature have used under 2mA and many reported successful modulations both at the behavioural and neural level. Recently, Filmer et al., (2019) demonstrated a linear trend between cathodal current intensity (1, 1.5 and 2mA) and increased mind-wandering propensity, however, only the 2mA cathodal condition significantly differed from sham. Therefore, the current intensity used in this thesis may have been too small to observe any effects. Despite this, the current intensity used within this thesis is higher than most of the previous studies that reported successful modulation of mind-wandering (Axelrod et al., 2015, 2018; Filmer et al., 2021; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Therefore, the lack of effects in the current thesis cannot solely be accounted for by insufficient current intensity. Furthermore, the relationship between current intensity and behavioural performance is not always linear. For example, Batsikadze et al., (2013) observed that cathodal stimulation elicited contradictory effects (opposed to linear) when using increased current over the motor cortex. Additionally, the effects of reduced muscle activity in a fatigue task following 2mA tDCS over the motor cortex (C3) disappeared under 4mA stimulation compared to sham (Workman et al., 2020). Therefore, the relationship between current intensity and behavioural changes is complex and currently poorly understood. Further research using within-subjects designs and with varying dosages is needed to investigate the nature of stimulation intensity and dose-response.

7.3.4. Brain states

The brain state during delivery of stimulation has previously been shown to be a potential influence on the ability of tDCS to elicit both neuronal and behavioural changes (Gill et al., 2015; Li, Violante, Leech, Ross, et al., 2019; Stagg et al., 2011). We delivered tDCS at rest in Chapters 3 and 4 and during the SART (online stimulation) in Chapter 5 with no effects of tDCS across all studies. To date, the literature investigating modulating mind-wandering via tDCS has used both stimulation at rest (Filmer et al., 2019, 2021; Kajimura et al., 2019) and online stimulation during a task, such as the SART (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020) to varying degrees of success. Given that we are attempting to modulate mind-wandering, using offline (at rest) tDCS would be beneficial considering the DMN is active during these periods (Greicius et al., 2003). To date, most of the research targeting the DMN, with electrodes placed over parietal areas or MPFC, used offline tDCS (Bertossi et al., 2017; T. Chou et al., 2020; Filmer et al., 2021; Kajimura et al., 2016, 2019; Kajimura & Nomura, 2015). Whereas all of the studies using online tDCS targeted the DLPFC (Axelrod et al., 2015, 2018; Boayue, Csifcsák, Aslaksen, et al., 2020; Boayue, Csifcsák, Kreis, et al., 2020). One of the drawbacks of offline tDCS is that it is entirely unconstrained, resulting in large variability in participant attention during stimulation which may add to the interindividual variability in responsiveness to tDCS.

A novel task, the FT-RSGT, which combines rhythmic finger tapping with the generation of random sequences, has recently been adopted to investigate the effects of tDCS on mind-wandering propensity (Boayue, Csifcsák, Kreis, et al., 2020). These two features, in conjunction, require participants to access executive functions whilst undertaking a monotonous task. During online 2mA anodal HD-tDCS over left DLPFC reduced mind-wandering compared to sham. Boayue, Csifcsák, Kreis, et al., (2020) suggest the FT-RSGT generates higher activity in the ECN, specifically the DLPFC, meaning this higher baseline cognitive recruitment of the DLPFC leaves it more susceptible to active stimulation and thus increases the possibility of neuromodulation. Overall, using tasks like the FT-RSGT, which includes a monotonous element that facilitates mind-wandering alongside a cognitively demanding random sequence generation task, may help engage the target areas and increase the ability of tDCS to modulate underlying neuronal activation. This modulation may then translate into changes in behavioural performance, as observed by modulated mind-wandering propensity. Despite this, the study from Boayue, Csifcsák, Kreis, et al., (2020) is yet to be replicated, and it is unclear whether the effects are attributable to the novel task, focal HD-tDCS montage, or a combination of both. Subsequent research contrasting conditions of HD-tDCS and SART with HD-tDCS and FT-RSGT are needed to distinguish the effects of task design and brain state on modulating mind-wandering. Neuroimaging would further allow insight into the neural recruitment engaged during the tasks and any modulations induced by HD-tDCS.

7.4. Future directions

Although the current thesis failed to provide evidence for the ability to modulate self-referential thoughts and related brain networks via tDCS, the literature in the field suggests there may still be promise for this technique. One of the montages found to modulate mind-wandering propensity is dual stimulation of the right IPL and left DLPFC (Kajimura et al., 2016; Kajimura & Nomura, 2015). Here, mind-wandering propensity was reduced when the anode was placed over the right IPL, compared to the cathode, with the return over the left lateral prefrontal cortex. Subsequent research outside of this lab has observed effects that partially corroborate this with cathodal right IPL stimulation increasing mind-wandering compared to sham, with the return over the left DLPFC (Filmer et al., 2021). These results suggest cathodal IPL are driving the effects. However, as the return electrode is placed over the left DLPFC, it is unclear whether stimulation of the right IPL or the left DLPFC is mediating the effects.

In Chapters 3-5, we provide Bayesian support for the lack of an effect of tDCS on mind-wandering when stimulating the right IPL and DLPFC independently. Therefore, dual stimulation of these regions may be necessary to induce consistent effects across individuals by simultaneously modulating the ECN and DMN. This may be driven by the classic notion of anticorrelations between these networks (Fox et al., 2005) with anodal (excitatory) stimulation of one network, coupled with cathodal (inhibitory) stimulation of the other driving the shift in attention. Based on the effective connectivity at baseline in Chapter 4, the right IPL displayed a predominantly inhibitory tone over the DMN, and the left DLPFC displayed an inhibitory tone over the ECN. Anodal stimulation of the left DLPFC would increase the inhibitory tone over the ECN, whilst cathodal stimulation of the right IPL would reduce the inhibition of the DMN from the right IPL. Together, this may allow for increased activation in the DMN, resulting in greater mind-wandering (as reported by this montage in all three studies, compared to the reverse (Filmer et al., 2021; Kajimura et al., 2016; Kajimura & Nomura, 2015)). Corroborating this, Kajimura et al., (2016) observed increased coupling between the MPFC and PCC following cathodal right IPL stimulation (return over the left DLPFC).

Conversely, the effects may be being driven solely by modulations to the DMN. Given the placement of the prefrontal electrode, and based on visual inspection of **Figure 1 B)**, current using bipolar montages over the prefrontal cortex will likely spread through the MPFC (Csifcsák et al., 2018). Therefore, the dual IPL/DLPFC montage could be inhibiting posterior regions of the DMN whilst simultaneously exciting prefrontal DMN regions (or vice versa), which may account for the modulations in mind-wandering. It is currently unclear which would be driving the effects. Furthermore, both labs that reported effects of the dual montage differed in the task they employed and the current intensity used. Kajimura and colleagues used the flanker task with 1.5mA stimulation, whereas Filmer and colleagues used the SART and observed effects at both 1 and 2mA. Therefore, replicating these studies with conditions employing both tasks and varying current intensities that including neuroimaging would help establish the most optimum protocol and provide insight into the neural basis of the observed effects of tDCS.

Opposing this polarity specific view, recent research using anodal 2mA HD-tDCS over the left DLPFC in conjunction with a novel task successfully reduced mind-wandering propensity compared to sham (Boayue, Csifcsák, Kreis, et al., 2020). The results contradict the direction of effects observed in the seminal research by Axelrod et al., (2015), that found increased mind-wandering after anodal left DLPFC stimulation; however, several methodological differences may account for this, including use of the novel FT-RSGT, change in return electrode position, and increased focality. Regarding the latter, in a computational current modelling study, Boayue et al., (2018) found that bipolar DLPFC montage resulted in higher intensity E-fields which was widespread beyond the target and demonstrated strong interindividual variability. Conversely, the HD-tDCS (4x1 electrodes) montage was more localised with a weaker E-field when comparing the same intensity (1mA) but stronger when using 2mA, with more focal excitatory effects found in the left DLPFC (Boayue et al., 2018). Corroborating the results from Boayue, Csifcsák, Kreis, et al., (2020) and suggesting a polarity-specific directional effect, additional research outside the lab observed increased mind-wandering using the bipolar montage with the cathode placed over the DLPFC (Filmer et al., 2019). However, it is worth noting that this study used the SART with the return electrode placed over the right orbitofrontal cortex.

As it stands, the research suggests montage-specific effects on modulating mind-wandering with effects reversed when the return electrode is placed over the parietal cortex. Specifically, solo anodal HD-tDCS of the left DLPFC reduced mind-wandering (Boayue, Csifcsák, Kreis, et al., 2020), and cathodal tDCS of the left DLPFC (return over orbitofrontal cortex) increased mind-wandering. Whereas, when the return electrode was placed over the right IPL the effect of polarity was reversed with anodal left DLPFC stimulation increasing mind-wandering compared to cathodal left DLPFC (Kajimura et al., 2016; Kajimura & Nomura, 2015) and sham (Filmer et al., 2019). The reversal in the direction of the effects of polarity may be attributed to significantly different current densities produced by the varying montages (see **Figure 1**). Stimulation using the IPL as a return would induce much more widespread current distribution across a number of regions, and the direct stimulation of the DMN (via the IPL) may account for the reversal in effects on mind-wandering propensity. However, the exact interplay between montage and behavioural effects remains unclear due to the numerous differences between the studies, including dosage, task, and brain state during stimulation. Pre-registered research aimed to replicate these studies, with large samples sizes and the inclusion of multimodal neuroimaging techniques, such as fMRI and EEG, is likely to help provide further insight into the neural basis of these effects.

7.5. General discussion of Chapter 6

Although the work carried out in Chapter 6 resulted from a COVID-19 mitigation plan and is not specifically related to the main work of the thesis, several links that tie the bodies of work together. Overall, we provide partial support for the mesocircuit hypothesis, observing reduced coupling in the AFM in PDOC, resulting in loss of inhibition to the DMN. Disruptions in the connectivity within the DMN are known to characterise PDOC, particularly given the networks established contributions to conscious awareness (Bodien et al., 2017). Perhaps these dysfunctions explain the lack of self-awareness in PDOC but do not reveal anything about what is experienced or disrupted in relation to awareness of the environment. Our earlier work in Chapters 3 and 4 attempted to separate internal and external awareness in our thought-probes to further understand the relationship between these two types of awareness and the underlying networks related to each. However, we were unable to delineate the specific network activation related to either nor manipulate them with tDCS. Additionally, a growing body of literature has recently investigated the effects of tDCS on PDOC (Aloi et al., 2021). Several studies have targeted the DLPFC with anodal stimulation and found short-term clinical improvements in CRS-R scores (Thibaut et al., 2014, 2017; Y. Zhang et al., 2017). These improvements have been attributed to tDCS modulating the DMN, allowing for increased covert awareness detected during behavioural assessments. However, in Chapter 5, we found no effect of tDCS on the functional nor effective connectivity of the DMN after stimulating DLPFC, which leaves the mechanisms of tDCS in PDOC unclear. Our results in Chapter 6 revealed disruptions in the DMN only concerning the self-connections of midline regions and not between regions in the network as was predicted from functional connectivity studies (Cauda et al., 2009; Silva et al., 2015; Soddu et al., 2011; Vanhaudenhuyse et al., 2010). Furthermore, the relationship between the DMN and AFM was opposite to what was predicted (Schiff, 2010), with healthy controls showing inhibitory tones from the AFM to the DMN, which was lost in PDOC. Therefore, in terms of the effects of tDCS, exciting the DMN with anodal stimulation may have opposing effects in patients, again questioning the mechanisms of tDCS that characterise improvements in PDOC.

As previously stated, the structural connectivity between the DMN and AFM is reduced in PDOC (Lant et al., 2016). Based on the work in Chapter 6, we observed healthy controls typically demonstrate an inhibitory tone from the AFM towards the DMN, which was disrupted in patients. The DMN is core network of the brain connected to multiple cortical networks and has been shown to be altered in varying states of consciousness, including during meditation (Panda et al., 2016). Understanding the neural correlates of consciousness have become a large area of research over recent years, particularly given the advances in neuroimaging techniques. Two of the main, and arguably competing, theories are the information integration theory (IIT) and the global neuronal workspace (GNW). The IIT posits that neural networks supporting consciousness must be highly connected and measures the amount of causally effective information that can be integrated (Tononi et al., 2016). In the GNW model, conscious perception of sensory stimuli results from long-range cortico-cortico axons (specifically, across prefrontal and parietal cortices), compared to when stimuli is not consciously perceived which elicits activation only in the associated primary sensory cortices (Dehaene & Changeux, 2011). The integration of the DMN is integral to the GNW model and our results may provide neurological support for the model given inhibitory projections from the sub-cortex to the DMN are disrupted in PDOC, which may reduce the ability to integrate and project cortico-cortico connections, therefore disrupting conscious activity.

PDOC patients present several practical and methodological challenges that should be incorporated into data collection and analysis pipelines. For example, minimising movement with appropriate head padding when placed in the scanner. The numerous brain injuries and lesions observed in PDOC patients makes using standard brain normalisation methods difficult, which is one of the reasons we visually located each ROI across all subjects. Research, particularly when focussing on structural connectivity, may choose to omit regions with large lesions or mask out the injured tissue. However, previous research employing DCM on PDOC patients chose to include all regions in their analysis so that the DCMs could be compared across all subjects (Crone et al., 2015). Extracting a time series that includes lesions would create more noise in the BOLD signal used for further analysis. For this reason, we ensured there were no macrostructural damage within each of the ROIs across all subjects. However, we acknowledge that we cannot rule out the influence of some minor injuries.

An additional issue is the use of small ROIs, particularly in complex structures, such as the thalamus. Our intention was to capture the activity and connectivity of the medio dorsal thalamus, which is a relatively large region of the thalamus. However, we cannot be certain what was captured within the 3mm spheres. It is therefore possible that, for some patients, the timeseries contributing to the DCM are coming from unrelated thalamic nuclei and would therefore be introducing noise. We acknowledge this as a limitation due to the lack of spatial specificity. Furthermore, due to the lack of spatial specificity, we did not include the globus pallidus into our DCMs. Not including the globus pallidus resulted in an inability to disentangle connections in the DCM that go from the thalamus to globus pallidus to the cortex (and vice versa) compared to those that go direct from the thalamus to the cortex. Across the DCM framework, none of the connections can be interpreted as direct, therefore, there is always the possibility that connections are mediated by a third region that is not included in the model. In cases where the two routes (direct and indirect), have competing effects, this would be problematic. Most of what we are capturing in our DCMs is likely driven by the indirect route (through the missing globus pallidus), however, we acknowledge this as a limitation and future studies with higher spatial specificity may incorporate the globus pallidus to corroborate this.

7.6. Conclusions

Overall, this thesis aimed to further understand the neural bases of mind-wandering, and the casual role tDCS plays in modulating it. Throughout this research, we consistently demonstrate evidence for the lack of an effect of tDCS on mind-wandering propensity and underlying brain activation and connectivity. Specifically, we observed support for the null effect of tDCS for right IPL stimulation and left DLPFC stimulation montages. The relationship between neural activity and cognitive function is extremely complicated, and operationalising this cognitive function is an ongoing challenge for the field. Insufficient and insensitive behavioural measures can be confounded by task design and difficulty (Bergmann & Hartwigsen, 2021). Additionally, numerous confounds (such as distribution of current and electrode placement) make it increasingly difficult to infer causality and observe the true effects of non-invasive brain stimulation. The results from this thesis add value to the growing literature within the field, demonstrating the issues of replicability and highlight the need for further research in this area. The work in this thesis also provides a methodological framework combining tDCS and fMRI to measure changes in underlying brain connectivity. Specifically, we demonstrate an ability to characterise dynamic functional network connectivity and effective connectivity in key intrinsic networks associated with mind-wandering. This technique can be used going forward to establish a causal link between any observed behavioural effects of tDCS and changes in connectivity.

In additional work, the findings from Chapter 6 revealed disruptions in the effective connectivity within and between the DMN and AFM in PDOC patients. The results provide support for the mesocircuit model of consciousness and add further insight into the neural basis of PDOC.

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