Neuromodulation of executive vigilance via transcranial direct current stimulation

Klara Hemmerich

UNIVERSIDAD DE GRANADA

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PhD Candidate

Klara Hemmerich

Supervisors

Juan Lupiáñez Castillo
Elisa Martín-Arévalo

Departamento de Psicología Experimental
Centro de Investigación Mente Cerebro y Comportamiento (CIMCYC)

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> *„Wenn wir die Menschen nehmen wie sie sind, so machen wir sie schlechter. Wenn wir sie behandeln, als wären sie, was sie sein sollten, so bringen wir sie dahin, wohin sie zu bringen sind.“*
>
> *“Trata a un ser humano tal como es, y seguirá siendo lo que es; trátalo como puede y debe ser, y se convertirá en lo que puede y debe ser”*
>
> — Johann Wolfgang von Goethe

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Alphabetical list of acronyms

ABI	Acquired Brain Injury
AeCi	Anodal-excitation Cathodal-inhibition
A	Anode
aCC	Anterior Cingulate Cortex
aI	Anterior Insula
aI/fO	Anterior Insula/Frontal Operculum
aPFC	Anterior Prefrontal Frontal Cortex
AE	Aperiodic Exponent
AO	Aperiodic Offset
AV	Arousal Vigilance
ADHD	Attention Deficit Hyperactivity Disorder
ANTI-Vea	Attentional Networks Test for Interactions and Vigilance- executive and arousal components
BW	Bandwith
BF	Bayes Factor
BOLD	Blood-Oxygen-Level-Dependent
C	Cathode
CEN	Central Executive Network
CF	Centre Frequency
CRT	Choice Reaction Task
CI	Confidence Interval
CTET	Continous Temporal Expectancy Task
CPT	Continuous Performance Test
CSA	Contralateral Supraorbital Area
CC	Corpus Callosum
DMN	Default Mode Network
DWI	Diffusion Weighted Imaging
DST	Digit Symbol Test
DAN	Dorsal Attention Network
dFC	Dorsal Frontal Cortex
DLPF-C	Dorsolateral Pefrontal-Caudate (tract)
DLPFC	Dorsolateral Prefrontal Cortex
DLPFC/dlPFC	Dorsolateral Prefrontal Cortex

Acronyms

DB	Double-Blind
ET	Echo Time
EEG	Electroencephalography
EI	Engagement Index
EFT	Ericksen Flanker Task
ERP	Event-Related Potential
EN	Excecutive Network
E/I	Excitation/Inhibition
EV	Executive Vigilance
FA	False Alarms
FFT	Fast Fourier Transform
FD	Fibre Density
FoV	Field of View
FOOOF	Fitting-Oscillations and One Over F
FA	Fractional Anisotropy
FEF	Frontal Eye Fields
FPN	Frontoparietal Network
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Amminobutyric Acid
HD	High-Definition
HD-tDCS	High-Definition Transcranial Direct Current Stimulation
HF-rTMS	High-Frequency Repeated TMS
HMOA	Hindrance Modulated Orientational Anisotropy
ICA	Independent Component Analysis
IFC	Inferior Frontal Cortex
IFOF	Inferior Fronto-Occipital Fasciculus
IPL	Inferior Parietal Lobe
IPS	Inferior Parietal Sulcus
IC	Inhibitory Control
ITPC	Inter-Trial Clustering of Theta
LC	Locus Coeruleus
LTD	Long-Term Depression
LTP	Long-Term Potentiation
LLCI	Lower Limit of the Confidence Interval
MCT	Mackworth Clock Test

MRI	Magnetic Resonance Imaging
mCC	Midcingulate cortex
mlPFC	Midlateral Prefrontal Cortex
MEP	Motor-Evoqued Potential
MOT	Multiple Object Tracking
NLP	Natural Language Processing
NMA	Network Meta-Analysis
NIBS	Non-Invasive Brain Stimulation
NE	Norepinephrine
NR	Not Reported
NS	Not Specified
PET	Positron Emission Tomography
pCC	Posterior cingulate cortex
PLIC	Posterior Limb of the Internal Capsule
PPC/rPPC	Posterior Parietal Cortex / right Posterior Parietal Cortex
PSD	Power Spectral Density
PW	Power
Pre-SMA	Presupplementary motor area
PVT	Psychomotor Vigilance Test
RVIP	Rapid Visual Information Processing
RVP	Rapid Visual Processing
RT(s)	Reaction Time(s)
rTMS	Repetitive Transcranial Magnetic Stimulation
rs-EEG	Resting-State EEG
SN	Salience Network
SB	Single-Blind
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SST	Stop Signal Task
SCWT	Stroop Color-Word Test
SLF	Superior Longitudinal Fasciculus
SPL	Superior Parietal Lobe
SPL	Superior Parietal Lobe
STG	Superior Temporal Gyrus

Acronyms

SUCRA	Surface Under the Cumulative Ranking
SART	Sustained Attention to Response Task
TLI	Task Load Index
TPJ	Temporoparietal Junction
TOT	Time-On-Task
TMT	Trail-Making Test
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
tRNS	Transcranial Random Noise Stimulation
TBI	Traumatic Brain Injury
ULCI	Upper Limit of the Confidence Interval
VFC	Ventral Frontal Cortex
vPMC	Ventral Premotor Cortex
vmPFC	Ventromedial Prefrontal Cortex
WCST	Winsconsin Card Sorting Test

Abstracts

Abstract

Many everyday tasks and working environments rely on our ability to keep our attention focused for prolonged periods of time. However, as we have all experienced, this ability is effortful and cannot be sustained indefinitely. Inevitably, as time goes by, our performance becomes less sharp and more error-prone, as our mind either falters in the face of demands it cannot sustain, or it slowly disengages from the task at hand, wandering elsewhere. This phenomenon is known as vigilance decrement.

This thesis begins by disentangling a working definition of the concept of vigilance, as its use across different disciplines, and its fuzzy description within cognitive psychology render it hard to grasp. By distinguishing vigilance from other processes such as arousal, alertness, and sustained attention, we land on the following working definition: *"the ability to monitor the environment and detect rare but critical stimuli".*

Further refining this definition, the present thesis accounts for a recent conceptualization of vigilance as a two-component process: (i) executive vigilance (EV), defined as the ability to monitor the environment to detect specific infrequent but critical signals, requiring the exertion of control to decide whether a response has to be emitted or not (Luna et al., 2018a); (ii) arousal vigilance (AV), on the other hand, defined as the general maintenance of a basic state of activation to emit fast and relatively automatic responses to those rare but critical stimuli requiring minimal top-down control (Luna et al., 2018a). A further aspect of relevance for the present thesis is the specific sensitivity of the EV decrement to the cognitive demands required by the task (Luna, Barttfeld, et al., 2022).

The inevitable decrement of vigilance over time will lead to consequences that can range from the trivial, such as missing the right exit on the motorway while driving, to the catastrophic, such as a fatal accident (Wundersitz, 2019). In addition to these everyday or work-related consequences, lesions or alterations in the development of the brain can reduce the capacity for exerting vigilance. This motivates the main aim of the present thesis: to study the potential of transcranial direct current

stimulation (tDCS) in mitigating this vigilance decrement. By applying a constant electrical current across the scalp, tDCS can influence the excitability of underlying neuronal populations. This modulation of neuronal activity, in turn, can modulate cognitive functions, including attention and vigilance (Coffman et al., 2014a). A review of the existing literature on the application of tDCS to attention deficits in clinical populations with attention deficit hyperactivity disorder (ADHD) or acquired brain injury (ABI), and to vigilance in healthy populations, shows that the large heterogeneity of tDCS parameters and outcome measures does not yet provide a clear picture of the efficacy of tDCS in mitigating vigilance decrements.

The present thesis aims to further explore the potential of applying anodal high-definition tDCS (HD-tDCS) over the right posterior parietal cortex (rPPC) to mitigate the EV decrement (Luna et al., 2020), by exploring the impact of differing cognitive demands as well as underlying neuroimaging data as outcome predictors.

In a first study, participants (N = 60) completed the ANTI-Vea task while receiving either anodal or sham HD-tDCS over the rPPC. Electrophysiological (EEG) recordings were completed before and after stimulation. Anodal HD-tDCS specifically mitigated executive vigilance (EV) and reduced the increment of alpha power with time-on-task, while further increasing the increment of gamma power. Through a new proposed index of $Alpha_{parietal}/Gamma_{frontal}$ a further dissociation is observed. The increment of this $Alpha_{parietal}/Gamma_{frontal}$ Index with time-on-task was associated with a steeper EV decrement in the sham group, which was abolished by anodal HD-tDCS.

In a second study, participants (N = 120) completed a modified ANTI-Vea task (single or dual task) while receiving either anodal or sham HD-tDCS over the rPPC. Joint analyses of this data and data from prior studies performing a triple task (combined N = 240, Study I and Luna et al. 2020) were completed. We observed that against the mitigated vigilance decrement observed in the triple task condition (standard ANTI-Vea) with anodal HD-tDCS, both the single and dual load conditions showed

significant EV decrements that were not affected by the application of HD-tDCS.

In a third study, EEG data collected in Studies I and II (N = 180) was analysed more in-depth, by parametrizing the EEG power spectra to disentangle periodic (oscillatory) from aperiodic (non-oscillatory, namely aperiodic exponent and offset) components. HD-tDCS led to a decrement of the aperiodic exponent extracted from the 30-45 Hz frequency range, suggesting an increased excitation/inhibition (E/I) balance with active stimulation. This increment of the E/I balance was associated with a mitigated EV decrement in the high-demand (triple) task and an exacerbated EV decrement in the low-demand (single) task. While these results require further research as the results were only observed considering a directional hypothesis and other interactions may obscure the effect, they illustrate a potential mechanistic explanation of the cognitive-load dependent effect.

A last empirical chapter contains a report with an initial exploration of the potential influence of microstructural white matter connectivity on the effect of the HD-tDCS protocol on the EV decrement. We analysed diffusion-weighted imaging (DWI) data collected from participants (N = 172) in Studies I and II (triple, dual, or single tasks combined with either anodal or sham HD-tDCS over the rPPC). The preliminary findings suggest the right third branch of the superior longitudinal fasciculus (SLF), the left second branch of the SLF, the Cingulum, and the Splenium of the Corpus Callosum as potentially relevant structures for future causal analyses, such as moderation analyses.

This thesis contributes to the understanding of the vigilance decrement and the potential of tDCS to mitigate it, highlighting the importance of considering cognitive load and individual differences in neurophysiological responses for a more nuanced understanding of its effects. Specifically, the results from this thesis highlight: (i) the need for replication studies and the integration of neurophysiological measures as a means to potentially predict stimulation outcomes, (ii) the need to consider the task used as an outcome measure due to the different brain states it will induce, (iii) the importance of considering the underlying brain state in interaction with the

effects of tDCS to better understand its mechanisms of action, and whilst no definitive predictions can be made yet, (iv) it offers a promising first look at the potential of predicting tDCS outcomes from pre-intervention structural neuroimaging data. With future research, the results of this thesis can aid in further exploring this interesting intersection of neuromodulation, vigilance, and neurophysiology, which may help design more precise future interventions to mitigate the inevitable decrement of vigilance over time.

Resumen

Numerosas tareas cotidianas y entornos de trabajo dependen de nuestra capacidad para mantener nuestra atención durante períodos prolongados. Sin embargo, como cualquiera ha podido experimentar, esta capacidad supone un considerable esfuerzo y no puede mantenerse indefinidamente. Inevitablemente, con el paso del tiempo, nos volvemos menos ágiles y aumenta nuestra propensión a cometer errores, ya que nuestra mente flaquea ante exigencias que no puede sostener, o bien se desengancha lentamente de la tarea que tenemos entre manos, desviándose hacia otra parte. Este fenómeno se conoce como decremento en vigilancia.

Esta tesis comienza desentrañando una definición de trabajo del concepto de vigilancia, ya que su uso en diferentes disciplinas y su descripción difusa dentro de la psicología cognitiva hacen que sea difícil de delimitar. Al distinguir la vigilancia de otros procesos como la activación, la alerta y la atención sostenida, llegamos a la siguiente definición de trabajo: "la capacidad de monitorizar el entorno y detectar estímulos poco frecuentes pero críticos".

Refinando aún más esta definición, la presente tesis contempla una reciente conceptualización de la vigilancia como un proceso formado por dos componentes: (i) la vigilancia ejecutiva (VE), definida como la capacidad de monitorizar el entorno para detectar señales específicas poco frecuentes pero críticas, que requieren el ejercicio de control para decidir si hay que emitir una respuesta o no (Luna et al., 2018); (ii) la vigilancia del arousal (AV), definida como el mantenimiento general de un estado básico de activación para emitir respuestas rápidas y relativamente automáticas ante aquellos estímulos infrecuentes pero críticos que requieren un mínimo control descendente (Luna et al., 2018). Otro aspecto de relevancia para la presente tesis es la sensibilidad específica del decremento de la VE a las demandas cognitivas requeridas por la tarea (Luna et al., 2022).

El inevitable decremento en vigilancia con el paso del tiempo acarrea consecuencias que abarcan desde lo trivial, como pasarse la salida correcta de la autopista mientras se está al volante, hasta lo catastrófico, como un

accidente fatal (Wundersitz, 2019). Además de estas consecuencias cotidianas o laborales, las lesiones o alteraciones en el desarrollo del cerebro pueden reducir la capacidad para ejercer la vigilancia. Esto motiva el objetivo principal de la presente tesis: estudiar el potencial de la estimulación transcraneal por corriente directa (tDCS) para mitigar esta disminución de la vigilancia. Mediante la aplicación de una corriente eléctrica constante a través del cuero cabelludo, la tDCS puede influir en la excitabilidad de las poblaciones neuronales subyacentes. Esta modulación de la actividad neuronal, a su vez, puede modular las funciones cognitivas, incluyendo la atención y la vigilancia (Coffman et al., 2014). La presente tesis incluye una revisión de la literatura existente sobre la aplicación de la tDCS a los déficits de atención en poblaciones clínicas como trastorno por déficit de atención con hiperactividad o daño cerebral adquirido, y a la vigilancia en poblaciones sanas. Dicha revisión muestra que la gran heterogeneidad de los parámetros de tDCS y las medidas de impacto aún no proporcionan una imagen clara de la eficacia de la tDCS para mitigar el decremento en vigilancia.

La presente tesis tiene como objetivo explorar más a fondo el potencial de la aplicación de tDCS anodal de alta definición (HD-tDCS) sobre la corteza parietal posterior derecha (rPPC) para mitigar la disminución de EV (Luna et al., 2020), explorando el impacto de las diferentes demandas cognitivas, así como los datos de neuroimagen subyacentes como predictores de resultados.

En un primer estudio, las/los participantes (N = 60) completaron la tarea ANTI-Vea mientras recibían HD-tDCS anodal o sham sobre el rPPC. Se realizaron registros electrofisiológicos (EEG) antes y después de la estimulación. La HD-tDCS anodal mitigó específicamente la vigilancia ejecutiva (EV) y redujo el incremento de la potencia en oscilaciones de la banda alpha con el tiempo en la tarea, mientras que aumentó aún más el incremento de la potencia en gamma. A través de un nuevo índice propuesto de $\text{Alpha}_{\text{parietal}}/\text{Gamma}_{\text{frontal}}$ se observa una mayor disociación. El incremento de este Índice $\text{Alpha}_{\text{parietal}}/\text{Gamma}_{\text{frontal}}$ Index con el tiempo en la tarea se asoció con un decremento en EV más pronunciado en el grupo simulado, que fue abolida por la HD-tDCS anodal.

En un segundo estudio, las/los participantes (N = 120) completaron una tarea ANTI-Vea modificada (tarea simple o doble) mientras recibían HD-tDCS anodal o sham sobre el rPPC. Se realizaron análisis conjuntos de estos datos y de los datos de estudios anteriores que realizaban una tarea triple (N = 240 combinados, Estudio I y Luna et al. 2020). Observamos que frente al decremento en EV observado en la condición de tarea triple (ANTI-Vea estándar) con HD-tDCS anodal, tanto la condición de carga única como la de carga doble mostraron decrementos significativos de la EV que no se vieron afectadas por la aplicación de HD-tDCS.

En un tercer estudio, los datos de EEG recogidos en los Estudios I y II (N = 180) se analizaron en mayor profundidad, parametrizando los espectros de potencia de EEG para separar los componentes periódicos (oscilatorios) de los aperiódicos (no oscilatorios, en concreto el exponente aperiódico y el offset). La HD-tDCS condujo a una disminución del exponente aperiódico extraído del rango de frecuencia de 30-45 Hz, lo que sugiere un aumento del equilibrio excitación/inhibición (E/I) neural con la estimulación activa. Este aumento de E/I se asoció con un decremento en EV mitigado en la tarea de alta demanda (triple) y una decremento en EV exacerbado en la tarea de baja demanda (simple). Aunque estos resultados requieren más investigación, ya que sólo se observaron considerando una hipótesis direccional y otras interacciones potencialmente pudieron enmascaran el efecto, ilustran una posible explicación mecanicista del efecto dependiente de la carga cognitiva.

Un último capítulo empírico recoge un informe la exploración inicial de la influencia potencial de la conectividad microestructural de la sustancia blanca cerebral sobre el efecto del protocolo de HD-tDCS sobre el decremento en EV. Analizamos los datos de imágenes ponderadas por difusión (DWI) recogidas de la muestra (N = 172) de los Estudios I y II (tareas triples, duales, y simples combinadas con HD-tDCS anodal o sham sobre el rPPC). Los resultados preliminares sugieren que la tercera rama del fascículo longitudinal superior (SLF) derecho, la segunda rama del SLF izquierdo, el cíngulo y el esplenio del cuerpo calloso son estructuras potencialmente relevantes para futuros análisis causales, como los análisis de moderación.

Esta tesis contribuye a la comprensión del decremento en vigilancia y el potencial de la tDCS para mitigarla, destacando la importancia de considerar la carga cognitiva y las diferencias individuales en las respuestas neurofisiológicas para una comprensión más matizada de sus efectos. En concreto, los resultados de esta tesis destacan: (i) la necesidad de estudios de replicación y la integración de medidas neurofisiológicas como medio para potencialmente porder predecir los resultados de la estimulación, (ii) la necesidad de considerar la tarea utilizada como medida de impacto debido a los diferentes estados cerebrales que inducirá, (iii) la importancia de considerar el estado cerebral subyacente en interacción con los efectos de la tDCS para comprender mejor sus mecanismos de acción, y aunque todavía no se pueden hacer predicciones definitivas, (iv) ofrece un primer vistazo prometedor al potencial de predecir los resultados de la tDCS a partir de datos de neuroimagen estructural registrados antes de la intervención. Con investigaciones futuras, los resultados de esta tesis pueden ayudar a explorar más a fondo esta interesante intersección de neuromodulación, vigilancia y neurofisiología, que puede ayudar a diseñar intervenciones futuras más precisas para mitigar el inevitable decremento en vigilancia con el tiempo.

PART I
General Introduction

Chapter 1

An Inevitable Slope: Characterizing the Vigilance Decrement

Abstract

The vigilance decrement refers to the gradual loss of the ability to monitor the environment and detect rare but critical stimuli as time progresses. This decrement inevitably manifests in many everyday scenarios, work environments, and as a consequence of brain damage or developmental disorders. This chapter highlights a working definition of vigilance for the present thesis, differentiating it from other related concepts, such as arousal, alertness, or sustained attention, as well as from definitions from other fields of knowledge. To better characterize the vigilance decrement, this chapter discusses different factors that alter the time-course or magnitude of the vigilance decrement, the different theories that co-exist to explain its occurrence, and the neural correlates that lay at its base.

"Let it be tonight,
For now they are oppressed with travel,
They will not, nor cannot, use such vigilance
As when they are fresh."

— William A. Shakespeare
The Tempest, Act 3, Scene 3

This observation by Shakespeare, albeit in a dramatic context, underscores a key attentional phenomenon: the vigilance decrement. Much like King Alonso of Naples and Gonzalo, we all have felt the inevitable pull of the vigilance decrement in our everyday interactions with the world. For instance, during a lecture or conference, where we are already familiar with the broader content being presented, we may notice that our ability to engage with new findings and information diminishes over time. Later on, while driving home, we may miss exits or turns, overlook a pedestrian about to cross the street, or fail to notice that a traffic light has turned red in time. While the consequences of the vigilance decrement might go mostly unnoticed in the first scenario, they can be dire in the second one. In fact, inattention causes almost a third of fatal road accidents (Wundersitz, 2019). Human errors related to attentional failures are reported in other realms as well, including railway (Edkins & Pollock, 1997) and aviation accidents (Kharoufah et al., 2018), missed threats at security screenings (Krüger & Suchan, 2015; Meuter & Lacherez, 2016; Näsholm et al., 2014), or medical errors (Barger et al., 2006; Caruso, 2014). Moreover, developmental or lesion-induced alterations in brain functioning can impair the ability to maintain vigilance, hindering a correct interaction with the environment and the proper functioning of higher-order cognitive processes (Fish et al., 2017; Zimmermann & Leclercq, 2002).

Given these real-life and clinical consequences, it is imperative to further study the vigilance decrement to better understand its causes and determining factors, as well as explore potential ways to mitigate it. The potential of neuromodulation techniques such as transcranial direct current stimulation (tDCS) in clinical and healthy populations will be reviewed in **Chapters 3** and **4**, respectively. However, before delving into this possibility, this chapter will first briefly outline the historical origin of vigilance and its decrement, examine the existing theories that explain it and the factors that

can modulate it, and identify the neural correlates associated with the phenomenon.

Brief history of vigilance and its decrement

The term vigilance stems from the Latin *vigilāre*, referring to being awake, watchful, or alert. The diverse meanings attributed to the concept's root may actually foreshadow the wide range of attributes it still holds today. The first conception of relevance stems from the medical field, where it was not considered a cognitive skill nor attributed to consciousness (Klösch et al., 2022), but rather to the organism's ability to reorganize itself in the process of restoration from damage or trauma (Head, 1923). Sir Henry Head's conceptualization 100 years ago viewed vigilance as signs of responsiveness from the organism in its recuperation process (e.g., reflex upon stimulation). Despite this more medical conceptualization, Head's argument that *"when vigilance is high, the body is more prepared to respond to an effective stimulus with a more or less appropriate reaction"* (Head, 1923), has carried over into the latter conceptualization of arousal, which plays an important role in vigilance.

Twenty years later, Normal Mackworth refined the concept of vigilance in terms more relevant for cognition as a *"psychological readiness to perceive and respond, a process which, unlike attention, need not necessarily be consciously experienced"* (Mackworth, 1948). Mackworth was commissioned in 1943 to study why operators from the British Air Force missed crucial detections of German submarines in their airborne radars. He examined the working conditions of these operators and then replicated the work environment's characteristics in a laboratory setting to systematically encompass the phenomenon at hand. For this purpose, the Mackworth Clock Test (MCT) was designed, imitating the sweeping radial motion of the radars: a fine line akin to a clock hand was projected onto a white background in a monotone setting. Observers had to keep their attention on the handle to detect the occurrence of an infrequent signal: a double jump of the clock handle. Through this experiment, the vigilance decrement was characterized by its now distinctive curve: during a 2-hour watch, the "operators" would face a steep drop in their detection accuracy in the first 30 minutes, followed by a more steady decline (Mackworth, 1948).

Since Mackworth's first experimental grasp of the vigilance decrement, the phenomenon has received heightened interest, mobilizing extensive efforts to further its understanding. However, the current literature still lacks a firm grasp on a unified time-course of the vigilance decrement, a unified theory on why it occurs, a clear unitary definition within attention taxonomy, or unequivocal neural correlates. Nonetheless, the following sections will delve into what we know about these aspects up to now.

Disentangling a working definition of vigilance

A challenge imposed by the concept of vigilance is its varied meanings across different fields. Even within experimental or cognitive psychology, its meaning is not unified. In neurophysiology or psychiatry, the meaning of vigilance is more tied in with natural or pathological fluctuations of arousal. Neurophysiologists place vigilance as an intermediate state within the sleep-wake cycle, which can range from hypervigilance (over-excited), to vigilant (relaxed awake state), to a drowsy or hypo-vigilant, and a sub-vigilant state that transitions into sleep (Klösch et al., 2022; Oken et al., 2006). Psychiatrists refer to abnormal states of vigilance: hypervigilance as a heightened attentiveness and response towards the environment, that may lead to perceiving innocuous stimuli as threatening and is often observed as a clinical symptom of post-traumatic stress disorder (American Psychiatric Association., 2013; Oken et al., 2006); and on the other extreme, hypovigilance as dampened responsiveness towards the environment, observable in depression (Weinberg & Harper, 1993). While some of the research overlaps with the concept of vigilance used in the present thesis, it is crucial to define the concept accurately—not as an immutable truth, but as a working definition specific to this thesis. Moreover, it is important to distinguish vigilance from other concepts, that are often used interchangeably, namely arousal, alertness, and sustained attention.

A first broad distinction can be made in terms of a component of *direction*, associated with attention, i.e., cortical activity that is directed to a specific stimulus or purpose (van Schie et al., 2021). This distinction helps to categorize vigilance and sustained attention into processes requiring a direction, and thus, specific to attentional functioning, whilst differentiating them from arousal and alertness as processes attributed to cortical activity

without a specific direction. Regarding the two directional processes, vigilance and sustained attention are often used interchangeably (Klösch et al., 2022; Oken et al., 2006; Sarter et al., 2001), as both require the focus of attention on a task over a prolonged period. Therefore, one can distinguish between the two in terms of the *intensity* of information processing required (van Zomeren & Brouwer, 1994; Zimmermann & Leclercq, 2002): whereas vigilance would refer to the detection of small and infrequent changes in the environment, sustained attention would require more active and ongoing processing towards a broader set of stimuli, as schematically depicted in **Fig. 1.1** (Singh-Curry & Husain, 2009). For example, vigilance, on the lower end of the intensity continuum, might involve driving down a long, straight highway with minimal traffic, where responding to external stimuli is rare (e.g., adjusting speed in accordance with a speed-limit change or braking if noticing cars ahead braking). On the opposite end, sustained attention, exemplified by driving through city traffic at rush hour, requires constant attention to a rapidly changing and stimulating environment (e.g., traffic lights, pedestrians about to cross the street, other cars, etc.).

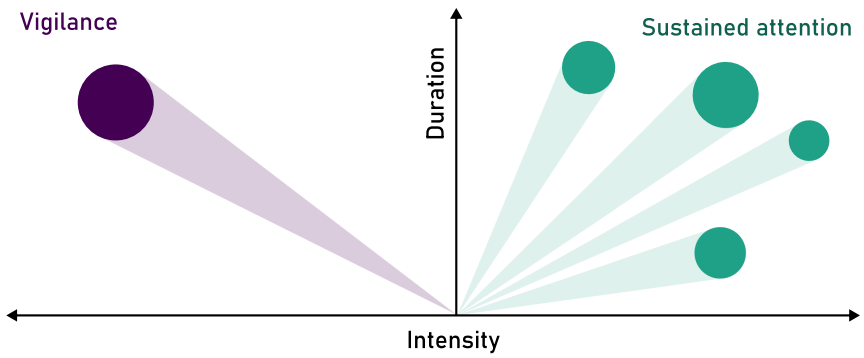

Figure 1.1. Vigilance and sustained attention share that they both have a focus or direction toward a specific stimulus but are distinct in terms of the intensity of said focus.

Other phenomena that overlap with the definition of vigilance but do not require a focus in a specific direction—arousal and alertness—can also be differentiated in a more nuanced way. Arousal can be understood as an overall physiological or psychological state of being awake or reactive to the environment, more in line with Head's original concept of vigilance (Head, 1923). It encompasses different levels of consciousness, from drowsiness or hypo-arousal to the opposite extreme of hyper-arousal (Aston-Jones &

Cohen, 2005; Klösch et al., 2022; Unsworth & Robison, 2017). Arousal can be considered as a pre-requisite for adequate cognitive processing (Aston-Jones & Cohen, 2005), and specifically for vigilance or sustained attention performance (Esterman & Rothlein, 2019). The monitoring required by vigilance tasks requires a certain level of cortical activation that depends on arousal (Sarter et al., 2001). The effects of arousal on these attentional processes are modulated by the effects of norepinephrine (NE) released by the locus coeruleus (LC): as low or high locus coeruleus activity is associated with poor task performance, either due to low task engagement (hypo-arousal) or hyper-arousal, respectively (Esterman & Rothlein, 2019). Thus, as depicted in **Fig. 1.2**, arousal can be considered as a filter that allows the input of adequate levels of task-relevant and task-irrelevant information.

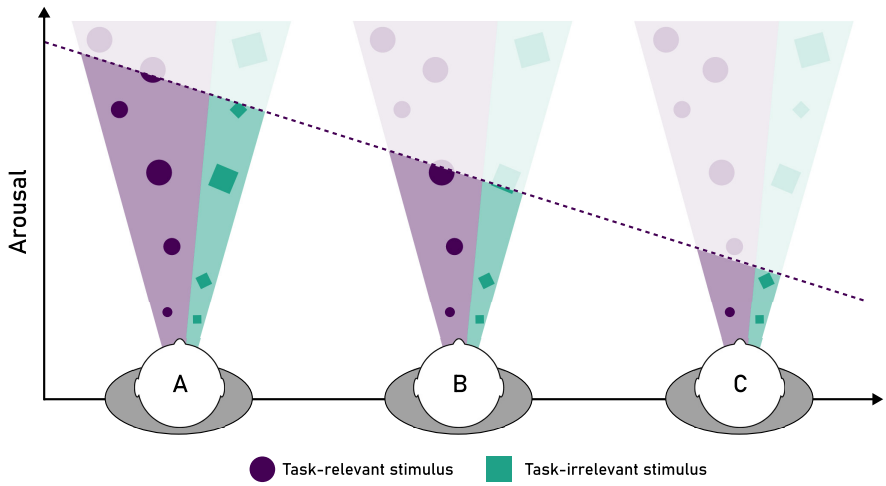

Fig. 1.2. Arousal, understood as a general level of cortical activation can lead to suboptimal inputs of information when activation levels are too high (hyperarousal, person A), or too low (hypoarousal, person C). With intermediate levels, the input of information is ideal (person B). Adapted from Esterman & Rothlein (2019).

Alertness, on the other hand, refers more specifically to the level of responsiveness to external stimuli. Therefore, it could be considered a specific state of optimal arousal that allows adequate sensitivity to incoming stimuli (Posner, 2008). Thus, it is also not linked to the duration, direction, or intensity aspects associated with vigilance, as it still reflects a more general state of preparation. Alertness has additionally been subdivided into a tonic component, referred to slow changes associated with circadian

rhythms (Posner, 2008; Sturm & Willmes, 2001), and a phasic component, which alludes to quick changes in response to specific environmental or internal changes (Petersen & Posner, 2012; Sturm & Willmes, 2001). While tonic alertness has sometimes been equated to vigilance (Posner, 2008), they would differ in the lack of direction attributed to the first concept.

Considering the ample discrepancies in the literature, the following definition of vigilance will be used from now on in the present text and underlying the presented studies and their discussion: **the ability to monitor the environment and detect rare but critical stimuli**. Nonetheless, please note that there might be a mismatch between the term used here and the cited literature for the discussion of neural correlates and applications of tDCS to modulate vigilance. The selection and discussion of studies will be made based on the conceptual overlap of the definition provided by the authors or the tasks used with the present definition rather than the terms employed in the studies.

Inevitable, but why? Theories on the vigilance decrement

The vigilance decrement can occur due to a heterogeneous set of causes that have been grouped into different theories, either attributing the vigilance to an extenuation of resources (overload) or to the task's monotony (underload). We will briefly discuss these theories and other more integrative approaches that have surfaced more recently.

Overload theories: resource-depletion account

Although the tasks and contexts wherein the vigilance decrement is observed are generally not very eventful or of apparent demand (as discussed in relation to the *intensity* component in the prior sections), they are by far not easy, as also evidenced by the above-outlined real-life consequences of the vigilance decrement. Overload theories posit that the combination of a sparse display with a highly demanding discrimination task may be a source of stress (Dillard et al., 2019; Hancock & Warm, 1989; Szalma et al., 2004; Warm et al., 2008a). This demand would soon give rise to the exhaustion of available cognitive resources, explaining the appearance of attentional lapses that constitute the vigilance

decrement (Grier et al., 2003; Warm et al., 2008a). This theory has been tested showing that with increasing task demands, a greater vigilance decrement is observed (Epling et al., 2016; Head & Helton, 2014; Smit et al., 2004). Furthermore, this effect seems to be aggravated by sleep deprivation (Chua et al., 2017), where available resources would be already diminished.

Underload theories: mindlessness and mind-wandering accounts

On the other hand, other accounts argue that the monotonous nature of vigilance tasks is mostly associated with boredom (Danckert & Merrifield, 2018; Yakobi et al., 2021), which leads to a gradual withdrawal from active or engaged task execution, towards a mindless execution of the task (Manly, 1999; I. H. Robertson et al., 1997). Furthering this idea, mind-wandering accounts pose that the attention that is withdrawn from the task does not merely vanish, but that its focus is actually conducted towards internal thought., i.e., mind-wandering (Smallwood & Schooler, 2006). These theories have been supported by finding worse performance in less demanding tasks compared to dual tasks (Ariga & Lleras, 2011). Furthermore, when tasks were made more engaging or more variable (imposing a higher cognitive demand), improved performance was observed (Pop et al., 2012; Stearman & Durso, 2016; Thomson, Smilek, et al., 2015).

Integrative approaches

Several theories have provided attentional insight that could potentially integrate the contradictory ideas and findings associated with under- and overload theories.

Underload and overload as part of a continuum

Several accounts integrate both underload and overload across a continuum, wherein a middle ground for optimal performance can be achieved. These accounts often explain that vigilance performance depends on the degree of arousal (Esterman & Rothlein, 2019) or cognitive load (McWilliams & Ward, 2021), following the reverse U-shaped function that Yerkes & Dodson (1908) used to relate stress and cognitive performance. In

this regard, underload would lead to what is coined *passive fatigue*, whereas overload would lead to *active fatigue* (McWilliams & Ward, 2021; Saxby et al., 2013). A recent study has in fact observed that both low and high cognitive load tasks led to a pronounced vigilance decrement, whereas performance did not decay during a task with intermediate cognitive load (Luna, Barttfeld, et al., 2022).

Dynamic resource allocation: the resource-control account

Thomson, Besner, et al. (2015), highlighted gaps within the underload and overload theories, proposing the resource control account. This model operates on the notion that resources are constant, the default state of the mind is mind-wandering, and what declines with TOT is our ability to exert executive control in order to maintain attention focused on the task at hand. This decline in executive control would progressively hamper the ability to allocate mental resources toward the task at hand, as they gradually shift to support other task-unrelated thoughts, i.e., mind-wandering (Cunningham et al., 2000; McVay & Kane, 2012; Thomson et al., 2014). Given that these authors posit that resources are constant, the decline in executive control with TOT is alternatively explained by the adoption of less effortful processing strategies, assuming that the individual adapts to the overall low signal-to-noise ratio of the task at hand (Thomson, Besner, et al., 2015).

Opportunity-cost model or cost-benefit models

The opportunity-cost model, while defined more broadly for overall cognitive control (Kurzban, 2016; Kurzban et al., 2013), can add an additional relevant perspective to explaining the vigilance decrement. This model considers that we operate with a limited but constant set of cognitive resources. However, with the ongoing performance of a task, we subconsciously weigh the benefit of continuing with this performance against the cost of losing the opportunity to perform other, potentially more rewarding or engaging tasks (Kurzban et al., 2013). The relevance of this model lies in the fact that the vigilance decrement can be considered not merely in terms of the loss of an ability, expended resources, or loss of sensitivity, but rather as a process that is tied in a more complex manner to

emotional and motivational factors (Kurzban, 2016). Boksem & Tops (2008) offer an interesting brain-based account of cost-benefit analyses that lead to performance declines, expanding the role of dopamine beyond reactivity to reward into a basic component for motivation-guided behaviour.

Decision making with an energy budget: the role of glycogen reserves

Many of the models that refer to resource overload or resource allocation more generally in regards to vigilance, often treat it as a fairly abstract concept (Grier et al., 2003; Thomson, Besner, et al., 2015; Warm et al., 2008a). Christie & Schrater (2015) argue that a decline in cognitive performance with TOT can be accounted for by a depletion of glucose, whereas there's also a dynamic allocation of resources based on rewards. How can performance pick up if resources are depleted? The authors argue that this could be explained by glycogen (mainly from astrocytes), which could act as an energy buffer to support a burst of elevated neural activity beyond what the general glucose supply allows (Christie & Schrater, 2015). This offers an interesting integration of resource-depletion models and cost-benefit models, as the two-fold expenditure of resources would explain different behavioural patterns based on cost-benefit analysis performed by the individual. Furthermore, this model could also potentially explain the reports of null effects of hypoglycemia on sustained attention tasks (McAulay et al., 2001), if glycogen reserves are factored in as a putative compensatory mechanism. On the other hand, other accounts posit that whilst different neural states operate under different levels of efficiency, declines in performance, and thus, indirectly the vigilance decrement, could be explained in terms of a "protective" neural mechanism against the potential damage of exerting extended high control over extended periods, that is experienced as cognitive effort (Holroyd, 2024).

A closer look at the vigilance decrement: executive and arousal vigilance components

Further refining the above-outlined working definition of vigilance, a recent theoretical dissociation between two different types of vigilance has

emerged. Luna et al. (2018) identify two distinct components that can be measured independently: an executive component and an arousal component.

The *executive vigilance (EV) component* refers to the ability to monitor the environment to detect infrequent but critical signals (Luna et al., 2018a). This process requires higher-order cognitive processing as it encompasses monitoring the environment, accessing, and updating working memory, making decisions, and executing accurate responses to the detected targets whilst inhibiting responses to non-targets according to task goals. This component can be observed in computerized tasks such as the above-mentioned MCT (Lichstein et al., 2000), the Sustained Attention to Response Task (SART; Manly & Robertson, 2005), or the Continuous Performance Test (CPT; Conners, 2000). In these tasks, participants are instructed to not respond to a frequently presented stimulus and respond only to a much less frequently presented target. Each trial, thus, requires one to evaluate whether one is presented with a target or not and emit the appropriate response. Within these tasks, the decrement of executive vigilance is observed as the diminished ability to detect infrequent targets (i.e., accuracy or hit rate with time-on-task [TOT]; Luna et al., 2018, 2021; Thomson et al., 2016).

The *arousal vigilance (AV) component* refers to the ability to maintain a fast response to any stimulus from the environment in a more general and automatic manner, as minimal top-down control is required to emit a correct response (Luna et al., 2018a). This component can be measured with a computerized task such as the Psychomotor Vigilance Test (PVT; Lim & Dinges, 2008), where a countdown appears in the centre of the screen at varying intervals, and it has to be stopped as fast as possible. In this context, the decrement of arousal vigilance would be evidenced in the increment of reaction times (RT) and their variability with time-on-task (Lim & Dinges, 2008; Luna, Barttfeld, et al., 2021; Luna et al., 2018a).

This distinction can further help integrate contradictory findings, especially when considering data beyond the behavioural responses. Differing profiles in EEG parameters, relation to structural components, or

manipulations of physiology could further elucidate the dissociation of these two components, beyond their conceptual relevance.

The malleability of the vigilance decrement: modulating factors

The theories outlined in the previous section suggest that the vigilance decrement is a multifaceted phenomenon that can be influenced by a myriad of factors, which have been compiled in **Table 1.1**.

Table 1.1. Factors that can modulate the vigilance decrement by categories

Factor	Relevant finding(s)
External task-related factors	
TOT	The gradual decrement of performance with TOT can be considered an inherent property of vigilance (Warm et al., 2008a). Although it is not always observed (Epling et al., 2019), and while evident at the group level, it is more difficult to grasp at an individual level (Parasuraman & Jiang, 2012).
Demands	There's evidence for worse performance under high demands (Epling et al., 2016; Head & Helton, 2014; Smit et al., 2004) explained by the resource overload theory, as well as evidence for worsened performance under low demand (Ariga & Lleras, 2011) explained by underload theories. Whilst reverse-U-shaped patterns have also been observed, with both low and high demands producing a vigilance decrement, that is reduced with intermediate demands (Luna, Barttfeld, et al., 2022).
Difficulty	Greater vigilance decrements have been observed with increased perceptual difficulty (i.e., when target stimuli are less salient or detectable) (Ballard, 1996; Helton et al., 2010). On the contrary, task difficulty induced by increasing targets' perceptual variability has led to better performance (Thomson, Smilek, et al., 2015). See *Engagement* for a potential explanation of these diverging results.
Modality	While visual targets are the most commonly used modality, the vigilance decrement can also be observed with auditory (Szalma et al., 2004) and vibrotactile targets (DeLucia & Greenlee, 2022); with auditory—compared to visual—stimuli posing an advantage on vigilance performance (Szalma et al., 2004).
Engagement and rewards	Additional steps or processing demands can improve the engagement of the task, facilitating performance (Pop et al., 2012; Thomson, Smilek, et al., 2015). Additionally, incorporating rewards into the vigil has shown to improve performance, albeit only for a brief burst (Reteig et al., 2019).

Rest	Vigilance performance can be restored or partially be restored by introducing breaks into the task (Arrabito et al., 2015; Helton & Russell, 2017; Helton & Wen, 2023).
Autonomous pacing	Having control over the pace of stimuli presentation in a vigilance task can benefit performance (Scerbo et al., 1993).
Internal factors	
Cognitive Load	On top of objective manipulations of cognitive demand, individuals may differ on their thresholds for what might be considered high or low load (Vergallito et al., 2018), which might be especially relevant in clinical contexts or during development and aging (Ballard, 1996).
Available resources	As pointed out above, resources are often used in an abstract manner. Direct measures of metabolic consumption suggest different potential resource storages that can be accessed, influenced by TOT, demand, or incentives (Christie & Schrater, 2015).
Working memory capacity	Working memory load affects the vigilance decrement when the overload occurs in the same modality in which the vigilance decrement is being measured, but not across modalities (Caggiano & Parasuraman, 2004). However, other studies find no effect of working memory load on the vigilance decrement within the same modality (Martínez-Pérez et al., 2023).
Executive control capacity	No correlation between executive vigilance and executive control of ANTI-Vea (Luna, Roca, et al., 2021). According to Thomson, Besner, et al. (2015), the dwindling of executive control impedes the correct allocation of resources to a task, leading to the vigilance decrement. While other studies find no correlation between the executive vigilance decrement and executive control measured within the same task (ANTI-Vea, Luna, Roca, et al., 2021), a correlation between the vigilance decrement and the decrement in cognitive control across TOT has been observed (Luna, Tortajada, et al., 2022).
Motivation	As discussed above, extrinsic motivation can be manipulated by providing incentives. However, intrinsic motivation may also play an important role in the vigilance decrement. In fact, Hancock (2013) proposes that the vigilance decrement stems from the external imposition of the vigil. Furthermore, it should be noted that laboratory tasks are detached from the consequences that arise from the vigilance decrement in real-life scenarios, which can impact the motivation to perform at a certain standard.
Circadian rhythms and chronotype	Cognitive performance (including vigilance), fluctuates across the day in line with circadian rhythms (Valdez, 2019). Vigilance can be further affected by performing outside of the optimal window determined by chronotype, especially for evening types (Martínez-Pérez et al., 2020) or when attentional deficits such as attention deficit hyperactivity disorder (ADHD) are present (Gabay et al., 2022).

Sleep deprivation	The vigilance decrement is exacerbated by sleep deprivation (Hudson et al., 2020), especially when task demands are higher (Chua et al., 2017).
Posture	Prolonged standing has shown to slow down responses in a vigilance task to keep the same level of accuracy (Baker et al., 2018). On the other extreme, lying down, as compared to sitting or standing, has been associated with increased mind-wandering and worse cognitive performance (Yang et al., 2022).
Environmental factors	
Noise	Noise has shown to affect the vigilance decrement in a variable way, and it is suggested that it may interact with other factors such as task demands (Ballard, 1996; Hancock & Warm, 1989). Considering the lack of clear effects, the best option in this case is to keep it constant and minimal, if controllable.
Temperature	Deviations from an intermediate temperature into either extreme seem to negatively affect vigilance performance (Ballard, 1996).
Light	Higher light temperatures (i.e., blue light) have been associated with better vigilance performance (Chellappa et al., 2011), although this effect, together with the impact of light intensity is not always observed (Souman et al., 2018).
External stimulation	
Caffeine or other stimulants	Sanchis et al. (2020) observed improved arousal vigilance with caffeine intake. Beneficial caffeine effects have also been reported for sustained attention, whereas methylphenidate reduced self-reported fatigue (Repantis et al., 2021).
Exercise	Exercise at moderate intensity has shown to mitigate the executive vigilance decrement (Sanchis et al., 2020).
NIBS	Interventions with non-invasive brain stimulation (NIBS), such as tDCS, have shown promising results in mitigating the vigilance decrement (Luna et al., 2020; McIntire et al., 2014; J. T. Nelson et al., 2014)

The decline in performance likely results from a complex interplay of external, internal, and environmental factors such as resource depletion, changes in arousal levels, task characteristics, and individual strategies for managing attention and workload. Understanding this interplay is crucial for developing effective interventions to mitigate the vigilance decrement. As research continues, a more comprehensive model integrating these various aspects may emerge, offering a deeper understanding of sustained attention and its challenges. On the other hand, it must be noted that this is not an exhaustive list of all potential factors of malleability and the evidence of some of them may in some cases originate from studies with smaller

samples that are less generalizable. For now, this list underlines the importance of adequately controlling and reporting these factors, and highlights some of the aspects that will be explored in more detail in the present thesis, such as the effects of cognitive load or demands.

On a positive note, the broad range of factors influencing the vigilance decrement may also offer different (and potentially additive) compensatory interventions, such as non-invasive brain stimulation (NIBS), as will be discussed in the next chapter. Before this, we will make a last stop at the neural correlates that are relevant to further understanding the vigilance decrement.

Neural correlates of the vigilance decrement

Through the use of neuroimaging techniques, we can gain a better look at what occurs in the brain when we exert vigilance and when it inevitably decays with time-on-task. This can be explored through the lens of more stationary cortical and subcortical regions or networks composed of multiple regions that show a consistent activation during vigilance tasks or in response to task manipulations. This can be achieved with the use of functional magnetic resonance imaging (fMRI) or metabolic imaging, such as positron emission tomography (PET). Additionally, anatomical structures, such as the integrity of white matter tracts can also be related to individual task performance. On the other hand, using techniques with a higher temporal resolution, more dynamic neural correlates of vigilance can be determined as well, mainly through the use of electroencephalography (EEG) data.

Stationary vigilance “hubs” and networks

Given the above-outlined overlap of vigilance with other attentional functions and its interaction with other cognitive processes, it is to be expected that it cannot be circumscribed to one specific neural location. Instead, it has been established that vigilance is related to neural activity distributed across different neural networks or clusters, many of which are lateralized towards the right hemisphere (Langner & Eickhoff, 2013). While this coordinate-based meta-analysis by Langner & Eickhoff (2013),

considered a considerably low duration criterion (> 10 seconds) to include studies; within the areas that were identified, a further right-lateralization was observed when looking at foci of brain activity correlating with longer task durations (see **Fig. 1.3.A**). In line with these results, the right-lateralization of vigilance or sustained attention processes has also been reported from lesion studies. Patients who had suffered a lesion to right frontal regions, presented a larger vigilance decrement, than patients with left frontal or other lesion sites (Koski & Petrides, 2001; Molenberghs et al., 2009; Rueckert & Grafman, 1996). A more recent study has additionally shown that patients with lesions to the right-hemisphere also present larger within-block vigilance decrements compared to healthy controls (Brosnan et al., 2022). Further evidence of this lateralization has also been gathered from neuroimaging studies with healthy participants. An earlier study showed that right frontal and parietal areas show activation during vigilance tasks in PET imaging (Pardo et al., 1991). On the other hand, perfusion fMRI data has shown that blood flow in the frontoparietal network is reduced from pre- to post-task, and this reduction in blood flow was associated with a vigilance decrement (Lim et al., 2010).

Furthermore, the regions identified by Langner & Eickhoff (2013) show an overlap with networks identified in other attentional models, such as the dorsal top-down stream and the ventral bottom-up stream identified by Corbetta & Shulman (2002), that integrate the orienting network identified by Posner & Petersen (1990) as depicted in **Fig. 1.3.B**, that regulates goal and stimulus-driven allocation of attentional resources to relevant stimuli. Furthermore, some overlap can also be observed with the executive control network (Petersen & Posner, 2012; Posner & Petersen, 1990), which encompasses what Dosenbach et al. (2007, 2008) characterized as a frontoparietal network, associated with initiating and adjusting control over ongoing performance; and the cingulo-opercular network, associated with a stable maintenance of task-goals across longer periods (see **Fig. 1.3.C**). As depicted in **Fig. 1.3.D**, most of these regions are reached by the alerting network, composed of the cortical projections of the LC. The cingulo-opercular network identified as part of the executive network has also been conceptualized as the salience network, which has been proposed to assist in balancing exogenous or task-driven activity in the central executive network (CEN) and the more endogenous or self-referential activity of the

default mode network (DMN), as shown in **Fig. 1.3.E** (Menon, 2011; Menon & Uddin, 2010). In a more directional model, Unsworth & Robison (2017) propose that the inhibitory effect of the frontoparietal network (FPN) on the DMN is aided by the SN, driven by the projections of the LC, as shown in **Fig. 1.3.F**.

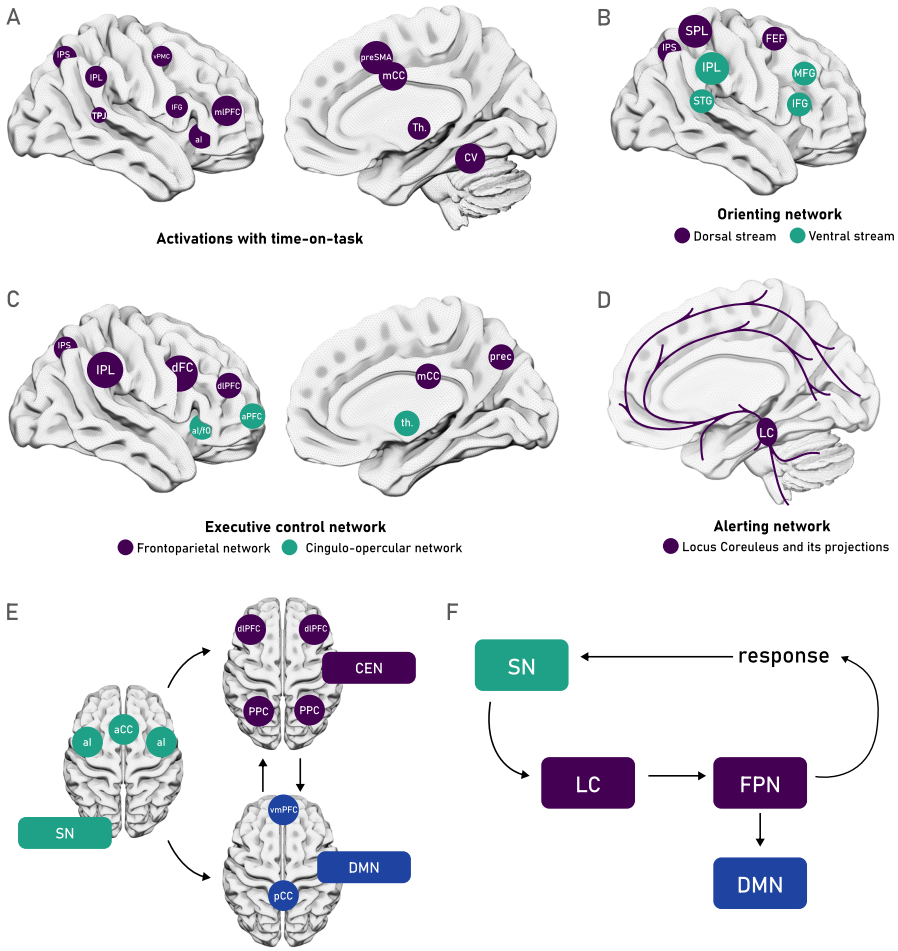

Figure 1.3. Schematic depiction of different neural networks relevant for attention and vigilance **(A)** Foci of brain activity that showed a greater activation with task duration identified within a general network of areas activated during vigilant attention in the coordinate-based meta-analysis performed by Langner & Eickhoff (2013). The right-lateralized set of areas obtained included the anterior insula (aI), presupplementary motor area (pre-SMA), midcingulate cortex (mCC), midlateral prefrontal cortex (mlPFC), ventral premotor cortex (vPMC), inferior frontal fyrus (IFG), inferior parietal sulcus (IPS), and adjacent inferior parietal lobule (IPL), temporoparietal junction (TPJ), thalamus, and cerebellar vermis. **(B)** Posner & Petersen's (1990) orienting network that can be subdivided as characterized by Corbetta

& Shulman (2002) into the dorsal top-down stream (depicted in purple), composed of the frontal eye fields (FEF) as well as the IPS and superior parietal lobe (SPL); and the ventral bottom-up stream (depicted in green) composed of the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC). **(C)** The executive control network identified by Posner & Petersen's (1990), spans the networks that Dosenbach et al. (2007, 2008) further distinguished into the frontoparietal network (in purple) composed of the IPS, IPL, dorsal frontal cortex (dFC), and dorsolateral prefrontal cortex (dlPLFC); and the cingulo-opercular network (in green), composed of the anterior insula/frontal operculum (aI/fO), and the anterior prefrontal cortex (aPFC). **(D)** The alerting network (Posner & Petersen, 1990) that is controlled by the release of norepinephrine from the cortical projections of the Locus Coeruleus. **(E)** The cingulo-opercular system has also been conceptualized as the salience network (SN, composed of the aI, and the anterior cingulate cortex (aCC)), which acts as a relevant relay point between the central executive networks (CEN, composed of the dlPFC and posterior parietal cortex [PPC], and the default mode network (DMN, composed of the ventromedial PFC [vmPFC], and the posterior cingulate cortex [pCC]) as proposed by Menon & Uddin (2010). **(F)** The SN has further been proposed to aid in the inhibition of the DMN by the frontoparietal network (FPN), driven by recruitment of the projections of the LC (Unsworth & Robison, 2017).

It must be noted that the role of the DMN as task-negative, or the attribution of its activity with degraded performance has been challenged by findings from Esterman et al. (2013), indicating that instead, a push-pull relationship between the DMN and the dorsal attention network (DAN) subserves different attentional states. An "in the zone", more stable and automatic processing that can arise in less challenging tasks, is characterized by higher DMN activity, and permits less effortful processing at the expense of risking errors if DMN activity increases past a certain threshold. During more demanding tasks, a second, more effortful processing state where DAN activity is higher emerges, and errors are more likely to occur if insufficient control is exerted by DAN (Esterman et al., 2013).

Furthermore, the intensity aspects of attention (vigilance and sustained attention, as discussed above) rely on the appropriate functioning of the parietal cortex (Malhotra et al., 2009). The right posterior parietal cortex (rPPC) plays a crucial role in spatial attention, given that the IPL is the main lesioned area in hemispatial neglect (Malhotra et al., 2009; Molenberghs et al., 2009). Neglect patients often present additional deficits in vigilance/sustained attention (Malhotra et al., 2009). While sustaining the idea that there is no unique location that subserves vigilance, the right posterior parietal cortex (rPPC) may play a fundamental role. The rPPC (depicted in **Fig. 1.4**) is a region comprised of the inferior and the superior parietal lobes (IPL and SPL, respectively), which can be identified as laying

beyond the post-central gyrus and divided from each other by the intraparietal sulcus (IPS). The rPPC shows a heightened hemodynamic response to the presentation of infrequent (Stevens et al., 2005) and novel (internal and external) stimuli (Singh-Curry & Husain, 2009). But, additionally, it has also been associated with the active maintenance of task goals (Singh-Curry & Husain, 2009). This has led some authors to establish the rPPC as a "convergence node" between the ventral attention network and the DMN: thus considering its relevant role in maintaining task goals active, whilst flexibly reacting towards novel or salient stimuli and relaying between task-relevant and task-irrelevant regions (Giacometti Giordani et al., 2023). This role can be feasible on a structural level due to the densely interconnected core that has been observed in this region, with further dense connections to other neural regions (Hagmann et al., 2008). Conceptually, the rPPC could play a relevant role as a relay switch in the complex interplay of forces that lead to the vigilance decrement: resources, mind-wandering, executive control, motivation, and cost-benefit.

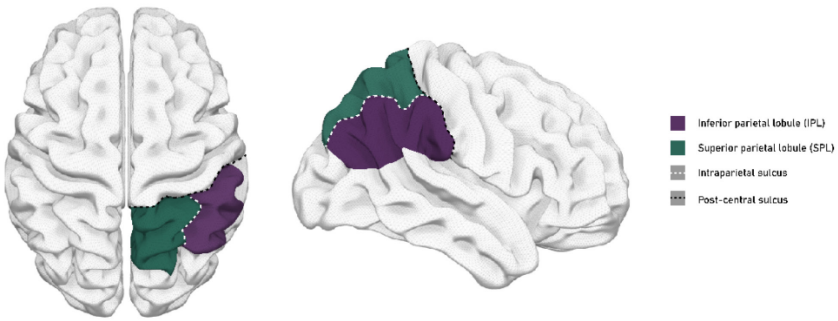

Figure 1.4. Schematic representation of the superior parietal lobule (SPL), in green, and the inferior parietal lobule (IPL), in purple, that jointly comprise the posterior parietal cortex (PPC).

As a counterpoint, some accounts suggest that the right-lateralization of vigilance is observed only in simpler, less demanding tasks, whereas in more complex tasks a bilateral hemispheric activation is observed (Helton et al., 2010). This observation highlights the fact that despite the above-discussed relevance of the rPPC for vigilance, the importance of broad networks in supporting the adequate functioning of vigilance must be considered. In line with this, Rosenberg et al. (2016) have established a connectome-based predictive model that can predict individual differences in sustained

attention functioning from task-based as well as resting-state functional connectivity data. This model can predict attentional fluctuations within and between task blocks and sessions, as well as responsiveness to external modulations of attention, such as the administration of sedatives (Rosenberg et al., 2016). It has also proven to effectively predict attention-deficit symptom severity in an independent sample (Rosenberg et al., 2020). Interestingly, this model includes regions beyond the canonical regions associated with attention (salience, frontoparietal, default), and implicates other regions such as the cerebellum (Rosenberg et al., 2016).

Lastly, regarding more stable anatomical features that are highly relevant for the adaptive signal transmission required by attentional processes, there is evidence linking different indices of white matter integrity to attentional functioning. Considering the above-reviewed evidence, pathways connecting frontoparietal areas, such as the branches of the superior longitudinal fasciculus (SLF) could be of special interest. These pathways can be studied by means of diffusion-weighted imaging (DWI) data. As a case in point, a higher fractional anisotropy (FA) in the SLF in typically developing children has been associated with better sustained attention performance (Klarborg et al., 2013). Moreover, adolescents with ADHD show a strong relationship between reported inattentive symptomatology and alterations in the right SLF (Chiang et al., 2015). Furthermore, this link has also been established in healthy adults, where higher fibre density (FD, an estimate of axon density) of the first branch of the superior longitudinal fasciculus (SLF-I) was associated with fewer attentional lapses during a global-local task (Clemente et al., 2021). Furthermore, Luna, Lupiáñez, et al. (2021) observed that higher white matter integrity of the SLF-I in healthy adults was associated with faster reaction times in correct responses to EV trials. However, no significant associations were observed with other more reliable or direct indicators of the vigilance decrement (such as the increment of hits or the decrement of sensitivity, with TOT) (Luna, Lupiáñez, et al., 2021). Theoretically, the SLF-I has been proposed as a mediator between the direct communication between dorsal and ventral attentional networks by the second branch of the SLF (SLF-II), and the salient events or targets identified by the third branch (SLF-III), as a foundation for goal-directed behaviour (Thiebaut De Schotten, Dell'Acqua, et al., 2011).

Another tract that has been associated with sustained attention is the right cingulate fasciculus, with higher FA in this tract associated with higher sensitivity to infrequent targets in the CPT task (Takahashi et al., 2010). Moreover, broader associations with attentional functioning have also been reported. For example, Niogi et al. (2010) associated white matter integrity with the functioning in Posner & Petersen's (1990) three attentional networks, reporting positive correlations between the FA of the left posterior limb of the internal capsule and alerting, the splenium of the corpus callosum and the orienting network, and the left anterior corona radiata with the executive control network. Lastly, considering the detrimental effect of sleep deprivation on the vigilance decrement (Lim & Dinges, 2008), it is worth noting that DWI data has been used to predict individual vulnerability to sleep deprivation. Wang et al. (2022) reported that the integrity of the SLF, posterior corona radiata, anterior limb of the internal capsule, as well as body and genu of the corpus callosum, best predicted vulnerability to sleep deprivation.

Dynamic models of vigilance: the role of neural oscillations

Despite the monotonous nature and unchanging demands imposed by vigilance tasks, neural regions and networks associated with attentional functioning are still highly dynamic (Fiebelkorn & Kastner, 2019). This characteristic can be grasped by associating vigilance with oscillations in specific frequency bands, such as those illustrated in **Fig. 1.5.A**. Fiebelkorn & Kastner's (2019, 2020) rhythmic theory of attention posits that lower-frequency oscillations in attentional networks organize neural activity into rhythmically alternating states. During tasks requiring vigilance this would lead to interspersed periods of lower perceptual sensitivity, during which for example an attended location is re-selected based on both stimulus properties and task goals (Fiebelkorn & Kastner, 2019). The rhythmic sampling is orchestrated by oscillations in the theta band (3-8 Hz) inherent to the frontoparietal network, which determines activity in higher frequency bands, influencing behavioural outcomes (Helfrich et al., 2018). In line with this, Reteig et al. (2019) observed an increment of the temporal variability in cortical responses, indexed through inter-trial phase clustering of theta, along with the expected decrement of performance with

time-on-task. Thus, a precise rhythmic stability may be required for stable vigilance performance, and its destabilization might be a putative origin of the vigilance decrement.

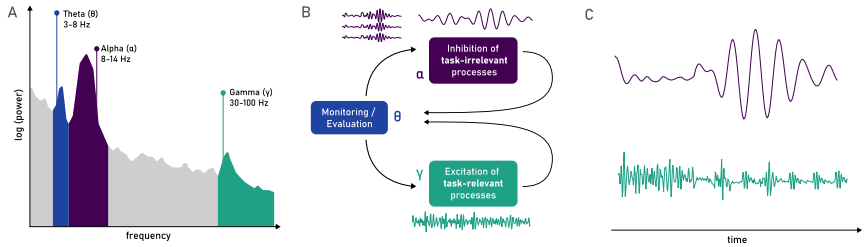

Figure 1.5. **(A)** Theta (θ), alpha (α), and gamma (γ) bands represented in a power density spectrum. **(B)** Oscillatory model of sustained attention proposed by Clayton et al. (2015), in which theta is responsible for supervising the attentional process (as proposed also by Fiebelkorn & Kastner (2019)), inhibiting task-irrelevant processes via oscillations in the alpha band, and re-energizing task-relevant process via oscillations in the gamma band. **(C)** Gating of gamma oscillations by alpha oscillations ((Osipova et al., 2008), that could constitute a relevant rhythmic purging of task-irrelevant information to sustain vigilance across time (Sadaghiani & Kleinschmidt, 2016).

This orchestrating role of neural oscillations in the theta band has been integrated into a more complex model in order to explain sustained attention via the interplay of different neural oscillations. Stuss et al. (1995) presented a schematic proposal of how sustained attention is orchestrated: a supervisory system must, on the one hand, reactivate target schemata that are necessary to detect the infrequent target stimulus, whilst on the other hand ensuring that other competing schemata do not capture behaviour by inhibiting them. Lastly, this monitored information must return back to the control of the schemata (Stuss et al., 1995). Clayton et al. (2015) attribute specific oscillations to these different functions in a proposed oscillatory model of sustained attention (see **Fig. 1.5.B**). The monitoring and evaluation of task performance in relation to task goals are associated with theta oscillations in frontomedial regions, and consequent frontomedial theta-band phase synchronization relays modulatory signals to low level, sensorimotor areas. Oscillations in the gamma band (> 30 Hz) are associated with the excitation of task-relevant processes, whilst oscillations in the alpha band (8-14 Hz) are associated with the inhibition of task-irrelevant processes or stimuli. Lastly, bidirectional communication across frontoposterior networks (i.e., the relegation of inhibition and excitation based on task-goals, as well as return of feedback from actual task

execution) is handled via low-frequency phase synchronization (Clayton et al., 2015a).

Regarding the specific role of alpha oscillations in vigilance, many studies (as, for example reviewed by Craig et al., 2012) report an increment of alpha power with TOT. Craig et al. (2012) specifically observe the greatest change in EEG data with progressing fatigue throughout a task in the theta and alpha bands. Another study observed increments of lower alpha power (7.5-10.5 Hz) with increased TOT and fatigue, especially in parietal electrodes; whilst other frequency bands showed no relationship to fatigue (Boksem et al., 2005a). Replicating the increment of alpha power with TOT, Benwell et al. (2019) also observed a reduction in the peak frequency of alpha with TOT. In a slightly different approach, during a driving task and an additional auditory vigilance task, Sonnleitner et al. (2014) observed an increment of both reaction times to brake in response to an on-road stimulus as well as the rate of alpha spindles (short bursts of alpha band activity, comprehended between 500 ms up to several minutes (Simon et al., 2011), depicted schematically in the top left of **Fig. 1.5.B**) with TOT, which were exacerbated by the addition of a secondary task. It has been argued that in some conditions (such as driving situations), alpha spindles can more accurately capture fatigue than measures of alpha band power (Simon et al., 2011). This increment in alpha power with TOT has been interpreted as: (i) indicating an attenuation in information processing over time (Pershin et al., 2023), or (ii) reflecting an increased effort to sustain attention, especially under conditions of higher demand, either due to external imposed load or due individual differences such as older age, brain injury or sleep deprivation (Klimesch, 1999).

On the other hand, data from oscillations in the alpha band has also been associated with mind-wandering. For example, Compton et al. (2019), observed that mind-wandering reports were positively associated with higher pre-stimulus alpha power. This has been further integrated with research that joins EEG and fMRI data recorded at rest. These concomitant recordings show a negative correlation between occipital alpha power and a frontoparietal network (Mo et al., 2013). On the other hand, a positive correlation between occipital alpha power and BOLD activity in nodes of the DMN is observed only in an eyes-open condition (Mo et al., 2013). The role

of alpha power in this context has been associated with its inhibitory role to block external visual input during introspective mental activity, which is not needed during the eyes closed condition.

Oscillations in the gamma band, on the other hand, as defined in the model by Clayton et al. (2015), are associated with the excitation of task-relevant processes. This may be achieved by the rapid firing of interconnected neurons (falling into the 30-100 Hz frequency range that broadly encompasses gamma (Fitzgibbon et al., 2004)), which would allow the sustained maintenance of information active in working or short-term memory (Jensen et al., 2007). This increment of gamma power, accompanied by a reduction in alpha power, in task-positive areas, has also been observed in intracranial EEG recordings (Ramot et al., 2012). While, in a complementary manner, intracranial EEG recordings have shown that gamma power is reduced in regions of the DMN during the performance of the CPT (J. Li et al., 2019). This shift away from task-irrelevant areas from gamma oscillations underscores the role of this neural signal, not only in areas relative to sensory processing but also in more complex cognitive functions. This has also been observed, not by absence, but by presence: as gamma power (orchestrated by and in feedback loops with theta power) in prefrontal regions has been associated with adequate conflict detection, resolution, and adaptation (Oehrn et al., 2014). On the other hand, during tasks that are simpler or allow for an easier automatization throughout their performance, such as the PVT, a fluctuating role of gamma with TOT has been observed: a decrement with TOT, with a sharp pick-up to initial levels in the final block (Curley et al., 2023). This decrement of gamma power could reflect either automatization and thus, mindless execution, that requires less constant firing of task-relevant neurons, or, on the other hand, a depletion of resources that impedes this activation of task-relevant areas. The increment of gamma power towards the end of the task, which was accompanied by improved performance, may reflect the selective deployment of cognitive resources if a supervisory system detects that performance is not aligning with task goals (Curley et al., 2023). Lastly, it is worth noting that whilst all the ranges defining narrow-band frequencies are somewhat arbitrary and vary between different studies (M. X. Cohen, 2021), this is especially accentuated in the gamma band, given its usually

large span (30-100 Hz), which may further hinder the integration between different studies relating to this frequency band.

A last relevant interaction between oscillations is a proposed interaction between alpha and gamma, in which oscillations in the alpha rhythm gate gamma oscillations, as depicted in Fig. 1.5.C (Osipova et al., 2008). The pulsed inhibition of alpha power has been described to act as a "windshield wiper" mechanism, where this regular purging of task-irrelevant or distracting information, may play a crucial role in sustaining vigilance in accordance with task goals (Sadaghiani & Kleinschmidt, 2016). In fact, when inspecting neural oscillations on a trial-by-trial basis, Luna et al. (2023) observed that incorrect detections of an infrequent target were predicted by increased occipital alpha power before the target's onset. This increment of alpha power in task-relevant areas has been argued to be a potential contributor to the vigilance decrement (Luna et al., 2023); as it may reflect an imprecise deployment of this rhythmic inhibitory process that does not serve task goals.

Conclusion

From this chapter it can be concluded that the vigilance decrement is hard to define and disentangle from other cognitive processes, it is explained by multiple—sometimes contradictory—theories, and it relies on the adequate functioning of many different neural regions and processes. The literature still seeks a unified theory that fully explains the vigilance decrement, its varied manifestations across different contexts, and the best approaches to counteract its effects. This ongoing quest underscores the importance of interdisciplinary research in unravelling the intricacies of vigilance, aiming not only to enhance our theoretical knowledge but also to improve practical outcomes in research, clinical, and everyday cognitive functioning.

Chapter 2

Origins, mechanisms, and models of transcranial direct current stimulation

Abstract

Transcranial direct current stimulation (tDCS) represents a prominent non-invasive brain stimulation (NIBS) technique characterized by the application of a weak constant electrical current across the scalp, influencing the excitability of underlying neuronal populations. This modulation of neuronal activity holds the potential for enhancing cognitive functions, including attention and vigilance. This chapter reviews the historical development of the technique, its underlying mechanisms, and models that have been proposed to understand its neural effects and cognitive outcomes. Finally, factors that induce intra- and inter-participant variability in tDCS outcomes are discussed.

Transcranial direct current stimulation (tDCS) is among the most used techniques of non-invasive brain stimulation (NIBS). It consists of applying a weak constant electrical current over the scalp, part of which can reach underlying brain regions (Priori, 2003). Given the low intensity and the dissipation of current on its way to the brain, tDCS cannot induce an action potential as compared to other NIBS techniques such as transcranial magnetic stimulation (TMS). However, it can alter the likelihood of the underlying neuronal populations to fire, which offers the potential to modulate ongoing brain activity to selectively boost a certain behavioural outcome (Bikson et al., 2013). In fact, the technique has shown to effectively modulate cognitive performance across a broad range of functions (Antal et al., 2022; Coffman et al., 2014a), including attention (Benwell et al., 2015; Filmer et al., 2017; Hanenberg et al., 2019; Roy et al., 2015), and specifically, vigilance (Gan et al., 2022; Luna et al., 2020; McIntire et al., 2014; J. T. Nelson et al., 2014). In this chapter, we will briefly review the origins of tDCS, its main mechanisms, and the current evidence on how it can be employed to target the vigilance decrement.

History and current use of tDCS

The origins of tDCS can be traced back to 43-48 A.D., when Scribonius Largus, a Roman physician, employed the natural defence and hunt mechanism of the torpedo fish—a pulsed electric discharge—as a means to treat headaches (Gebodh et al., 2019; Sarmiento et al., 2016). In the 11th Century, the same active principle was used by the Persian Ibn-Sidah to treat epilepsy (Gebodh et al., 2019; Sarmiento et al., 2016). Note that the torpedo fish produces pulsed electric discharges, therefore they are not a direct precursor for direct current (DC) stimulation, but they constitute a relevant historic precursor. Later electrotherapy approaches that emerged during the 1750's used static or frictional electricity (Elliott, 2014). Through experiments inducing muscular movements via externally applied electricity, Luigi Galvani proposed in 1791 that the brain generates electricity that is communicated via the nerves through the muscular system (Parent, 2004). An attempt to refute this idea, by explaining that these findings in fact stemmed from generating electricity by creating contact between two different metals, led Alessandro Volta to invent the first known DC battery,

the voltaic pile, in 1800. The voltaic pile consisted of a stack of alternating discs of zinc and copper, separated by layers of cardboard or felt soaked in saltwater, which created an electrical current when connected at both ends. Giovani Aldini, Galvani's nephew, then employed the voltaic pile for therapeutic purposes. After first experimenting with the technique on his own head, he reportedly successfully treated depression in a patient in 1801 (Parent, 2004).

Towards the end of the 19th Century, different electrical stimulation machines were used prolifically in the medical field with numerous psychiatric applications (Sarmiento et al., 2016), with alternating current generated by electromagnetic induction being the most popular application (Elliott, 2014). This widespread use came to a halt around 1930 when the growing scepticism towards the technique and concern due to its unregulated and non-systematic application coincided with the emergence of electroconvulsive therapy (Elliott, 2014). In 1964 animal studies revealed polarity-specific effects of stimulation: with anodal weak DC stimulation increasing neural firing rate and cathodal stimulation decreasing it (Bindman et al., 1964; Gebodh et al., 2019). Furthermore, these studies showed that stimulation with prolonged (> 5 min.) DC currents led to lasting changes in neural excitability which sparked a renewed interest in its application to neuropsychiatric diseases (Gebodh et al., 2019). This period was characterized by increased systematicity in finding the adequate dose for a desired effect and generally coincided with the use of smaller active electrodes (compared to those later used in conventional tDCS), lower current intensities (0.1-0.5 mA), longer stimulation sessions (some patients actually went home with their devices), and most commonly applying the "active" montages applied one electrode over the supraorbital area, and the other one on the body (extracephalic) (Gebodh et al., 2019).

The birth of modern tDCS can be attributed to the development of more compact stimulation devices and renewed efforts to further understand its neurophysiological mechanisms (Gebodh et al., 2019). Intensity, duration, polarity-specific effects, and their malleability were explored testing how tDCS affected the excitability of the motor cortex, by measuring the amplitude of motor-evoked potentials (MEP) evoked by TMS after tDCS applications (Nitsche & Paulus, 2000, 2001). An additional approach that

emerged in this period was the manipulation via pharmacological agents of neurotransmitters and their receptors, to further understand mechanistic neural pathways of tDCS (Stagg & Nitsche, 2011; Yamada & Sumiyoshi, 2021). These studies, initially more focused on understanding mechanisms, later on, branched out into protocols targeting specific cortical regions to modulate different cognitive processes (Gebodh et al., 2019).

A later refinement of the technique constitutes the substitution of the two saline-soaked sponge-based electrodes with a larger amount of smaller, gel-based electrodes, referred to as high-definition (HD) electrodes (Minhas et al., 2010). HD-tDCS allowed optimizing stimulation outcomes in terms of stimulation intensity and focality (Dmochowski et al., 2011). The development of concurrent tDCS and neuroimaging with functional magnetic resonance imaging (fMRI-tDCS) further refined the understanding of the mechanisms behind the technique (Antal et al., 2011).

Further developments have facilitated the ease of application with wireless stimulation headsets, and pre-soaked or dry electrodes, which may prove especially useful for remote clinical applications (Truong & Bikson, 2018). Note that this constitutes a representative overview of key historical moments for the development of tDCS (summarized in **Fig. 2.1.A**), but it is not an exhaustive list. Furthermore, depending on the documents consulted the historical details vary slightly [for more in-depth historical accounts please see: (Parent, 2004; Priori, 2003; Sarmiento et al., 2016), and for a more detailed timeline on technical developments from 2000 onwards, see: Truong & Bikson (2018)].

We have come a long way from the first attempts to "electrify" the brain via electrics eels, to the refinement of a technique that has the potential to modulate our cognitive functions (Begemann et al., 2020; Coffman et al., 2014a). Publications relative to cognition and specifically attention in combination with tDCS have grown exponentially in the last few years (see **Fig. 2.1.B**). A similar pattern, albeit in a smaller proportion, can be observed for publications on tDCS and vigilance as shown in **Fig. 2.2.C** (and sustained attention, given the conceptual overlap discussed in **Chapter 1**). Before discussing some of these relevant findings, we will first delve into a brief overview of how these effects may be achieved, exploring the mechanisms behind tDCS.

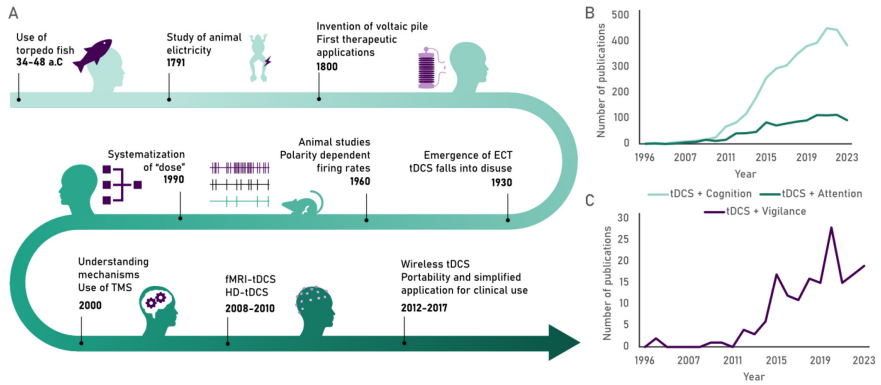

Figure 2.1. **(A)** Historical development of tDCS. **(B)** Number of publications by year on tDCS and cognition, as well as tDCS and attention. **(C)** Number of publications by year on tDCS and vigilance. Note that search results stem from January 2024, but are capped off in 2023 to encompass a full year. See the footnote for specific search terms[1]. *Note:* ECT = electroconvulsive therapy.

Mechanisms and models of tDCS effects

The history of tDCS is by far not a finished one. Despite the advances that have been made up to today, the exact mechanisms by which tDCS achieves its effects are still under critical exploration (Bestmann et al., 2015; Yamada & Sumiyoshi, 2021). We will discuss what is currently known about the effects of tDCS on neural activity as *mechanisms*, and the different proposed ways in which this yields behavioural outcomes, as *models*.

Mechanisms of tDCS

The currently understood mechanisms of the technique can be discussed in two distinct steps: (i) understanding the basic physical principles of how the electric field is induced in the brain, and (ii), understanding how this electric field produces an effect on neural activity (Reato et al., 2019).

Regarding the physical principles behind tDCS mechanisms, the application of tDCS requires a minimum of two electrodes to achieve a constant flow of DC. This corresponds to conventional tDCS protocols,

[1] Note that the following search equations were used on PubMED (January 2024), for tDCS + Cognition results: ((tDCS) OR ("transcranial direct current stimulation")) AND ((cognit*) OR ("cognitive performance")), for tDCS + Attention results: ((tDCS) OR ("transcranial direct current stimulation")) AND (attent*), and for tDCS + Vigilance: (tDCS OR "transcranial direct current stimulation") AND (vigilance OR "vigilant attention" OR "sustained attention").

depicted in **Fig. 2.2.A**, where larger saline-soaked sponge-like electrodes are used, resulting in a larger and more diffuse e-field (Gebodh et al., 2019). A more focal e-field can be achieved by the use of smaller and multiple gel-based electrodes, which is referred to as HD-tDCS (see **Fig. 2.2.B**) (Alam et al., 2016; Edwards et al., 2013; Kuo et al., 2013). The main characteristic of tDCS, is that current is held at a constant intensity (excluding its gradual onset and offset, referred to as ramp-up and ramp-down, respectively) during the duration of a protocol (see **Fig. 2.2.C**). As the current has a constant direction (polarity), current flows inwards (to the brain) at one electrode, referred to as **anode**, and outward at the other, referred to as **cathode**. The flow of current between the anode and cathode induces an electric field (e-field) in the brain. Only a fraction of the applied current actually reaches the brain itself, as part of the applied current dissipates or shunts when it passes through the different protective layers around the brain (skin, skull, meninges, and cerebrospinal fluid), as depicted in **Fig. 2.2.D**. Whilst polarity remains constant, what can be changed for a given protocol is the intensity of stimulation, and the duration of the protocol (See **Fig. 2.2.C**).

Once the e-field reaches the brain, its effects on brain functioning can be categorized into acute or primary effects, which occur during the stimulation protocol, and aftereffects, which develop during the application of the stimulation and can persist beyond its duration. Within the acute effects, the most discussed mechanism of tDCS is its effect on the resting membrane potential of neurons. As discussed above, given its low intensity, tDCS lacks the potential to directly induce an action potential, i.e., firing of a neuron. Rather, it operates by changing the resting membrane potential, which facilitates or inhibits the firing of near-threshold neurons (Stagg & Nitsche, 2011). As illustrated in **Fig. 2.2.D**, what under normal circumstances would lead to the failed initiation of an action potential, by not surpassing the threshold, could lead to an action potential with anodal tDCS. Not by directly induced firing, but because the potential of the cell membrane at rest is raised, facilitating the occurrence of an action potential in response to a stimulus, permitting the information to travel along the cell's axon (Reato et al., 2019). With cathodal tDCS the resting membrane potential would be lowered, reducing the likelihood of the response to a stimulus to cross the threshold.

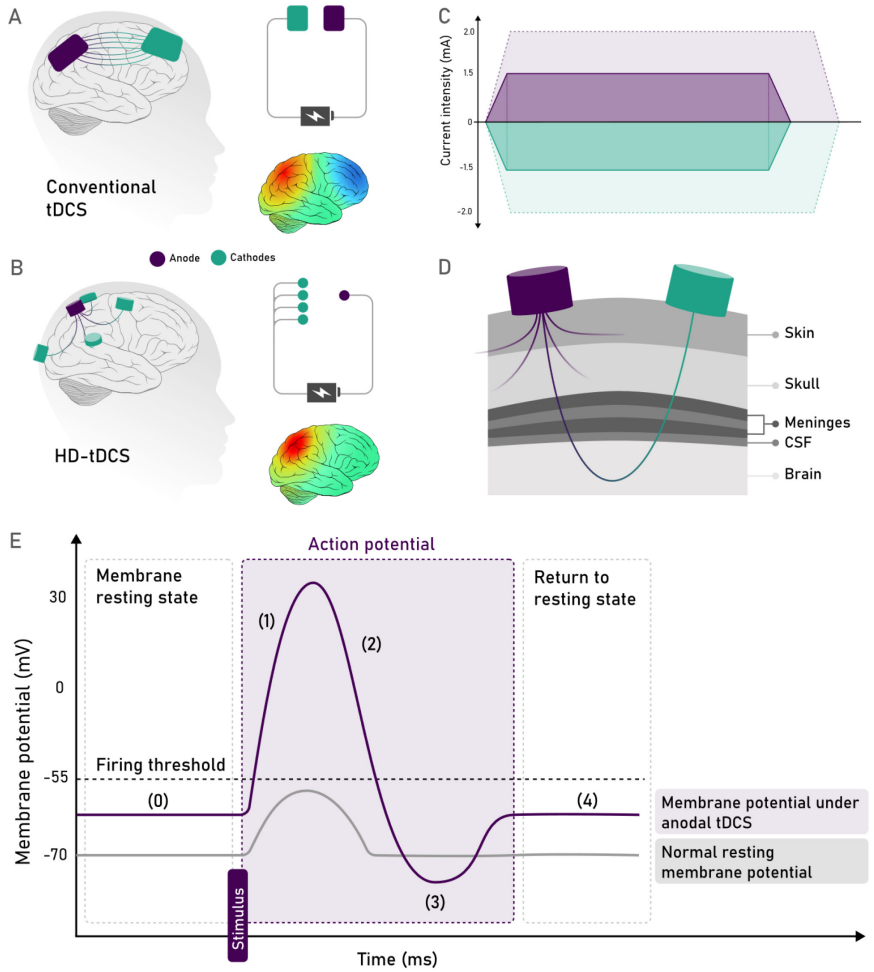

Figure 2.2. (A) Schematic depiction of an example of a conventional tDCS setup on the head, the electric circuit that is built up, and the resulting e-field from this protocol. **(B)** Schematic depiction of an example of an HD-tDCS protocol, with its corresponding electric circuit and e-field. **(C)** Representation of anodal (purple) and cathodal (green) tDCS protocols. The current intensity is gradually built up from zero to the desired intensity (ramp-up), then held constant for the duration of the protocol (between the dotted vertical lines) and lowered again at the end (ramp-down). The light purple and light green protocols reflect higher stimulation intensities and longer protocol duration. **(D)** Schematic depiction of the brain's protective layers that the e-field has to pass through in order to reach the brain. Each layer's composition will result in a different e-field distribution and lead to shunting of the e-field (depicted lines that fade out). **(E)** Depiction of a failed initiation for an action potential in a near-threshold neuron (gray line), and how with the same stimulus and under the influence of anodal tDCS, by raising the resting membrane potential (0), this impulse can surpass the firing threshold and derive in an action potential (purple line), that leads to the neuron's depolarization (1), repolarization (2), and consequent hyperpolarization (3), before returning to its resting state (4). *Note:* CSF = cerebrospinal fluid.

These facilitatory and inhibitory effects can be thus conceptualized both at the electrochemical and cellular levels. At an electrochemical level, due to the flow of Sodium and Potassium ions flowing in and out of the cells generating the electrical and chemical gradients that are required to produce an action potential. Furthermore, a complex cascade of neurochemical reactions is associated with the effects of tDCS in the brain. Anodal tDCS is likely facilitating excitatory glutamate and suppression of inhibitory gamma-aminobutyric acid (GABA) transmission in the cortex (Yamada & Sumiyoshi, 2021). These effects can further trigger the activity of other neurotransmitters, such as dopamine, serotonin, or acetylcholine (for an in-depth review see Medeiros et al., 2012; and Yamada & Sumiyoshi, 2021).

At the cellular level, the effects of tDCS can be observed on excitatory (pyramidal) neurons and clusters of inhibitory neurons. The delicate homeostatic balance between cortical excitation and inhibition is crucial for adequate information processing and plastic restructuring of the brain in response to an input. On a cellular level, this can be understood as the interaction of excitatory pyramidal cells (purple triangle in **Fig. 2.3.A**) and clusters of inhibitory neurons (green array of cells in **Fig. 2.3.A**). A balanced response to an input, as depicted in **Fig. 2.3.B,** would carry the excitatory signal along the adequate path shaped by inhibitory connections (Ahmad et al., 2022; Krause et al., 2013). The remaining two panels in **Fig 2.3** depict what would occur in the case of an E/I imbalance. If an excess of excitation is present, without any inhibitory breaks, would lead to runaway excitation, and ultimately to a disorganized neural state. This excess of excitation (**Fig. 2.3.C**), at its extreme, can be associated with the appearance of epileptic seizures (Žiburkus et al., 2013). On the other hand, an E/I imbalance towards excessive inhibition, would impede that the excitatory impulse travels along the required path (**Fig. 2.3.D**), hindering the emission of an appropriate response (Poil et al., 2012). It is believed that the effect of tDCS on cognition can be explained by how the technique shifts this E/I balance (Krause et al., 2013).

In addition to these different acute effects, tDCS has also shown to induce changes in cortical excitability that can outlast the stimulation period, even up to a few hours (Sparing & Mottaghy, 2008). These after-effects are believed to be mediated by changes in membrane polarization

thresholds via GABAergic and glutamatergic synapses for anodal tDCS, and via glutamatergic synapses in cathodal tDCS (Stagg & Nitsche, 2011). It has been shown that the application of repeated sessions of tDCS can induce plasticity processes akin to long-term potentiation (LTP) in the brain (Monte-Silva et al., 2013). Furthermore, animal studies have shown that the LTP or long-term depression (LTD) effects are not linearly linked to stimulation polarity, but rather interact in a complex manner with ongoing brain activity (Kronberg et al., 2017).

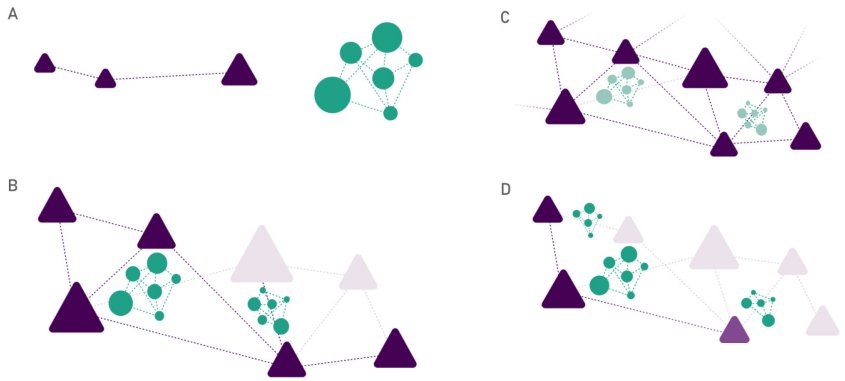

Fig. 2.3. **(A)** Excitatory pyramidal neurons (left, purple triangles) and clusters of inhibitory neurons (right, green circles). **(B)** With adequate E/I balance, in response to an input, a path is shaped by inhibition, to excite relevant connections. **(C)** An example of runaway excitation, where a lack of inhibition leads to an excessive and indiscriminate excitation of other excitatory cells. **(D)** An example of an excess of inhibition that would lead the excitatory input to die out before reaching the appropriate cells to emit a response.

To conclude this section, it must be pointed out that this already complex overview of mechanisms becomes even more complex, the further one looks into each specific explanation. For a more in-depth account of the mechanisms behind the direct and after-effects of tDCS, we refer the reader to Bikson et al. (2019). Just as an example, whilst the current explanations have been based on the effects of tDCS on neurons, there's evidence that tDCS can also act on non-neuronal targets, such as glial and endothelial cells (Morya et al., 2019). And lastly, a relevant recent discussion on emerging putative mechanisms for tDCS has emerged by the proposal that its effects could also be explained by transcutaneous[2] and not transcranial

[2] The term *transcutaneous* is used here as proposed by van Boekholdt et al. (2021) as a potential alternative mechanism for tDCS. However, other non-invasive stimulation approaches are based

mechanisms. As explained above, the shunting of electricity as it passes through the different protective layers of the brain, would mean that the e-field is highest in the skin, where peripheral nerve endings can be found. It is proposed that this higher e-filed can operate at a suprathreshold instead of at a subthreshold level, activating cranial and cervical nerves, which can in turn activate the locus coeruleus, triggering the release of norepinephrine (van Boekholdt et al., 2021). This mechanism is highly interesting, especially for considering the role of the locus coeruleus in arousal processes that serve to sustain vigilance processes as discussed in **Chapter 1**.

Models of tDCS

How behavioural effects can be achieved via these neurophysiological and neurochemical effects of tDCS is a much more complex issue. There are several models that have been proposed to explain how these effects come about.

The **stimulation-dependent model** is based more directly on the above-mentioned initial findings on firing rates and MEPs. This model assumes that the facilitatory and inhibitory effects observed at the neural level with anodal and cathodal tDCS (anodal-excitation cathodal-inhibition, AeCi), translate linearly into improved or worsened behaviour (Bestmann et al., 2015; Fertonani & Miniussi, 2017). This approach however has several limitations: it considers the brain as a passive organ, and it neglects to account for the need for both inhibitory and excitatory activity to adequately perform a cognitive operation (e.g., excitation of task-relevant processes, whilst holding other task-irrelevant processes at bay). Furthermore, this account neglects the fact that to achieve an inhibitory effect, excitation may be required in a different area to exert this control. Confirming these shortcomings, a meta-analysis by Jacobson et al. (2012) reports that the AeCi effect is observed reliably in studies that target motor functions with tDCS, but becomes much less clear in the cognitive realm.

more directly on this mechanism. This is the case of transcranial vagus nerve stimulation (tVNS) where, by access over the ear, the auricular branch of the vagus nerve is stimulated (Briand et al., 2020). This constitutes an interesting approach of bottom-up stimulation, where the effects of stimulation on the cortex emerge from a direct effect on nuclei of the brain stem.

Regarding cognitive effects, they specifically observe that the Ae effects are more common, whereas Ci effects are rarely observed (Jacobson et al., 2012).

The issues established with the stimulation-dependent model lead to the establishment of more complex models that consider potential non-linearity between tDCS-induced effects at the cellular or chemical level and the consequent behavioural outcomes (Fertonani & Miniussi, 2017). A first relevant consideration is made by the **activity dependent model**. Given that tDCS cannot directly lead to an action potential, but merely increase or decrease the chances of this occurring, the outcome of the technique is much more sensible to the underlying pattern of neural activity (Bikson et al., 2013). The effect of tDCS will affect neurons that are near-threshold, which can therefore be controlled by the external application of a task that induces a certain pattern of activity, which has been referred to as functional targeting (Bikson et al., 2013). This was more directly tested by Bortoletto et al. (2015), comparing the combined application of anodal tDCS with either a motor practice that would induce learning and motor excitability, or a motor practice inducing neither learning nor cortical excitability changes. The results showed that excitability-induced changes (as evidenced via MEPs) y the first motor practice (aimed at learning and excitability), hindered the learning effects, whereas in the second motor practice (aimed at not inducing learning nor excitability), they were facilitated. These results serve as evidence for task-dependent effects of tDCS. Furthermore, they show that the additive use of excitability-inducing practices (from the task and tDCS protocol, in this case) does not necessarily yield an added beneficial effect.

Extending this prior idea, it must also be considered that there will be activity-dependent effects beyond the targeted area, as the effects of tDCS may spread through anatomical or functional networks (Bikson et al., 2013; Miniussi et al., 2013). This **network activity-dependent model**, could further predict more specific effects within the overall low spatial and temporal resolution of tES techniques (Fertonani & Miniussi, 2017). This idea is also supported by the fact that stimulating a specific hub that may connect different networks or areas, will likely induce a network-wide effect beyond the target area (Luft et al., 2014; Morya et al., 2019). This could potentially also explain how the effects of tDCS spread across different networks.

At this point, the resulting cascade of effects can become quite complex and difficult to predict, as the excitatory effects in one network could trigger an inhibitory effect in a distal area (Bergmann & Hartwigsen, 2021). What's more, the combination of antagonist effects could potentially cancel each other out, leading to null net changes, in what is known as **zero-sum models** (Brem et al., 2014). In line with this idea, Iuculano & Cohen Kadosh (2013) have observed dissociated effects with different protocols: one tDCS protocol enhanced numerical learning, but impaired the automaticity for the learned material, whereas another protocol produced the opposite effect. The zero-sum model also raises an important point regarding the availability of resources. If cognitive resources are believed to be constant, it would be expected that altering the normal functioning of a neural network to boost its functioning, would necessarily determine that a different network or region must function sub-optimally. On the other hand, if the improved network functioning can be achieved more efficiently, without consuming additional resources, that would not be the case. This still remains an open question (Brem et al., 2014).

A last refinement of the models explaining tDCS effects is the **stochastic resonance model**. This model is based on the phenomenon that weak signals can be perceived better when a certain amount of noise is added (Miniussi et al., 2013). If applied to how tDCS affects the brain, this would mean that the addition of noise (by means of external stimulation) would affect neurons that are more proximal to the firing threshold (Abrahamyan et al., 2011; Miniussi et al., 2013). Therefore, according to this model, the intensity of the noise induced via tDCS and the state of the brain that it is applied to will determine whether a subthreshold signal is inhibited or facilitated, with subsequent behavioural outcomes (Fertonani & Miniussi, 2017).

The models outlined above raise the important point that the effects of tDCS on behaviour are far from linear and straightforward, encountering a myriad of potential factors that could determine one outcome or the other. If the more simplistic assumption as done by the stimulation-dependent or AeCi models (depicted in Fig. **2.4.AB**) is scrutinized in more detail, we can uncover the different interacting variables affecting the pathway from applying tDCS to observing a behavioural effect. As illustrated in **Fig. 2.4.B**, the application of tDCS will lead to the induced e-field in the brain, which

will induce changes in the local neural activity of the targeted region, as well as producing remote or distal network effects, as outlined above. The combination of this activation may induce changes in the cognitive function of interest, which can be measured by the performance in a task.

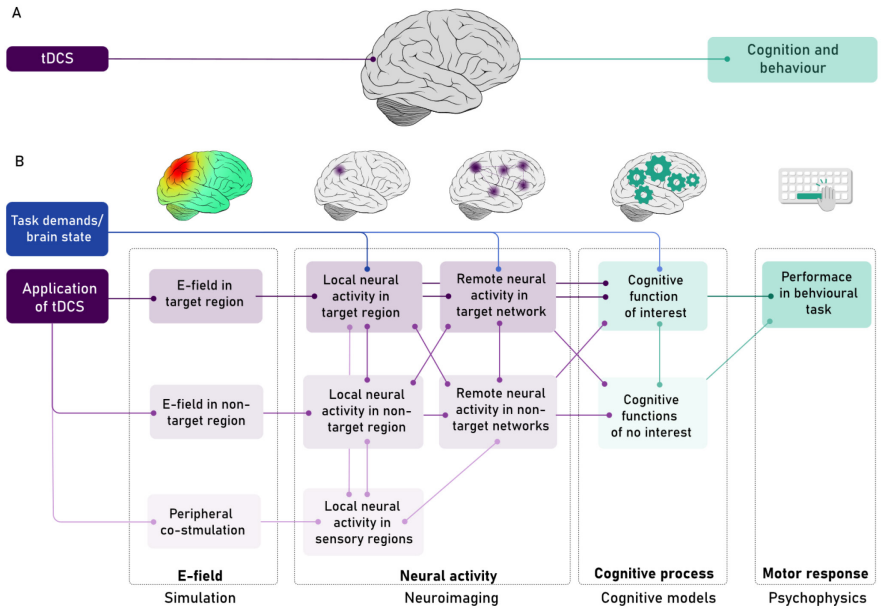

Figure 2.4. **(A)** The more naïve and straightforward linear assumptions which can be made from a stimulation-dependent point of view about the cognitive and behavioural effects of tDCS. **(B)** Causal chain of possible events that can unfold from the application of a tDCS protocol. The darker connecting lines (dark purple and dark green) represent the direct or core chain of causal events, whereas the lighter lines represent broader network or peripheral effects, and the blue arrows represent the impact of task demands or the current brain state during stimulation. The dotted boxes enclose the different measures that can be obtained in each level, and the appropriate measuring technique below. *Note.* Adapted with permission from Bergmann & Hartwigsen (2021).

And yet, this already complex and subject to variability chain of events is merely the tip of the iceberg. At each level of the chain of events, secondary effects may be taking place that corresponds to the brain's response to the input from the stimulation protocol, and not the researcher's desired outcome. The e-field that is induced is likely to affect beyond the target regions (especially if we consider applications of conventional tDCS with larger electrodes), triggering a parallel cascade of activity in local and remote networks that were not intended to be targeted, potentially affecting other cognitive functions that are not the object of the stimulation

protocol. The e-field may also lead to peripheral co-stimulation, which can trigger local activity in sensory regions as well as activity in subcortical structures such as the locus coeruleus as outlined above. As indicated in **Fig. 2.4.B** the crossover and interaction between all these different levels, highlights the difficulty in estimating tDCS outcomes.

Variability in tDCS outcomes

The effects of tDCS can vary due to multiple causes. A first group of external factors relate more directly to the stimulation protocol or dose used. In tES, the term dose refers to the different parameters that determine the electromagnetic field that is generated in the body (Peterchev et al., 2012). Furthermore, a myriad of other internal more individual factors can modulate tDCS outcomes as well. An overview of potential factors of variability is summarized in **Table 2.1**.

Table 2.1. Factors that can modulate tDCS outcomes

Factor	Relevant finding(s)
External factors (tDCS dose)	
Montage	Stimulation outcomes can be determined by the type of protocol that is being used. A first distinction would be the use of conventional vs. HD-tDCS (Masina et al., 2021), with the latter inducing more focal e-fields (Datta et al., 2009; Edwards et al., 2013), and inducing a pseudo-unipolar effect (more on this in Polarity). Furthermore, the shape, size, material, and/or saline or gel-based electrodes will also influence outcomes (Gebodh et al., 2019).
Duration	Earlier studies had established that a linear relationship existed between the duration of a session of tDCS and the observed aftereffects on motor cortical excitability (Nitsche & Paulus, 2001). However, more recent studies have observed that with stimulation durations exceeding 26 minutes, a reversal of the positive effect of tDCS was observed both on corticospinal excitability (Hassanzahraee et al., 2020a) and motor cortex excitability (Monte-Silva et al., 2013). These results may be explained as a means of homeostatic regulation, in the sense that, after a certain duration, a counterregulatory process is activated in order to avoid excessive neural excitation. A potential second wave of reversal may be observed with time if plastic processes take place (Hassanzahraee et al., 2020b).
Intensity	The relationship between stimulation intensity and tDCS-induced cortical excitability is also non-linear, in the sense that more does not always lead to a larger effect (Esmaeilpour et al., 2018; Ho et al., 2016). For example, Hassanzahraee et al. (2020b) showed that lower intensities (0.7 mA) led to the expected increments in

	corticospinal excitability, whereas this effect is reversed at higher intensities (1-1.5 mA). The translation of these effects on motor components is likely to lead to an even more complex picture when applied to cognitive effects.
Polarity	Stimulation protocols can never be completely unipolar, as the injection and consequent exit of the current from the brain will always induce both anodal and cathodal effects respectively (Gebodh et al., 2019). However, a pseudo-unipolar effect (Karabanov et al., 2019) can be achieved by the use of HD-tDCS, as the polarity is skewed in favour of the central electrode (e.g., anodal) (Alam et al., 2016), with a peak of the electric field below the central electrode, that is reduced considerably at the ring perimeter (formed by the surrounding return electrodes), and is rendered non-observable outside the ring (Edwards et al., 2013). As discussed in the *Models* section, excitatory and inhibitory effects induced in the brain do not translate to straightforward beneficial or detrimental behavioural effects when inspecting tDCS effects beyond the motor realm (Jacobson et al., 2012). Depending on the application, behavioural improvements can also be observed with cathodal tDCS (Pirulli et al., 2014).
Repetition	Some studies show that the repeated application of tDCS can lead to cumulative increments of cortical excitability (Ho et al., 2016), which could further enhance LTP-like plasticity-inducing processes (Monte-Silva et al., 2013) that facilitate behavioural outcomes. This multisession approach is therefore used commonly in clinical applications where permanent changes are sought after (Ulam et al., 2015).
Online/ Offline	While not directly a tDCS dose parameter, the use of either a concurrent behavioural task (online-tDCS), or passive stimulation (with the brain at rest, offline-tDCS) where the effects of tDCS are tested immediately after, is an important external factor to control. Online tDCS has proven to more effectively aid in skill acquisition as compared to offline tDCS (Martin et al., 2014). See more details below in *Brain state during tDCS*.
Internal factors	
Anatomy	Individual differences between the thickness and morphology of the different protective layers will affect current shunting and dissipation, which can lead to differences in the current that reaches the brain (Datta et al., 2009). Furthermore, once in the brain itself, the e-field is highly sensible to cortical thickness (Filmer, Ehrhardt, Shaw, et al., 2019), and cortical folding (Salvador et al., 2010). Current advances are emerging to better approximate, calculate and simulate the e-field induced by a given protocol, and for a highly precise calculation of induced current, an individual's own MRI data can be used for e-field modelling (Antonenko et al., 2019).
Brain-state during tDCS	As already highlighted in the **Models of tDCS** section, while the choice of an anatomical region to be targeted with tDCS is important, further selectivity can be achieved by the use of online tDCS, where the stimulation protocol is applied in combination with a task (Bikson et al., 2013; Bradley et al., 2022). In fact, some studies show that a certain degree of activation by a task leads to beneficial effects,

	whereas when excessive activation is present, the effects of tDCS can be detrimental (Bortoletto et al., 2015).
Baseline performance	Low baseline behavioural performance has predicted greater tDCS-related improvements in sustained attention in healthy adults (Gan et al., 2022) and in older adults who were vulnerable to sustained attention deficits (Brosnan et al., 2018).
Baseline brain-state	By using magnetic resonance spectroscopy, Filmer, Ehrhardt, Bollmann, et al., (2019) showed that participants with a lower E/I balance (higher GABA concentrations relative to glutamate) prior to receiving tDCS, showed a greater response to the stimulation protocol. Although other studies report no impact of baseline measures on the effects of tDCS, such as short intracortical inhibition (SICI) (López-Alonso et al., 2014).
Arousal	Objective and subjective indicators of arousal show that moderate levels of arousal facilitate tDCS effects (Esposito et al., 2022)
Beliefs about tDCS and group assignment	Participants' beliefs about whether they belong to the sham or active intervention group have shown to, in some cases, better predict the outcomes of the tDCS intervention in reducing inattention symptoms in adults with ADHD, as well as predicting intervention-induced increments in mind-wandering in healthy adults (Fassi et al., 2023). While still surrounded by controversy (Gordon et al., 2022), this highlights the need to assess and account for these potential effects and adequately assess blinding efficacy in tDCS studies (Fassi & Cohen Kadosh, 2021).
Age	The plasticity-inducing effects of tDCS can be reduced with older age (Perceval et al., 2016). Furthermore, age-related changes in brain function and morphology may cause results obtained in younger adults to not translate linearly (Hartwigsen & Silvanto, 2023). This is also the case for the application of tDCS in children and adolescents, with the addition of ethical concerns (Cohen Kadosh et al., 2012).
Others	Hormonal differences, such as those produced by sex differences, can account for some of the variability observed in tDCS effects as well (Kuo et al., 2006; Ridding & Ziemann, 2010). Furthermore, certain genetic polymorphisms can also modulate responsiveness to tDCS (Nieratschker et al., 2015; Ridding & Ziemann, 2010).

The listed factors do not constitute an exhaustive list, as there are many more nuances behind each factor, as well as their potential interactions. As a case in point, Benwell et al. (2015), for example, reports an interaction between baseline behavioural performance and stimulation intensity, wherein participants with a high discrimination sensitivity at baseline responded better to lower tDCS intensities (1 mA), and participants with a lower discrimination sensitivity at baseline responded better to higher intensities (2 mA).

With emerging evidence of null findings of behavioural effects (Jacoby & Lavidor, 2018) or induction of neurophysiological changes (Horvath et al., 2015), it becomes clear that to adequately advance tDCS research, in-depth knowledge about the technique and careful consideration of all these different factors that can affect at the inter- (L. M. Li, Uehara, et al., 2015; López-Alonso et al., 2014) and intra-individual levels (López-Alonso et al., 2015; Willmot et al., 2024), is paramount (Bergmann & Hartwigsen, 2021; Filmer et al., 2020; Guerra et al., 2020). Furthermore, it is important to use reliable and comparable methods that allow for the growth of a more solid base of evidence. In conclusion, i) the higher specificity obtained by functional targeting achieved through online tDCS, ii) the use of HD-tDCS, which has shown to produce more reliable outcomes (Masina et al., 2021) likely due to increased focality (Edwards et al., 2013), and iii) the use of additional neuroimaging data to not solely rely on behavioural effects, are three strong contenders to achieve this purpose.

Conclusions

The exploration of tDCS as a tool to modulate cognition, with the aim to further inspect its role in modulating vigilance more specifically in **Chapters 3** and **4**, reveals that whilst significant advances have been made to understand and refine the technique, much is yet to be explored. By means of using more focal stimulation protocols, such as those employing HD-tDCS, and by more specifically targeting task-relevant neurons via functional targeting (i.e., online stimulation), more predictable outcomes can be achieved. However, outcomes are still subject to a long and varied list of factors, from specific stimulation parameters to individual neuroanatomical differences. Adequate control or reporting of these factors is needed in research going forwards to aid in more precisely predicting tDCS outcomes. While we have come a long way since the first historic and rudimentary applications of tDCS, a long road is still ahead for further refinement in our understanding of the technique and its applications.

Chapter 3

Transcranial direct current stimulation and its applications in attention deficits

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Abstract

This chapter synthesizes recent evidence on whether transcranial direct current stimulation (tDCS) can effectively help to enhance or maintain attention and/or boost the effects of cognitive training, focusing on attention deficits that occur in attention deficit hyperactivity disorder (ADHD) and acquired brain injury (ABI). Meta-analyses of tDCS studies show inconsistent or null clinical and cognitive results. However, more recent studies with finer-grained approaches, such as more precise electrode placements, larger sample sizes, and/or more sessions, provide reliable evidence that not only individual brain areas are activated or inhibited, but that functional networks are positively influenced by tDCS. We can conclude that the formal "one size fits all" neurostimulation approaches do not adequately address the wide-ranging effects of developmental, vascular, and traumatic origin that affect entire networks. Recommendations for clinical applications are not yet possible due to the still partly contradictory results and not yet unified research approaches.

Introduction

Attention shapes our everyday interactions with our external environment and our internal thoughts. It can be considered as a window to the world, which, when narrowed or distorted, leads to attention deficits. Attention deficits result from developmental or maturational alterations of brain function or structure (as occurs in attention deficit hyperactivity disorder, ADHD) or due to brain lesions that lead to the loss of an acquired function (acquired brain injury, ABI).

ADHD is a neurodevelopmental condition characterized by persistent, age-inappropriate patterns of inattention and/or hyperactivity-impulsivity (American Psychiatric Association., 2013), with a prevalence of 5.9% in childhood and 2.5% in adulthood (Faraone et al., 2021). On a cognitive level, ADHD has been associated with difficulties in vigilance, working memory, and response inhibition, among other areas (Pievsky & McGrath, 2018).

The most common causes of ABI are vascular injuries (stroke) or traumatic brain injuries (TBI). A stroke is caused by the interruption of blood supply (and therefore oxygen) to the brain, most commonly due to a blood clot (ischemic stroke), or due to the burst of a blood vessel (hemorrhagic stroke). TBI is caused by sudden trauma to the brain due to an external force (open or closed head injury). Overall, ABI has been considered a silent epidemic, as higher post-injury survival rates have led to an increase in patients suffering from cognitive impairments that are often overlooked in light of other more physical consequences (Kapoor et al., 2017). Whilst recovery rates vary greatly, cognitive deficits, and especially attention deficits, often persist into chronic phases (Catroppa & Anderson, 2005).

In fact, both ADHD and ABI can be linked. On the one hand, the impulsive or often reckless behavior observed in ADHD patients increases the risk of sustaining brain injuries; whereas, on the other hand, without pre-existing attentional impairments, the prevalence of these deficits following an ABI has led to the characterization of secondary ADHD, documented for TBI (Max et al., 2004).

Currently, the evidence for stand-alone cognitive training to maintain or improve attentional functioning is limited, both for ADHD (Rubia, 2018) and for ABI (Virk et al., 2015). In addition, across both disorders,

pharmacological treatments for attention deficits can have limited to no long-term effects (Molina et al., 2009; Sivan et al., 2010) or cause adverse effects (Cortese, 2020). This highlights the need for improved intervention strategies, such as using non-invasive brain stimulation (NIBS) in combination with cognitive training. This approach has already shown beneficial effects in healthy subjects (Martin et al., 2014), and thus, offers an excellent potential for clinical application. Among NIBS techniques, transcranial direct current stimulation (tDCS) sparks special interest, not only due to its safety, tolerability, portability, and relative low cost; but also due to its capacity to reinforce neural learning patterns (namely, long-term potentiation), especially considering the cumulative effects of a multi-session approach (Chan et al., 2021). Given that both ADHD and ABI-related attention deficits are related to specific alterations in brain structure and function (as will be reviewed below), tDCS may help "rewire" –via strengthening of synapses– altered, new, and/or more functional circuits for improved attentional functioning.

Attentional networks and tDCS

Traditionally, neuroimaging in healthy brain and lesion studies have converged on a right-lateralized network of cortical and subcortical areas, involved in attention (Langner and Eickhoff 2013; Molenberghs et al. 2009). However, recent whole-brain functional connectivity analyses paint a more complex picture: cortical, subcortical, and cerebellar regions beyond the more traditionally considered "hubs" are involved in sustaining attention (Rosenberg et al., 2016). As a case in point, a recent meta-analysis across a wide range of brain disorders showed that active tDCS effectively improved attention and/or vigilance/sustained attention, compared to sham tDCS and also to active transcranial magnetic stimulation (TMS) (Begemann et al., 2020). This apparent superiority of tDCS may be related to the fact that the diffuse and broad electric field (e-field) produced by the technique –especially by conventional montages with large electrodes (Datta et al., 2009)– might (1) better target the broad networks required for attention, and (2) produce more relevant cognitive outcomes given that attentional processes share considerable functional and anatomical overlap with executive functions and working memory.

Applications of tDCS in ADHD

Neuroanatomical correlates

Evidence from structural (mainly diffusion-weighted imaging, DWI) and functional magnetic resonance imaging (fMRI) indicate that ADHD patients show a maturational delay in neural development (Rubia, Alegria, and Brinson 2014; Rubia 2018). Further fMRI evidence suggests that during attentional tasks ADHD patients show reduced activation in areas of the visuospatial attention network, such as the right dorsolateral prefrontal cortex (rDLPFC), left posterior basal ganglia, right thalamic regions, and right inferior parietal regions (Hart et al., 2013). This is, on the other hand, accompanied by enhanced activation in the cerebellum and occipital lobe, suggesting a compensatory activation of posterior regions of the DLPFC-parieto-cerebellar network of sustained attention (Hart et al., 2013).

The neural alterations underlying attention deficits in ADHD could be summarized as (1) an abnormal under-activation of task-relevant areas, such as inferior and dorsolateral prefrontal, striatal, parietal, and cerebellar regions, and (2) an abnormal over-activation of task-irrelevant areas, comprising areas of the default mode network (DMN), which is observed especially when task demands increase (Rubia, 2018). Given these deficits, two potential principles of action for tDCS interventions could be deduced: (1) facilitating neural activity of task-relevant areas via anodal tDCS, or (2) inhibiting/reducing neural DMN activity via cathodal tDCS.

Interventions on attention deficits in ADHD with tDCS

Recent meta-analyses evaluating the efficacy of tDCS in attentional functioning in ADHD patients suggest at least partial effects of tDCS on clinical or cognitive outcomes. A meta-analysis focusing on studies using tDCS to target inhibitory control (IC) and working memory across pediatric and adult ADHD patients observed a robust improvement in IC, especially with anodal tDCS over the DLPFC (Salehinejad et al., 2019). A more recent meta-analysis focusing on clinical outcomes such as self-report of symptom severity observed that tDCS had immediate effects on overall symptom severity, and on inattention symptoms, mainly with protocols involving pediatric samples, applying offline stimulation, targeting the left

dorsolateral prefrontal cortex (lDLPFC) and using anodal stimulation polarity (Brauer et al., 2021). Neuropsychological tests yielded significant results only for IC, but not for attention or working memory. Exploring follow-up measures revealed a maintenance of the benefits on overall symptom severity. In contrast, inattention improvements remained significant only at trend-level, and hyperactivity showed a delayed effect (as it had not been impacted immediately after the intervention).

However, Westwood, Radua, and Rubia (2021) completed a meta-analysis focused on cognitive outcomes (attention, inhibition, and processing speed) of tDCS interventions in ADHD, where no significant effects of tDCS on attention were observed, attributed to overall low sample sizes and methodological limitations within the included studies. In view of these largely discouraging results, at least regarding the more cognitive effects of tDCS on attention, we will now review some studies (summarized in **Table 3.1**) that may still be relevant to the reader because they were published after the reviewed meta-analyses, or because they used substantial sample sizes, longer total study durations, or additional neuroimaging techniques.

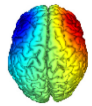
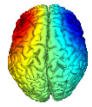
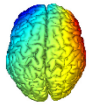
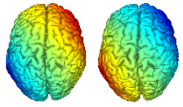
Leffa et al. (2022) recently published the largest study to date, both sample-wise (N = 64) and session-wise (28 sessions). This study shows that repeated application of anodal tDCS at 2 mA over the right (r)DLPFC (with the cathode over lDLPFC) reduced inattention scores in adult ADHD patients' symptom ratings, underlining the potential relevance of treatment duration/intensity. Breitling et al. (2016) applied 10 minutes of anodal tDCS over the right inferior frontal cortex (rIFC) in adolescent ADHD patients, facilitating their performance in a cognitive control (flanker) task to levels comparable to healthy controls, while patients in the sham tDCS group showed impaired performance. However, these analyses considered only the first session of each participant, as the cross-over design led to considerable learning effects. Lastly, with a broader age range, but larger sample size and intervention duration/intensity, the rIFC was again targeted with anodal tDCS, combined with online cognitive training (Westwood, Criaud, et al., 2021). This study showed no effect of tDCS on ADHD clinical symptoms or cognitive performance. Although, it must be noted that the placement of the cathode in this study over Fp1 might not be

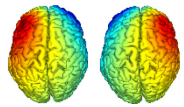
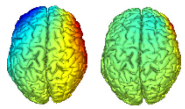
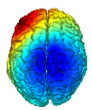
ideal as it is relatively close to other left frontal areas that have been used as effective targets for anodal stimulation in other studies (Dubreuil-Vall et al., 2021; Soff et al., 2017), leading to potentially undesirable inhibitory effects in this area.

We can also gain relevant information from studies that include neural data in their study design, to expand on cognitive and clinical outcomes. Regarding electroencephalography (EEG) data recorded in tDCS studies, Cosmo et al. (2015), observed increased functional EEG connectivity for sixty adults with ADHD after applying anodal tDCS over the lDLPFC. The effect on functional connectivity was observed under the anode but also spread to other occipital, left and right temporal, and centroparietal areas, indicating network effects following tDCS (Cosmo, Ferreira, et al., 2015). Although, the same researchers have reported null effects of the same tDCS protocol on go/no-go performance in a smaller sample (Cosmo, Baptista, et al., 2015).

Two further studies exploring EEG correlates of tDCS in ADHD have reported effects on event-related potentials (ERPs). Breitling et al. (2020) observed increased mean amplitudes of P300 and N200, in response to both anodal conventional and HD-tDCS over the rIFC, reflecting more resemblance to these ERP components in healthy controls, i.e., greater attentional control. While no behavioral effect was observed in this study (n-back task), it was noted that for HD-tDCS, patients with higher hyperactive/impulsive symptom load showed larger positive effects of tDCS on the task, which was not observed for the conventional tDCS montage (Breitling et al., 2020). Furthermore, Dubreuil-Vall et al. (2021) observed a beneficial effect of anodal tDCS over the lDLPFC (but not sham, nor rDLPFC tDCS) on cognitive control (faster RTs on incongruent flanker task trials). These behavioral results correlated with increased amplitudes of P300 and decreased amplitudes of N200. In another cognitive control task (stop signal task) of the same experiment, stop trials were not affected by tDCS, but anodal lDLPFC tDCS also led to reduced RTs for go trials, which correlated with increased P200 amplitude (Dubreuil-Vall et al., 2021). Importantly, a state-dependent effect of tDCS is shown: reduced P300 amplitudes and small N200 amplitudes at baseline (associated with impaired cognitive performance) correlated with greater P300 amplitude increases and N200 decreases after tDCS (associated with improved cognitive performance).

Table 3.1. Selected studies targeting attentional deficits in ADHD with tDCS

Reference	*N*	Groups	Age	Design	Protocol	Intervention	Outcome	Estimated e-field[1]
Leffa et al. (2022	64	Active Sham	38.2 (10.3) 38.4 (9.1)	Parallel, sham, DB	2 mA | 30 min **A**: rDLPFC, **C**: lDLPFC 3.14 cm^2	28 sessions | Offline	Reduction of inattention symptom scores in active tDCS group.	
Cosmo, Ferreira, et al. (2015)	60	Active Sham	31.8 (11.6) 32.7 (10.4)	Parallel, sham, DB	1 mA | 20 min **A**: lDLPFC, **C**: rDLPFC 35 cm^2	1 session | Offline	Increased functional EEG connectivity after tDCS under anode (lDLPFC), spread to occipital, left/right temporal, and centroparietal areas.	
Westwood et al. (2021)	50	Active Sham	13.1 (2.0) 14.2 (2.1)	Parallel, sham, DB	1 mA | 20 min **A**: rIFC, **C**: CSA 25 cm^2	15 sessions | Online (cognitive training)	No improvement of clinical symptoms, nor cognitive performance.	
Breitling et al. (2016)	42	ADHD Controls	14.33 14.24	Cross-over, sham, SB	1 mA | 20 min **A/C**: rIFC, **C/A**: left mastoid 35 cm^2	1 session each protocol | Online (Flanker Task)	No overall effect. Analyzing only the 1st session of each participant revealed a benefit of tDCS on omission errors and RTs.	

Dubreuil-Vall et al. (2021)	40	EFT SST	43.9 (14.8) 31.2 (13)	Cross-over, sham, DB	2 mA | 30 min **A**: r/lDLPFC, **C**: CSA 35 cm^2	1 session each protocol | Offline	Improvement with anodal tDCS over lDLPFC reduces RTs in Flanker Task. Small N200 and large P300 were linked to better performance. Better effect of tDCS in participants with ERP indicators of worse performance at baseline.	
Breitling et al. (2020)	30	ADHD Controls	13.3 (1.9) 12.3 (1.8)	Cross-over, sham, DB	*Conventional:* 1 mA | 20 min **A**: rIFC, **C**: CSA 35 cm^2 *HD (4 × 1):* 0.5 mA | 20 min **A**: rIFC **C**: NS 1 cm diameter	1 session each protocol | Online (5 minutes after tDCS onset: n-back task)	Higher mean P300 and N200 amplitudes both with active conventional and HD-tDCS protocols, more in resemblance to healthy controls.	
Sotnikova et al. (2017)	13	Active Sham	14.2 ± 1.3	Parallel, sham, DB	1 mA | 20 min **A**: lDLPFC (13 cm^2), **C**: Vertex (35 cm^2)	1 session | Online (n-back task)	Greater activation of lDLPFC (+ correlated areas) during 1-back and 2-back tasks with active tDCS, maintained for 20 min. post-stimulation.	

Note. **DB:** double-blind**, SB:** single-blind**; A:** anode placement; **C:** cathode placement; **HD:** high-definition, **CSA**: contralateral supraorbital area (corresponding to Fp1 or Fp2 electrode positions); **NS**: not specified; **EFT**: Eriksen flanker task; **SST**; stop-signal task

[1]E-field estimates were completed in NIC v2.1.0 software (Neuroelectrics®,Barcelona, Spain) with the stimulation procedure reported in each study. Note that the electrode size (as specified in the Protocol column) could not be adjusted for each protocol and were calculated with a standard size for high-definition tDCS (3.14 cm^2). Therefore, the representation should only be taken as an approximation. The e-field is represented in mV, and while the scale varies across protocols, red tones reflect positive values and blue tones, negative values.

Lastly, Sotnikova et al. (2017) conducted a concurrent tDCS and MRI experiment, showing that adolescents with ADHD receiving anodal tDCS over the lDLPFC showed greater activation of the lDLPFC, left premotor cortex, left supplementary motor cortex, and precuneus during 1-back and 2-back tasks. This effect was maintained for 20 min after stimulation (Sotnikova et al., 2017). Notably, this sample of adolescent patients continued receiving the same tDCS protocol for 4 additional sessions, reporting a reduction of clinical symptoms of inattention, which was especially notable at a 7-day follow-up (Soff et al., 2017).

From this overview, we can gauge that meta-analyses show partial evidence of the effectiveness of tDCS in improving attentional functioning in ADHD patients. With a prominent focus on the DLPFC or rIFC as a stimulation site, some individual studies show beneficial effects on clinical and cognitive outcomes, highlighting the potential benefits of using longer interventions for the long-term maintenance of effects. Additionally, several neuroimaging studies show increased functional connectivity and activation of relevant brain regions during tasks following tDCS. However, the limitations of sample size, methodology, and inconsistent results should be considered. Further research is needed to determine optimal stimulation parameters, target regions, cognitive tasks, and/or treatment duration to maximize the benefits of tDCS in ADHD.

Applications of tDCS in ABI

Neuroanatomical correlates

After TBI, widespread and diffuse axonal injury is commonly observed (Bonnelle et al., 2011; Wilde et al., 2006), associated with overall impairments in cognitive functioning, attention, memory, and executive functions (Oehr & Anderson, 2017). Following a stroke, white matter lesions can also be observed, which have been linked to the level of cognitive impairment (Sun et al., 2014). Attentional functioning in ABI patients has been mainly linked to the following white matter tracts: the arcuate fasciculus, corpus callosum, fornix, cingulum, and superior longitudinal fasciculus (Verhulst et al., 2023; Wallace et al., 2018). Furthermore, lower integrity of white matter nodes of the DMN has been linked to higher RT variability (Bonnelle et al.,

2011). Additionally, resting-state fMRI data show that lower functional connectivity within the DMN is related to worse attentional functioning (Verhulst et al., 2023), specifically predicting worse sustained attention, i.e., reduced vigilance, in TBI patients (Bonnelle et al., 2011). Regarding brain volume, worse attentional performance has been observed with smaller overall grey matter volumes and cingulate gyrus volumes (Verhulst et al., 2023). Higher atrophy rates of the cortex, white matter, and other regions have also been linked to worse attentional functioning after ABI, predicting attentional and executive functioning at 12 months (Verhulst et al., 2023). In the case of pediatric TBI, the overall amount of damaged tissue seems to be more predictive of cognitive outcomes than its specific location (Power et al., 2007), perhaps due to a lower functional specification to exact cortical areas at earlier ages.

In summary, numerous brain regions can be affected by ABI and lead to attentional deficits, which highlights the widespread and network-based neural integration of attention. Consequently, finding a specific "one size fits all" neurostimulation protocol becomes quite challenging, if not impossible.

Interventions on attention deficits in ABI with tDCS

Two meta-analyses on tDCS studies applied to stroke patients reveal that tDCS can improve attention or concentration performance, as well as overall cognition (Khan et al., 2022; Yan et al., 2020). Khan et al. (2022) observe a high specificity, with tDCS benefitting attention (and aphasia), but not other cognitive domains such as working memory or visual neglect; although it must be noted that the number of studies included for each domain is quite low. Additionally, Yan et al. (2020) determined that tDCS seems to be more effective for (1) shorter elapsed time between stroke-onset and the tDCS intervention, and (2) ischemic rather than hemorrhagic stroke. While these modulators will likely vary with the specific stimulation protocol used, they should be controlled in future research to maximize intervention outcomes and improve predictions based on clinical characteristics.

A more recent network meta-analysis (which allows comparing the relative effectiveness of several different intervention techniques in the same analysis, even when those have not been directly compared by the trials that are being analyzed) of NIBS interventions for stroke reported network effects of NIBS on general cognition and memory performance (Y. Wang et al., 2023). Despite all tDCS (anodal, cathodal, and bilateral) and high-frequency repetitive TMS (HF-rTMS) interventions showing a beneficial effect on attentional enhancement compared to sham stimulation in the meta-analysis (i.e., pairwise comparisons of each intervention with its corresponding sham or opposite polarity group), no significant effects were observed in the network meta-analysis for this cognitive domain: thus no intervention can be singled out as being conclusively more effective for attentional functioning from the NMA. However, when ranking the different interventions based on their surface under the cumulative ranking line (SUCRA), the authors observed that bilateral montages (targeting contralateral regions with anodal and cathodal tDCS) may be the most effective intervention for attention deficits, closely followed by anodal tDCS in the ranking. However, given the myriad of protocols underlying this classification, and the apparent lack of control for other modulators such as stimulation target, duration, or number of sessions, this information is too limited for specific clinical applications. Furthermore, whilst the answers obtained by an NMA are highly relevant for deciding on effective interventions, given the heterogeneity found among tDCS studies in ABI patients, it might be too soon to reliably apply this analysis approach.

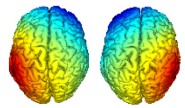
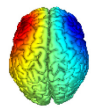
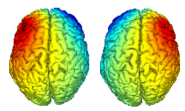
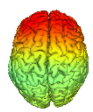
Hara et al. (2021) conducted a meta-analysis more specifically focused on the effect of NIBS on attention and memory in stroke patients. While rTMS significantly improved attention, memory, working memory, and global cognition, tDCS showed no effect on these processes. It must be noted that, whilst the studies included in this meta-analysis overlap with other reports, the number of included tDCS studies is again quite low. There's only one meta-analysis focusing specifically on NIBS interventions for cognitive functions in TBI patients, which concludes that NIBS can be effective to benefit attention (Ahorsu et al., 2021). However, a distinction between the two NIBS techniques (tDCS and rTMS) is not made, and the representation of tDCS studies was low (3 studies). This study also analyzed

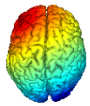
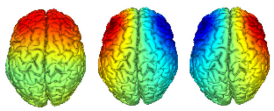
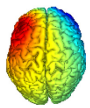
session number and duration but found that they did not significantly affect intervention outcomes.

As discussed above, attentional deficits can have quite a diffuse neural localization, and ABI can lead to many different lesions that explain the observed attentional deficits. This is also represented in the current literature, with quite a few stimulation protocols and large heterogeneity between parameters. While reviewing all individual studies applying tDCS in ABI-related attention deficits is beyond the scope of this chapter, we will now review a small selection of studies (summarized in **Table 3.2**) considered of higher relevance given their sample size, intervention magnitude, or the inclusion of additional neuroimaging measures.

Regarding studies using relatively large sample sizes, Hosseinzadeh et al. (2018) applied only routine treatment (control group), 2 mA anodal tDCS over the left superior temporal gyrus (STG) (intervention 1), cathodal stimulation over the right STG (intervention 2), or sham tDCS (sham control) for 12 sessions in a sample of 100 older adults (25 per group) who had suffered a stroke. They reported increased performance in the trail-making test (TMT) in the anodal group, compared to the cathodal, sham, and control group both directly and 3 months after the intervention. However, they reported differences in TMT performance at baseline between the different groups, that are not further mentioned or accounted for during the remaining analyses, which put the post-intervention group differences into question. Additionally, the reported data and analyses are in some instances incomplete and present some inconsistencies between the in-text reports and the data visualization. Therefore, the results of this study should be interpreted with caution. Liu et al. (2021) applied 20 sessions of 2 mA anodal tDCS over the lDLPFC (with the cathode on the contralateral DLPFC) simultaneous to cognitive training in a sample of 50 stroke patients, observing improved performance in tasks measuring executive functions that can share some overlap with attentional functioning (see **Table 3.2** for details).

Table 3.2. Selected studies targeting attentional deficits in ABI with tDCS

Reference	*N*	Groups	Age	Design	Protocol	Intervention	Outcome	Estimated e-field[1]
Hossein-zadeh et al. (2018)	100 [Stroke]	Active 1 Active 2 Sham Control	58 (8) 60 (7) 59 (8) 59 (7)	Parallel, sham, DB	2 mA | 30 min *1*: **A**: lSTG, **C**: CSA *2*: **C**: rSTG, **A**: CSA 35 cm^2	12 sessions |Offline	Improved performance in TMT, which was maintained at 3-month follow-up. Given the study' s methodological limitations, these results should be interpreted with caution.	
Liu et al. (2021)	50 [Stroke]	Active Sham	65 64	Parallel, sham, SB	2 mA | 20 min **A**: lDLPFC, **C**: rDLPFC 25 cm^2	20 sessions Online cognitive training	Improved executive functions as measured through WCST, SCWT and DST.	
Shaker et al. (2018)[2]	40 [Stroke]	Active Sham	55 ± 5 53 ± 6	Parallel, sham, SB	2 mA | 30 min **A**: r/lDLPFC, **C**: CSA | Electrode size NR	12 sessions Offline cognitive training	Both groups received cognitive training and showed general cognitive improvement, which was significantly greater in the active tDCS group.	
Park et al. (2013)	11 [Stroke]	Active Sham	65 ± 14 66 ± 11	Parallel, sham, DB	2 mA | 30 min **A**: bilateral DLPFC, **C**: extracephalic |	17-18 sessions Online cognitive training	Improvement in auditory and visual CPT scores.	

Kolskår et al. (2021)	54 [Stroke]	Active Sham	69 ± 7	Parallel, sham + only cog. training, DB	1 mA | 20 min **A**: lDLPFC, **C**: occipital/ cerebellum region (O2) 35 cm^2	6 sessions |Offline	All groups performed cognitive training and showed improvement in cognitive tests. No effect of tDCS. No effect of baseline fMRI data on outcomes, nor any effects of intervention on fMRI.	
Sacco et al. (2016)	32 [TBI]	Active Sham	38 (10) 35 (13)	Parallel, sham, Blinding NR	2 mA | 20 min r/lDLPFC[3], contralateral DLPFC or extracephalic return 35 cm^2	10 sessions (2 daily) Offline cognitive training	Improvement in dual attention task, maintained at 1-month follow-up. No impact on other cognitive functions.	
Ulam et al. (2015)	26 [TBI]	Active Sham	31 (10) 38 (15)	Parallel, sham, DB	1 mA | 20 min **A**: lDLPFC, **C**: CSA 3.8 × 4.4 cm	10 sessions Offline	Immediately after and one day after the intervention, delta power decreased, while alpha power increased, under both stimulation electrodes.	

Note. **DB:** double-blind; **SB:** single-blind; **A:** anode placement; **C:** cathode placement; **CSA**: contralateral supraorbital area; **STG**: superior temporal gyrus; **TMT**: trail-making test; **NR**: not reported; **WCST**: Wisconsin Card Sorting Test; **SCWT**: Stroop Color-Word Test; **DST**: Digit Symbol Test; **CPT**; Continuous Performance Test.

[1]E-field estimates were completed in NIC v2.1.0 software (Neuroelectrics®, Barcelona, Spain) with the stimulation procedure reported in each study. Note that the electrode size (as specified in the Protocol column) could not be adjusted for each protocol and a standard size for high-definition tDCS (3.14 cm^2) was used for estimations. Therefore, the representation should only be taken as an approximation. The e-field is represented in mV, and while the scale varies across protocols, red tones reflect positive values and blue tones, negative values.
[2]The montage and simulated e-filed have been altered given that the authors report a montage with bifrontal anodal stimulation over the right and left DLPFC and the cathode over CSA, which is not reproducible given the apparatus employed in this study (2-channel stimulator) and that identifying a contralateral region is only suitable for unilateral montages.
[3]The right or left DLPFC was targeted depending on patients ' lesions.

Similarly, targeting the DLPFC in stroke patients, Shaker et al. (2018) reported that applying bifrontal anodal tDCS at 2 mA for 12 sessions in combination with cognitive training (applied offline) led to an improvement of attention in both the active and the sham groups, with greater overall performance observed in the active stimulation group. However, this report lacks crucial information on the protocol used, which would be necessary for its replicability. Therefore, these results should again be interpreted with caution. Although with a considerable drop in sample size (N = 11), Park et al. (2013) applied a large number of sessions (17-18) of 2 mA anodal tDCS, in a bifrontal montage over the left and right DLPFC, with an extracephalic return. The tDCS intervention was paired with online cognitive training and resulted in an improvement in both auditory and visual attention.

Lastly, we would like to highlight some results from studies using neuroimaging in combination with tDCS interventions. Kolskår et al. (2021) recorded fMRI data during an attention task before and after 6 sessions of 1 mA anodal tDCS over the lDLPFC in combination with cognitive training in stroke patients. At the behavioral level, an improvement in the trained tasks was observed, however, with no additional gain from the application of tDCS, which could potentially be explained by the lower amperage used in this protocol. Furthermore, neural activation prior to the intervention did not predict training outcomes, nor did training gains reflect as any differences in neural activation, which should, however, be considered in light of the absence of behavioral outcomes of tDCS.

Further fMRI results were reported by Sacco et al. (2016), where 10 sessions of anodal tDCS at 2 mA were applied over the lDLPFC of TBI patients in combination with cognitive training (applied offline). At the behavioral level, faster RTs and fewer omission errors were observed after the intervention and, notably, maintained at a 1-month follow-up assessment. Furthermore, neuropsychological tests administered before and after the intervention reflected improved performance in attention (trend level significance), without effects on working memory or other cognitive processes. This argues for specific and long-lasting effects on attention for TBI patients with the present protocol. Furthermore, fMRI data recorded during a dual attention task at baseline and after the intervention (immediately and follow-up) reflected a decreased activation in the right

superior temporal gyrus (rSTG), middle frontal gyrus, and post-central gyrus, as well as middle and frontal gyrus. A particularity of this study is its intervention intensity, as tDCS was applied twice daily, which, given its positive outcomes, makes it a factor that should be explored further for its potential efficacy.

Finally, Ulam et al. (2015) recorded EEG measures at different time points throughout an intervention of anodal tDCS at 1 mA over the lDLPFC in TBI patients. At the behavioral level, the intervention improved performance in neuropsychological tests, regardless of whether active or sham tDCS was applied, which the authors attribute to spontaneous post-injury recovery, and could also be explained by lower stimulation intensities, as discussed above. Regarding EEG data correlated to outcomes on neuropsychological tests several interesting results were observed: (1) alpha power increments correlated positively with improved test scores in both groups, (2) delta power correlated negatively with test scores for a higher number of tests in the active group, and (3) TBI patients who showed greater slowing in EEG at baseline improved in a greater number of tests with active tDCS, compared to patients of the active group who showed no slowing at baseline or patients from the sham group. Regarding the effects of tDCS purely on EEG measures, both immediately after the intervention and at a 1-day follow-up, TBI patients who had received active tDCS showed decreased delta power, while alpha power increased under both stimulation electrodes (anode and cathode). This reflects long-lasting and widespread effects of tDCS on cortical activity, which could "prime" the brain for future neuroplastic behavioral improvements.

To close this section, we will briefly touch upon visual neglect, given its prevalence as a consequence of ABI (Wilson et al., 2017), although delving into the complexities of this topic lies beyond the scope of this chapter. Neglect is characterized by difficulty or inability to detect, orient attention toward, or respond to information presented in the contralesional hemifield (Wilson et al., 2017). It is most commonly observed after right-hemisphere stroke and can affect the sensory, representational, and motor levels, leading to impaired activities of daily living (González-Rodriguez et al., 2022). A recent review from the Cochrane Library concluded that immediate and long-lasting (1-month) effects of NIBS on neglect outcomes count with

favourable evidence, although its certainty was very low (Longley et al., 2021). Interestingly, the potential of tDCS for neglect rehabilitation ties in with the interhemispheric rivalry model of neglect (Kinsbourne, 1977), as the lesioned hemisphere is believed to show reduced activation, while the undamaged hemisphere is overactive (Fasotti & Van Kessel, 2013). In a recent review by González-Rodriguez et al. (2022), it is concluded that tDCS may indeed restore this interhemispheric balance observing positive outcomes when applying cathodal tDCS over the intact hemisphere, to reduce its hyperactivation, and anodal tDCS over the damaged hemisphere, to reduce its hypoactivation. Furthermore, bilateral tDCS (targeting the hypo and hyperactivation simultaneously) seems to be more effective than single tDCS protocols where only one of these approaches is applied (either anodal or cathodal over the damaged, or undamaged hemisphere, respectively). Notably, these results were observed especially for protocols applied over the posterior parietal cortex. Furthermore, programs combining tDCS with other interventions (physical or cognitive therapy, or specific neglect treatments, such as prism adaptations or feedback training) seemed to show higher efficacy than tDCS protocols applied on their own (González-Rodriguez et al., 2022).

In summary, the findings from meta-analyses and individual studies suggest that tDCS can improve attention and overall cognition in ABI patients, with the DLPFC being the most commonly targeted region. We can highlight factors such as the elapsed time since stroke onset and stroke type that may influence the effectiveness of tDCS as potential modulators of its outcomes. Additionally, the need to consider sample sizes, intervention intensity, systematization of cognitive tasks, and/or neuroimaging measures is emphasized. Overall, further research is needed to optimize tDCS protocols and gain a better understanding of its effects on attention in patients with ABI-related attention deficits.

Challenges and Future Outlook

At this point, no specific implications for clinical application/practice can be extracted from the current evidence, given the limited findings, and the constraints of the current literature. Some of these limitations and other outstanding issues will be briefly discussed, to ascertain what should be

considered in future research practice to build more solid evidence that can be of clinical use.

Firstly, regarding sub-optimal study designs and methodological issues, we can highlight the use of overall relatively small samples, leading to underpowered studies. Given the difficulty of data collection in clinical settings, a solution for building evidence with fewer but larger studies could be the emerging "many-labs" approach. Furthermore, there's ample heterogeneity among the stimulation protocols used. An additional aspect often neglected in tDCS interventions is the lack of follow-up measures. Inclusion of these measures is highly recommended, as some studies have shown very beneficial long-term effects (Sacco et al., 2016), or delayed effects of tDCS (Brauer et al., 2021).

Secondly, regarding sub-optimal stimulation protocols, whilst most studies oscillate between applying 1-2 mA for 20-30 minutes, stimulation sites (and specific electrode placements), electrode sizes, and therefore the potential stimulation area/e-field are highly variable, and any small change in the protocol combined with the extensive individual differences observed in clinical samples can produce diverging results. Regarding stimulation targets, both for ABI and ADHD, the DLPFC seems to be the most targeted, and some meta-analyses conclude that it is the most effective stimulation target. However, it might also be over-represented in the literature employed for analyses. Given that many studies consider attentional outcomes only as secondary, diverging the focus from the lDLPFC and towards areas more directly relevant to attentional networks could lead to more clearly beneficial results (Westwood, Radua, et al., 2021). Furthermore, intervention parameters such as the total number and frequency of sessions should be regarded in closer detail, considering the beneficial effects of longer and more frequent interventions (Sacco et al. (2016), and that optimizing this parameter can aid in adequately estimating intervention cost-efficiency. Additionally, most studies (especially in ADHD) use offline stimulation, whereas results from healthy participants suggest that the combined effect of cognitive training and online tDCS is more effective than cognitive training on its own (combined with sham tDCS) (Martin et al., 2013). However, this potential added benefit of cognitive training comes with its own caveats, as differences in training strategies and protocols add

further heterogeneity to the studies. Further systematization of these parameters will positively impact the state of the evidence in this regard.

Especially in clinical research and application, considering individual differences should be crucial. Interventions can be tailored to patients'/participants' neuroanatomy, for example, by modeling the desired e-field onto individual MRI data and altering stimulation parameters to target the same area in the same way across different individuals. A more rudimentary approach, as seen by Sacco et al. (2016) was to apply the stimulation dependent on the lesioned hemisphere, which seemed to show beneficial effects. In the opposite direction, more complex approaches are being developed, such as using Bayesian optimization to individualize stimulation protocols (Lipka et al., 2021; van Bueren et al., 2021). Apart from current modeling and protocol optimization, the inclusion of additional neuroimaging measures should be crucially considered to explore and understand (1) possible neural markers (structural or functional) that can predict stimulation outcomes, and (2) the effects that tDCS has on brain structure and function, beyond and/or along with behavioral effects. Other individual aspects that should be considered are disorder specifications, such as ADHD subtypes, type of stroke, chronicity, or elapsed time between disorder onset and the tDCS application. These factors can largely vary between studies and are often not identified as possible moderators (in meta-analysis) or controlled for in analyses.

Conclusions

While promising results are emerging, the evidence is not clear on specific set parameters, or overall efficacy to the point of widespread clinical application. Therefore, and unfortunately, no specific recommendations on stimulation protocols and parameters can be made to conclude this chapter. Nonetheless, the combination of tDCS with cognitive training or rehabilitation techniques seems to be more promising than applying either of them on its own, due to the "synergistic effects of functional targeting" (Rubia, 2022; Rubia et al., 2021). While it might be too soon for clinical wide-spread application, many new emerging approaches can aid in conducting more high-quality research to better understand the intricate relationship between attentional functioning and brain stimulation.

Chapter 4

Mitigating the vigilance decrement in healthy populations via transcranial direct current stimulation

Abstract

This chapter offers an overview of recent evidence on the effects of transcranial direct current stimulation (tDCS) on the vigilance decrement. Mitigatory, null, and even detrimental findings have been reported with varied tDCS parameters and experimental conditions. The high variability in protocols and outcomes does not allow to establish firm conclusions on the efficacy of tDCS in mitigating the vigilance decrement. This is further limited by the exploration of vigilance (or sustained attention) only being studied as a secondary or additional outcome measure, and not as part of the core design of the study. Overall, the reviewed findings highlight the need for further and more systematic research and the incorporation of additional neuroimaging data to better understand if and under what conditions the vigilance decrement can be mitigated via the application of tDCS.

This chapter offers a review of relevant findings from transcranial direct current stimulation (tDCS) applications targeting attentional functioning, with a special focus on vigilance. The prior chapter has reviewed current evidence of applying tDCS in clinical populations with attention deficits. Given the lack of sparsity of studies specifically exploring vigilance, broader applications on attention were also included. Furthermore, while offering a promising view, specifically how tDCS can benefit vigilance remains inconclusive. Therefore, this chapter aims to narrow this question by more specifically reviewing studies in healthy populations, where less intra-participant variability is expected as compared to clinical populations (López-Alonso et al., 2015; Salehinejad et al., 2019), and a slightly larger body of evidence more specifically centred on vigilance can be found. Nonetheless, as was outlined in Chapter 1, vigilance is, as a concept, difficult to grasp. Therefore, it must be noted that the working definition of vigilance for the present thesis distinguishes vigilance and sustained attention, the definition is treated more loosely to gain a better overview of the literature.

Review strategy

To identify relevant studies, the same following search equation was used: [(tDCS OR "transcranial direct current stimulation") AND (vigilance OR "vigilant attention" OR "sustained attention")]. The search was run on PubMED, Scoupus and Web of Science, returning 362 results in total. After removing duplicates, 200 records were screened by title and abstract to identify experimental studies, using tDCS, and focused specifically on vigilance/sustained attention in healthy samples. Therefore, studies with attributes to clinical samples, consciousness, and sleep-related research, or studies using other forms of NIBS were excluded. The full text of the remaining 91 records was reviewed to screen for the same inclusion/exclusion criteria once more, considering an additional criterion of sample size (minimum > 10 participants per experimental condition) and control (lack of sham or active control condition). One additional record was included through backwards searching (i.e., through the references of one of the included records). This led to a final selection of 23 records[3], which

[3] Two records fulfilling inclusion criteria were not included in the final selection. One record was excluded because it constitutes one of the studies that are included in the empirical section of this thesis, and thus, will be discussed in full detail in **Chapter 6**. Another record was excluded due to

have been divided into tDCS studies exploring purely behavioural effects (**Table 4.1**), studies including EEG measures (**Table 4.2**), studies including other neuroimaging measures (**Table 4.3**), and studies that directly compare the effect of tDCS on the vigilance decrement with other interventions (**Table 4.4**).

Overview of findings

Behavioural effects of tDCS on vigilance/sustained attention

As can be seen in **Tables 4.1**., **4.2**, and **4.3**, there's a high variability among study parameters. We here summarize behavioural findings among the three tables. Samples (which were filtered above a minimum of 10 participants per experimental condition) most commonly ranged between 15 and 30 participants per experimental condition. Moreover, most revised studies employed samples of young adult participants, except for one study with a sample of older healthy adults (Brosnan et al., 2018). The heterogeneity between studies and their findings does not allow any straightforward conclusion about the general efficacy of tDCS to mitigate the vigilance decrement. Nonetheless, several studies observed beneficial effects. For example, both anodal and cathodal tDCS over the left frontal eye field (FEF), with an extracephalic return, led to increased accuracy in a visual search task (Nelson et al., 2015). Gan et al. (2022), similarly, observed that anodal tDCS over the left FEF led to higher sensitivity in detecting targets. This effect was observed online, i.e., during the application of tDCS, and was sustained for another 10 minutes after tDCS offset (Gan et al., 2022). Continuing in the left frontal region, Alfonsi et al. (2023) observed that anodal tDCS over the left dorsolateral prefrontal cortex (lDLPFC) led to faster RTs in the psychomotor vigilance task (PVT). Furthermore, other studies also report beneficial effects when targeting right frontal regions. Anodal tDCS over the right DLPFC (rDLPFC) led to fewer attentional lapses in the continuous temporal expectancy task (CTET), and fewer omission and commission errors in the sustained attention to response task (SART) in a

mismatched reporting. The study claims that there is no effect of tDCS in the abstract, results, and discussion section, whereas a significant group difference is reported in a summary table. Personal communication with the authors has clarified that the group difference is significant but given that the current version of the paper states the opposite, it is excluded to avoid confusion.

sample of older adults (Brosnan et al., 2018). Comparing both anodal HD-tDCS over the rDLPFC and over the right posterior parietal cortex (rPPC), (Luna et al., 2020) observed a mitigated EV decrement (a less pronounced drop of accuracy in detecting infrequent targets with time-on-task), but no effect on the AV decrement (increment of RT and RT variability with time-on-task). Lastly, two studies employing bifrontal tDCS (i.e., anode and cathode in either hemisphere in symmetric positions), also observed beneficial results (Nelson et al., 2014; Sakai et al., 2014). Nelson et al. (2014) observed a mitigated vigilance decrement when the onset of a 10-minute-long tDCS protocol occurred earlier during the task (10 minutes in), compared to a later onset (30 minutes in), both when positioning the anode over the rDLPFC and cathode over lDLPFC, and with the reversed position. In a task that was more applied, as it featured a simulated driving scenario, a specific benefit was observed with a protocol targeting the rDLPFC with the anode, and the lDLPFC with the cathode, as indexed by improved inter-car distance and lane-keeping (Sakai et al., 2014).

In contrast, many other studies observe no effect of tDCS at the behavioural level, with protocols ranging from anodal tDCS over frontocentral, central, and centroparietal regions (Adelhöfer et al., 2019; Erdoğan et al., 2023; van Schouwenburg et al., 2021), anodal and cathodal tDCS over the right rPPC (Coulborn et al., 2020), anodal tDCS over the lDLPFC (Borragán et al., 2018; Dai et al., 2022; Filmer, Griffin, et al., 2019; Martínez-Pérez et al., 2023; Naka et al., 2018), or cathodal tDCS over the lDLPFC at different intensities (Filmer, Griffin, et al., 2019).

And lastly, a last subset of studies reported detrimental effects resulting from the application of tDCS. For example, Li et al. (2015) observed that biparietal tDCS with the anode over the rPPC and the cathode over the lPPC, was associated with slower RTs in a choice reaction task (CRT). Moreover, Roe et al. (2016) observed that both modalities of biparietal tDCS over the PPC led to an overall lower accuracy in a visual search task with high cognitive demand, whereas no effect of tDCS was observed for low or medium load conditions.

Table 4.1. Selected studies targeting exploring the behavioural impact of tDCS on vigilance/sustained attention

Reference	*N*	Groups	Age	Design	Protocol	Task	Moment	Outcome
Brosnan et al. (2018) – Experiment 2	23	Active Sham	73	WP | SB	1 mA | ~ 3 min. (×5) **A:** F4, **C**: Cz 35 cm^2	CTET	Online	Active tDCS was associated with fewer attentional lapses.
Coulborn et al. (2020)	23	Active-1 Active-2 Sham	18-23 (20)	WP | DB	1.5 mA | 20 min. **A/C**: P4, **C/A**: contralat. cheek 25 cm^2	SART	Offline	No effect of tDCS on accuracy or error rate in the SART task.
Erdoğan et al. (2023)	21	Active Sham	18-22 (20)	WP | SB	2 mA | 20 min. **A**: ~Inion, **C**: extracephalic 35 cm^2	CPT	Offline	Changes in CPT performance from pre- to post-stimulation were not affected by cerebellar tDCS.
Filmer, Griffin, & Dux (2019)	150 (30)	Active-1 Active-2 Active-3 Active-4 Sham	23	BP | SB	1 mA | 20 min. **1) A**: F3, **C**: CSA 1/1.5/2 mA | 20 min. **2-4) C**: F3, **A**: CSA 25 cm^2	SART (40 min)	Offline	No effect on accuracy to detect targets in SART by tDCS condition.
Gan et al. (2022)	27	Active Sham	18-24 (19)	WP | SB	2 mA | 28.8 min. **A**: left FEF, **C**: Fp2 25 cm^2	Visual search	Online	Higher sensitivity to detect targets was observed in the anodal tDCS condition, during active stimulation, and after stimulation offset.

Li et al. (2015)	18	Active-1 Active-2 Sham	20-42	WP | SB	2 mA | 30 min. **A/C**: P4, **C/A**: P3 25 cm^2	CRT, RVP	Online Offline	Slower reaction times in last versus first block of CRT with right-anodal/left-cathodal protocol.
Naka et al. (2018)	20 (10)	Active Sham	23	BP | SB	1.5 mA | 15 min. **A**: F3, **C**: C3, F7, Fp1, Fz 4 cm^2	Mod. RVIP	Online Offline	No online or post-stimulation effects of HD-tDCS on sustained attention were observed.
Nelson et al. (2015)	11	Active-1 Active-2 Sham	24-42 (25)	WP | DB	2 mA | 30 min. **A/C**: left FEF, **C/A**: extracephalic 35 cm^2	Visual search	Online	Both active tDCS protocols improved accuracy, compared to sham tDCS.
Roe et al. (2016)	32	Active-1 Active-2 Sham	21-35(25)	WP | SB	1 mA | 24 min. **A/C**: P4, **C/A**: P3 35 cm^2	MOT task	Online	Active tDCS conditions led to lower overall accuracy in a high cognitive load condition. No effect of tDCS was observed under medium and low load.
Sakai et al. (2014)	13	Active-1 Active-2 Sham	35	WP | SB	1.5 mA | 20 min. **A/C**: F3, **C/A**: F4 35 cm^2	Driving simulator	Online	Improved inter-car distance maintenance and lane-keeping with right anodal left cathodal tDCS over DLPFC.
van Schouwenburg et al. 2021)	97 (33/34/30)	Active-1 Active-2 Sham	23	BP | DB	1 mA | 20 min. **A/C**: between Cz-Fz, **C/A**: cheek 9 cm^2 and 35 cm^2	Sustained attention paradigm*	Online	No effect of either active tDCS protocol on pre-post stimulation sensitivity in target detection.

Note. A = anode placement, C = cathode placement, WP = within-participant, BP = between-participant, NR = not reported, FEF = frontal eye field, CTET = continuous temporal expectancy task, CPT = continuous performance test, SART = sustained attention to response task, CRT = choice reaction task, RVP = rapid visual processing task, RVIP = rapid visual information processing task, MOT = multiple object tracking task. The age of participants is reported as a range (if provided) and mean.

While some studies find directly opposite effects, especially surrounding the use of different tDCS polarities over the DLPFC and PPC, the results are difficult to integrate given the vast heterogeneity among the stimulation protocols used. Furthermore, these results highlight the potential relevance of the type of outcome measure that is used, which in the studies here is equally varied. As pointed out by Li, Uehara, et al. (2015), this factor may be greatly contributing to the variability that is observed between studies.

As highlighted in Chapter 2, the inclusion of neuroimaging measures in tDCS studies may help elucidate how and when tDCS can effectively mitigate the vigilance decrement, which will be reviewed in the next section.

Studies exploring the mitigatory effect of tDCS on the vigilance decrement with additional EEG measures

In the studies that reported beneficial behavioural effects, different interesting effects on EEG data were observed. Luna et al. (2020) observed that anodal HD-tDCS over the rPPC led to a reduced increment of pre-post stimulation power in the alpha band (7.5-12.5 Hz), compared to the sham condition and remaining HD-tDCS conditions. Notably, however, this effect seemed to occur independently of the behavioural effects HD-tDCS on the vigilance decrement reported in the previous section. The role of alpha power is difficult to grasp as this reduced increment via tDCS could denote more efficient processing (i.e., less requirement to deploy inhibition of task-irrelevant processes) or task disengagement and/or resource depletion (i.e., where the inhibition of task-irrelevant processes is not taking place or no longer possible). This conceptualization is made more complex by taking into account that oscillations in the alpha band, can reflect many more processes beyond inhibition (Clayton, Yeung, & Cohen Kadosh, 2018). As a case in point, a different study observed an increment of alpha power, as well as beta power, and a reduction of theta and delta power with anodal tDCS over the lDLPFC (Alfonsi et al., 2023). However, no direct association between the beneficial behavioural effects and the EEG correlates was tested in this study. Lastly, in the studies where beneficial effects on vigilance performance with anodal tDCS over the lDLPFC were observed, analysis of event-related potentials (ERP) revealed an increment of the visual evoked selection negativity component in parieto-occipital regions, and an

enhanced frontal P2 component (Brosnan et al., 2018). These results were taken as indicators of increased visual processing and deployment of attentional resources with tDCS (Brosnan et al., 2018).

Furthermore, in the studies observing null findings of tDCS of measures of the vigilance decrement, we similarly find a myriad of effects on EEG measures. Dai et al. (2022) report observing an increment of alpha and beta power—akin to what was observed by Alfonsi et al. (2023) with opposite behavioural outcomes—with anodal tDCS over the lDLPFC. Also contrary to the findings of Alfonsi et al. (2023), Adelhöfer et al. (2019) observe an increment of theta power, regardless of the stimulation condition. Notably this effect was observed specifically for trials featuring no-go targets, which would require the deployment of cognitive control exerted by frontal regions as outlined in the models mentioned in Chapter 1 (Clayton et al., 2015a; Helfrich et al., 2018). Lastly, Martínez-Pérez et al. (2023) observed no pre-post-stimulation changes in alpha power, nor any associations between alpha power changes and the vigilance decrements. Furthermore, they report that baseline alpha power did not predict the vigilance decrement.

Table 4.2. Selected studies exploring the behavioural impact of tDCS on vigilance/sustained attention with additional EEG measures

Reference	*N*	Groups	Age	Design	Protocol	Task	Moment	Outcome
Alfonsi et al. (2023)	20	Active Sham	26-37 (31)	WP SB	1.5 mA | 15 min. **A**: F3 and F4, **C**: temporo-occipital 25 cm^2	PVT	Offline	Reduced RTs in PVT with active tDCS compared to sham. Post-stimulation: power decrement in delta and theta in fronto-central regions, and power increment in alpha and beta bands
Adelhöfer et al. (2019)	19	Active Sham	20-24 (22)	WP SB	2 mA | 900 s **A**: ~Cz, **C**: Fpz 25 cm^2	SART	NR	No behavioural effect of tDCS. Higher theta power in frontocentral electrodes in No-go than Go trials in the sham and anodal groups. After sham tDCS, correlation between pupil diameter and theta band activity, not observed after anodal tDCS.
Brosnan et al. (2018) – Experiment 1	26	Active Sham	74	WP SB	1 mA | ~ 8 min. (×4) **A:** F4, **C**: Cz 35 cm^2	SART	Online	Fewer commission and omission errors in SART with active tDCS. Enhanced signals of frontal engagement (increased P2 component) and early visual attention (increased visual evoked selection negativity component).

Dai et al. (2022)	29 (14/15)	Active Sham	20-25	BP Blind NR	1.5 mA | 30 min. **A**: F3, **C**: Fp2 25 cm^2	MCT, Oddball task, Go/No-Go	Offline	No effect of tDCS on vigilance measures. With active tDCS an increment of power in alpha and beta bands was observed compared to the sham group.
Luna et al. 2020	92 (30/32 /30)	Active-frontal Active-parietal Sham	23	BP SB	1 mA | ~ 28 min. **1) A**: F4, **C**: AF4, Fz, FC2, FC6 **2) A**: P4, **C**: CP2, CP6, PO4, PO8 3.14 cm^2	ANTI-Vea	Online	Mitigated executive vigilance, but not arousal vigilance decrement with both active HD-tDCS protocols. Alpha power increment with time-on-task, was reduced in the parietal electrodes in the parietal HD-tDCS group.
Martínez-Pérez et al. 2023)	78 (~20)	Active-High/Low Sham-High/Low	20	BP DB	1.5 ma | 25 min. **A**: F3, **C**: T7, Cz, Fp2 3.14 cm^2	SART (High/Low load)	Online	A larger vigilance decrement was observed in the high-demand SART, regardless of the stimulation condition. No pre-post changes in alpha power were observed, which were neither affected by tDCS. Baseline alpha power did not predict the vigilance decrement.

Note. A = anode placement, C = cathode placement, WP = within-participant, BP = between-participant, NR = not reported, MCT = Mackworth clock test, PVT = psychomotor vigilance task, SART = sustained attention to response task, ANTI-Vea = attention networks test for interactions and vigilance—executive and arousal components. The age of participants is reported as a range (if provided) and mean.

Studies exploring the mitigatory effect of tDCS on the vigilance decrement with other additional neuroimaging measures

Apart from EEG measures, other studies incorporated measures of functional connectivity or cerebral oxygenation and blood flow to further understand behavioural effects. In line with the null behavioural effect of the anodal tDCS protocol over the lDLPFC, Coulborn & Fernández-Espejo (2022) report that tDCS had no significant effect on the connectivity of the default mode network (DMN), salience network (SN), or executive network (EN). However, another study that also reported null findings with anodal tDCS over the lDLPFC, observed that whilst in the sham group, after performing a fatigue-inducing task, the decrement of cortical oxygenation observed in the right hemisphere was mitigated with anodal tDCS (Borragán et al., 2018). These results highlight the potential of observing neural indicators of tDCS efficacy in the absence of behavioural effects, as well as the potential widespread effects of the technique (i.e., effect on blood oxygenation in the contralateral hemisphere to tDCS application). Lastly, Nelson et al. (2014), who had observed a beneficial effect of tDCS on vigilance performance, observed that the employed tDCS protocol also counteracted the time-on-task induced decrement of blood flow velocity, and increased cerebral blood oxygenation, especially in the right hemisphere.

Table 4.3. Selected studies exploring the behavioural impact of tDCS on vigilance/sustained attention, and additional neuroimaging measures

Reference	*N*	Groups	Age	Design	Protocol	Task	Moment	Outcome
Borragán et al. (2018)	N = 22	Active Sham	23	WP | SB	1.5 mA | 15 min. **A**: F3, **C**: extracephalic 25 cm^2	PVT, TloadDBack	Online	No effect of tDCS on TLoadBack or PVT performance. With sham tDCS decreased cortical oxygenation was observed in the right hemisphere after the task, which was mitigated by active tDCS.
Coulborn & Fernández-Espejo (2022)	N = 20	Active Sham	19-35 (25)	WP | SB	1.8 mA | 20 min. **A**: F3, **C**: Fp2 25 cm^2	SART	Online	No effect of tDCS on SART performance or mind-wandering propensity. No effect of tDCS on functional connectivity of DMN, SN, or EN.
Nelson et al. (2014)	N = 19 (10/9)	Active-anodal Active-cathodal Sham	NR	WP Blind NR	1 mA | 10 min. **A/C**: F3, **C/A**: F4 35 cm^2	Simulated air traffic controller	Online	A mitigated vigilance decrement observed with active tDCS protocols with an early onset compared to late onset. The right-cathodal/left-anodal tDCS protocol counteracted the TOT-induced decrement of blood flow velocity and increased cerebral blood oxygenation.

Note. A = anode placement, C = cathode placement, WP = within-participant, BP = between-participant, NR = not reported, PVT = psychomotor vigilance task, SART = sustained attention to response task, DMN = default mode network, SN = salience network, EN = executive network. The age of participants is reported as a range (if provided) and mean.

Studies comparing tDCS with other interventions

Lastly, three studies directly compared the effect of tDCS on the vigilance decrement in contrast with other substances or activities that could modulate it: caffeine and physical exercise. Details of each study have been summarized in **Table 2.5**. In Chapter 1 we already reviewed exercise as a potential moderating factor of the executive vigilance decrement (Sanchis et al., 2020). In contrast, Hussey et al. (2020) observed no effect of either aerobic exercise, anodal tDCS over the lDLPFC, or their combination on the vigilance decrement as measured by the Mackworth Clock Task (MCT), which would measure a similar executive facet as was measured by Sanchis et al. (2020).

On the other hand, two further studies compared the differing effects of caffeine and tDCS on vigilance during a night of sleep deprivation. The results suggest that the effect of anodal tDCS over the lDLPFC might be more specifically mitigating the decrement of vigilance indexed by the MCT (McIntire et al., 2014, 2017), which could represent the executive vigilance component. A more general effect was seen for the PVT, measuring the arousal vigilance component, where, both caffeine and tDCS seem to be effective earlier during the vigil (McIntire et al., 2014), but not later on into the night (McIntire et al., 2017). This result aligns with the findings from Sanchis et al. (2020), where an effect of caffeine on PVT performance was observed as well. Furthermore, a later re-analysis of the data collected by McIntire et al. (2014) revealed that the effects of tDCS were only significant when inspecting overall means of performance measures, but no decrement of task performance with time-on-task when each of the tasks was performed at different points during the night (McKinley et al., 2015). This last finding points towards a relevant shortcoming among many of the studies summarized above: the term vigilance decrement or sustained vigilance decrement is often uncoupled from an inspection of time-on-task effects (e.g.: pre-post measures, block-based analyses), which could partially also explain the wide range of different results that are reported, and potentially obscure relevant findings.

Table 4.4. Selected studies comparing the effects of tDCS and other interventions on vigilance/sustained attention

Reference	*N*	Groups	Age	Design	Protocol	Task	Moment	Outcome
Hussey et al. (2020)	96 (24)	Active-seated/aerobic Sham-seated/aerobic	22	BP Blind NR	2 mA | 30 min. **A**: F3, **C**: extracephalic 2.01 cm^2	MCT	Offline	No effect nor any interaction of aerobic exercise and tDCS on vigilance measured by MCT
McIntire et al. (2014) and McKinley et al. (2015)	30 (10)	Active-placebo caffeine Sham-placebo caffeine Sham-caffeine	29	BP Blind NR	2 mA | 30 min. **A**: F3, **C**: extracephalic 2.01 cm^2	MCT, PVT	Offline	Better performance in MCT in active tDCS group, compared to sham and caffeine groups under conditions of sleep deprivation. Better performance in MCT and PVT groups with tDCS and caffeine compared to sham. Added by McKinley, the differences are attributed to overall better performance, as no vigilance decrement within each testing session
McIntire et al. (2017)	50 (10)	Active-placebo caffeine at 18 PM/4 AM Sham-active caffeine at 18 PM/4 AM Sham-placebo caffeine at 18 PM and 4 AM	27	BP Blind NR	2 mA | 30 min. **A**: F3, **C**: extracephalic 2.01 cm^2	MCT, PVT	Online	Active tDCS administered at 18 PM provided a mitigated vigilance decrement (accuracy and RT in MCT) over 6 hours of sleep deprivation compared to sham tDCS and caffeine. PVT performance was enhanced both with tDCS and caffeine administered at 18 PM, but only tDCS had an effect when administered at 4 AM

Note. A = anode placement, C = cathode placement, BP = between-participant, NR = not reported, MCT = Mackworth clock test, PVT = psychomotor vigilance task. The age of participants is reported as a range (if provided) and mean.

The potential of microstructural white matter connectivity

In concluding this chapter and identifying gaps within the reviewed studies, one significant aspect emerges: the need for a more comprehensive approach to understanding the network effects of tDCS. Specifically, while dynamic neural measures like EEG or blood perfusion offer valuable insights, integrating studies of more static anatomical structures could provide a deeper understanding of tDCS effects on the vigilance decrement. Recent simulation advances show the relevance of considering white matter anisotropy as a relevant factor in the distribution of the e-field (Suh et al., 2012). Furthermore, recent studies have shown tDCS outcomes can be impacted by the presence of white matter lesions due to brain damage (Kurtin et al., 2021) or ageing (Indahlastari et al., 2021). Notably, some studies have also used these measures as a means to test pre-post structural changes induced by tDCS protocols (Antonenko et al., 2023; Sherwood et al., 2021), providing a method to gauge the structural impact of tDCS. More importantly, clinical studies have shown that the integrity of different white matter tracts can predict outcomes of a tDCS intervention in tract-specific cognitive functions (Zhao et al., 2021). While this approach has shown promising findings in healthy populations with other non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS, Botta et al., 2021; Martín-Arévalo et al., 2019; Martín-Signes et al., 2019, 2021; Quentin et al., 2016), this critical factor remains scarcely explored in healthy participants in the tDCS literature (Lin et al., 2017). This identifies a relevant gap for further research to provide a potentially powerful way of further understanding tDCS effects and even provide potential estimations for cost-efficacy.

Conclusions

The exploration of tDCS as a tool for modulating vigilance has unveiled a complex landscape of outcomes influenced by a myriad of factors, from stimulation parameters to individual neuroanatomical differences. The variability in study findings regarding the vigilance decrement underscores the challenge of drawing generalized conclusions about its efficacy. The

potential of tDCS to mitigate vigilance decrements, as seen in some of the select studies, contrasts with other findings showing no effect or even detrimental outcomes, highlighting the importance of considering task-specific effects, stimulation protocols, and inter- and intra-individual differences. The incorporation of neuroimaging measures offers promising avenues for elucidating the mechanisms by which tDCS could potentially mitigate the vigilance decrement. Nonetheless, further research is still required to more adequately elucidate if and how tDCS can mitigate the vigilance decrement.

PART II
Aims and overview of the research

Chapter 5

Rationale, aims and overview of the research

After outlining the vast array of factors that induce variability in both tDCS outcomes and the vigilance decrement, it becomes evident that investigating their interaction requires a conservative research approach operating in small steps (Guerra et al., 2020). This approach aligns with a growing trend of endorsing *slow science* (Frith, 2020), as a means to produce less but more robust scientific outcomes. The present chapter summarizes the rationale behind the empirical research contribution of this thesis, as derived from the different aspects reviewed in the preceding chapters. Furthermore, this chapter outlines the main aims and objectives of the presented studies. Lastly, the transparent and open research practices followed within the research contributions are highlighted.

Rationale

The literature reviewed in the preceding chapters identified several gaps that the present study aims to address. Firstly, most of the studies reviewed for Chapter 2 constitute one-time applications of specific tDCS protocols and outcome measures. Except for the overlap between the stimulation protocol used in studies comparing caffeine or exercise to tDCS (Hussey et al., 2020; McIntire et al., 2014, 2017), the current literature clearly lacks attempts to replicate the mitigatory, null, or detrimental findings of tDCS on the vigilance decrement. The first two studies presented in the present thesis have a clear goal of replicating and expanding prior findings (Luna, Barttfeld, et al., 2022; Luna et al., 2020). Whilst still being greatly constrained to the study parameters, the replicated findings may allow building a solid basis of evidence onto which further research can expand with modifications. With this in mind, the present study uses the same behavioural paradigm throughout: the standard and modified ANTI-Vea task, which offers a direct measure of the executive vigilance (EV) component that is of central interest in this thesis. The ANTI-Vea task has a broad trajectory and has been applied to different healthy and clinical populations both in the lab and online (Coll-Martín et al., 2023). Moreover, the use of an HD-tDCS protocol allows for the induction of a more focal e-field (Alam et al., 2016; Edwards et al., 2013), that is associated with more predictable outcomes (Masina et al., 2021). Lastly, the use of online tDCS (i.e., its application simultaneous to a task), ensures further specificity by means

of engaging task-specific connections (Bikson et al., 2013; Fertonani & Miniussi, 2017).

A second gap emerging from the literature review is the under-exploration of external factors introducing variability in tDCS research, such as the outcome measure chosen to test its efficacy. By consistently using the same outcome measure (EV decrement as measured by the ANTI-Vea task), we include a manipulation of the cognitive load imposed by the task to test the robustness of stimulation effects under varying conditions. Systematically examining these effects can highlight the role of cognitive load in designing future interventions, especially for real-life or clinical settings.

Finally, considering the disparate results across studies, the use of outcome measures beyond the behavioural ones becomes paramount (Bergmann & Hartwigsen, 2021). To this end, the experiments in this thesis collected electroencephalography (EEG) and diffusion-weighted imaging (DWI) data to explore individual variability factors that could clarify behavioural outcomes. Using EEG and DWI data permits investigating both the dynamic and static aspects of vigilance functioning, focusing on potential broader network effects of tDCS. Understanding these factors improves our grasp of the technique's efficacy and could aid in identifying potential responders and non-responders prior to an intervention in future applications. Future research will also offer insights into the tDCS parameters that need adjustment for individual differences.

Aims and overview of the research

The main aim of the present thesis is to investigate and understand the potential of tDCS as a neuromodulatory technique to mitigate the executive vigilance (EV) decrement. More specifically, this thesis aims to achieve the following goals, across four experimental series, for which DWI data was collected before an experimental procedure where either sham or anodal HD-tDCS was applied concurrent to performing the ANTI-Vea Task, and on-task EEG data was collected before and after the tDCS application, across a total sample of 180 participants across studies:

Aim 1: viability of the rPPC HD-tDCS protocol to mitigate the EV decrement

The first aim of this thesis was to establish the viability of an HD-tDCS protocol targeting the right posterior parietal cortex (rPPC) to mitigate the EV decrement. This aim was approached in **Study I** (**Chapter 5)** through the following specific objective:

Aim 1 – Objective 1. To establish the viability of the HD-tDCS protocol targeting the rPPC with anodal stimulation, the first objective was to replicate prior behavioural findings from . By replicating these findings, we expected to observe the same dissociated effect of HD-tDCS on the vigilance components identified by Luna et al. (2018): a significant mitigation of the EV decrement via HD-tDCS over the rPPC, in the absence of an effect over the AV decrement.

Aim 2: explore cognitive load-dependent effects of the HD-tDCS protocol

The second aim of this thesis was to explore the potential interaction of a cognitive load manipulation with the above-established efficacy of the rPPC HD-tDCS protocol to mitigate the EV decrement in the standard ANTI-Vea Task (triple task). This was accomplished by creating two additional task versions where the cognitive load was reduced to form a dual task and a single task, whilst keeping the environment and timing of stimuli presentation constant. This second aim was covered in **Study II** (**Chapter 7)** through the following specific objectives:

Aim 2 – Objective 1. In line with previous research (Luna et al., 2022), the first objective of this study was to further investigate the effect of cognitive load on the EV decrement when an EEG and HD-tDCS setup is used (i.e., we expected to observe similar findings to previous studies in our sham conditions). Specifically, based on these prior findings and in addition to the pronounced decrement of EV reported for Study I in the triple task condition, we expected to also observe a pronounced EV decrement in the single task sham condition, in the absence of a decrement in the dual task sham condition.

Aim 2 – Objective 2. Second, and more importantly, in regards to the interaction of these effects with the application of the HD-tDCS protocol over the rPPC: we expected to observe a mitigated EV decrement with active HD-tDCS in the single task condition, where under normal circumstances (i.e., sham) a pronounced decrement of EV was expected, in the same way that it was observed for the triple task in Study I.

Aim 3: understand the efficacy of the rPPC HD-tDCS protocol by means of neuroimaging data

The third and more critical aim of this thesis was to explore the potential contribution of neuroimaging data to understand the efficacy (or lack thereof) of the HD-tDCS protocol in mitigating the EV decrement across the different task load conditions. This aim was achieved by the use of EEG data collected during the first and last task blocks (i.e., before and after the online stimulation protocol) across all task load conditions, as well as DWI data collected as a first step before the application of HD-tDCS. The specific objectives regarding EEG data were explored with different approaches in **Study I (Chapter 6)** and **Study III** (**Chapter 8**), whilst a first look into DWI data is provided in **Study IV** (**Chapter 9**). This broader aim was thus dissected into the following specific hypotheses.

Specifically, in **Study I (Chapter 6)** the following specific objectives were addressed in regards to EEG data:

Aim 3 – Objective 1. Firstly, we expected to replicate the findings regarding the effect of the parietal HD-tDCS protocol over alpha power that had been observed by Luna et al. (2020). Specifically, a time-on-task (from pre- to post-stimulation) increment in alpha power, to be significantly reduced over electrodes in the parietal region in the active stimulation group.

Aim 3 – Objective 2. Secondly, in order to expand upon the findings relating to oscillations in the alpha band, this study set out to explore the remaining canonical frequency bands (i.e., delta, theta, beta, and gamma) in a similar fashion (i.e., inspect pre-post stimulation changes in power in relation to the application of the HD-tDCS protocol). In order to gain statistical power, these analyses were carried out over the data collected for

the present thesis, as well as the data collected by Luna et al. (2020). In this way, despite not having explored this in the prior study, a similar "replication" approach could be followed to test which changes occurred reliably across the datasets collected from both studies.

Aim 3 – Objective 3. Lastly, as was reviewed in Chapter 2, Luna et al. (2020), did not find an association between HD-tDCS-induced changes in alpha power and the behavioural effects. Considering the addition of the power in other frequency bands to alpha; this study set out to explore the potential link along the tDCS-EEG-behaviour axis that could aid in understanding tDCS efficacy in a more nuanced way depending on individual differences.

Then, in **Study III** (**Chapter 8**), EEG data across all cognitive load conditions was analysed in more detail.

Aim 3 – Objective 4. The first objective regarding neuroimaging data was to expand on the findings from Study I, by studying the contribution of pre-post stimulation changes in the periodic (oscillatory) and aperiodic (non-oscillatory) components of the EEG signal, in explaining the cognitive-load dependent effect of HD-tDCS on the EV decrement. This was done through mediation analyses in order to reach a potential causal or mechanistic explanation of the effects of tDCS on the EV decrement via the different EEG components. The recent development of algorithms to parametrize the power density spectrum to disentangle periodic and aperiodic contributions (Donoghue, Haller, et al., 2020), as well as a growing interest in aperiodic components as a mean to quantify the balance of neural excitation and inhibition (Gao et al., 2017; Waschke et al., 2021) can be a relevant source of information in the intersection of behavioural and neuromodulatory effects (Krause et al., 2013).

Aim 3 – Objective 5. Secondly, we explored whether the baseline values (pre-stimulation) in either of the extracted periodic and aperiodic EEG components could predict the outcomes of the HD-tDCS protocol on the EV decrement in the different task scenarios. As reviewed in Chapter 2, a previous study inspecting pre-task alpha power observed no such effect (Martínez-Pérez et al., 2023). However, given the disparity between the EEG measures (resting state versus on-task EEG data), stimulation protocols,

tasks, and outcome measures, this warrants a specific inspection in this study, together with the inspection of aperiodic components at baseline, which have shown promising findings with other forms of transcranial direct stimulation, such as transcranial random noise stimulation (tRNS, Sheffield et al., 2020; van Bueren et al., 2021).

Lastly, a preliminary exploration of DWI data adhered to the following objective:

Aim 3 - Objective 6. Third, and last, the DWI data collected before the experimental procedure with tDCS may serve as a relevant pre-intervention data point from which, similarly as outlined for Objective 2, predictions about the efficacy of the HD-tDCS protocol can be made (Zhao et al., 2021), based on the integrity of underlying white matter tracts associated with attentional functioning (Luna, Lupiáñez, et al., 2021). This variable is currently still highly underexplored in regards to tDCS outcomes, but some initial promising findings from a clinical study (Zhao et al., 2021), suggest that this data could provide valuable insight into further understanding individual factors that determine brain stimulation outcomes.

Transparency

Pre-registration and data-availability

To comply with transparent and open research practices, the completed studies of the present thesis have been pre-registered on the Open Science Framework (OSF), as detailed in **Table 4.1**. The datasets corresponding to each manuscript have been or will be made available when submitting the study for publication.

It must be noted that the analyses performed in Study III (Chapter 7), had to deviate substantially from the pre-registered plan of analysis. The hypotheses had been built up sequentially and based on data from prior studies using different stimulation techniques. As the initial hypotheses were not observed, the hypotheses and analyses depending on them were unsubstantiated. This has led to other relevant analyses and results, with the caveat that they must be considered exploratory.

Due to this experience and given the novelty of results and lack of prior evidence to guide specific hypotheses, we have decided that for the DWI

data, the analysis will be performed in two distinct steps. The first step encompasses a first exploratory look at the data, providing a descriptive review of the outcomes and an overview of the predictive power of white matter integrity and behavioural outcomes in the different experimental conditions (stimulation condition × task load condition). The results of this first look are reported in Chapter 8. The chapter concludes with a description of the specific and more comprehensive analyses, to be integrated with EEG data as well, as means of a pre-registration for the second step of analyses.

Table 4.1. Overview of pre-registered studies and their corresponding datasets.

Study	Pre-registration (DOI)	Data (DOI)	Status
I	10.17605/OSF.IO/NCBW9	10.17605/OSF.IO/EZX53	Published: 10.1093/cercor/bhac540
II	10.17605/OSF.IO/9WFBX	10.17605/OSF.IO/876FE	*Under review*
III	10.17605/OSF.IO/UMJC8	To be published*	*In preparation*
IV	To be published**	To be published*	*In preparation*

Note. *The datasets corresponding to Study III will be published on OSF when the final manuscript is submitted for publication. **Data from this study has only been pre-processed and broadly analysed to check the reliability of DWI indices as well as explore their preliminary relationship with behavioural outcomes of tDCS. The pre-registration corresponding to Study IV will be published before commencing with the formal data analysis that is sketched out in Chapter 8.

Visual materials: creation and permission

Most of the figures in the present thesis have been originally created for the specific chapters and papers. In the few cases where a figure has been re-used and/or adapted from an external source, the appropriate permission has been granted by the publisher, and this is explicitly acknowledged in the figure caption.

A note on the use of AI in this thesis

The course of this doctoral thesis has run parallel to major global events. At the beginning of the thesis, the outbreak of the COVID-19 pandemic brought

scientific research to a near standstill and, more critically, had profound impacts across the globe. Towards the end of the thesis, on the other hand, the popular use of new technologies has emerged, such as natural language processing (NLP) models (e.g., GPT), which have opened up new ways of working in Academia.

Given that from an ethical standpoint, the use of such technologies can be controversial, I want to be transparent with their use in this thesis. The use of NLPs, specifically via ChatGPT (OpenAI, 2024) in the present thesis is limited to the three following uses. Firstly, it was used to revise the definition of more abstract concepts or statistical methods via questions and examples (e.g.: "Can you explain the concept of "stochastic resonance" in simple terms and provide an applied example?"). Secondly, it has been used as an aid in the writing process to edit and improve grammar. At no point has it been used to generate text from scratch to be included in this thesis. Furthermore, the edits provided have been manually revised and implemented where seen fit, with the aim of improving readability. Thirdly, ChatGPT has been used to generate and edit code used for analyses implemented in RStudio, specifically for Chapter 7 and Chapter 8.

Summary

In conclusion, the present thesis aims to further explore the potential of HD-tDCS to mitigate the EV decrement, by exploring the impact of differing cognitive demands as well as underlying neuroimaging data as outcome predictors. The results from the presented studies could contribute to building evidence towards reducing the uncertainty in regard to tDCS outcomes by controlling and/or considering external and internal factors of inter and intra-variability.

PART III
Empirical contribution

Chapter 6

The mitigation of the executive vigilance decrement via HD-tDCS over the right posterior parietal cortex and its association with neural oscillations

The contents of this chapter have been published as:

Hemmerich, K., Lupiáñez, J., Luna, F. G., & Martín-Arévalo, E. (2023). The mitigation of the executive vigilance decrement via HD-tDCS over the right posterior parietal cortex and its association with neural oscillations. *Cerebral Cortex*, *33*(11), 6761–6771.

Abstract

Vigilance —maintaining a prolonged state of preparation to detect and respond to specific yet unpredictable environmental changes— usually decreases across prolonged tasks, causing potentially severe real-life consequences, which could be mitigated through transcranial direct current stimulation (tDCS). The present study aimed at replicating previous mitigatory effects observed with anodal high-definition tDCS (HD-tDCS) over the right posterior parietal cortex (rPPC) while extending the analyses on electrophysiological measures associated with vigilance. Sixty participants completed the ANTI-Vea task while receiving anodal (1.5 mA, n = 30) or sham (0 mA, n = 30) HD-tDCS over the rPPC for ~28 min. EEG recordings were completed before and after stimulation. Anodal HD-tDCS specifically mitigated executive vigilance (EV) and reduced the alpha power increment across time-on-task, while increasing the gamma power increment. To further account for the observed behavioural and physiological outcomes, a new index of $Alpha_{parietal}/Gamma_{frontal}$ is proposed. Interestingly, the increment of this $Alpha_{parietal}/Gamma_{frontal}$ Index with time-on-task is associated with a steeper EV decrement in the sham group, which was mitigated by anodal HD-tDCS. We highlight the relevance of replicating mitigatory effects of tDCS and the need to integrate conventional and novel physiological measures to account for how anodal HD-tDCS can be used to modulate cognitive performance.

Introduction

The ability to maintain a sufficient level of attention over a prolonged time to detect infrequent yet critical stimuli—referred to as vigilance—requires extensive effort and degrades quickly over time (Warm et al., 2008a). Unfortunately, this gradual loss of attention, hindering the detection of critical stimuli—known as vigilance decrement—can, among many other consequences, lead to fatal and harmful car crashes (Wundersitz, 2019), aviation accidents (Kharoufah et al., 2018), accidents during medical procedures (Gök & Koçbilek, 2022), or overlooked threats at security screenings (Yin et al., 2019). The concept of vigilance also faces several theoretical challenges (van Schie et al., 2021), as its understanding is blurred through different tasks, measuring different behavioural markers. Luna et al. (2018) proposed a division of vigilance into two dissociated components: (i) *arousal vigilance* (AV), defined as sustaining a certain level of preparation or reactivity to respond to environmental stimuli over time in a rather automatic manner, manifesting its decrement as a progressive increase in the mean and variability of reaction times (RTs) and lapses; whereas (ii) *executive vigilance* (EV) requires the exertion of control to distinguish critical signals from noise stimuli, observing its decrement as a gradual decrease in correct responses to targets (Luna et al., 2018b).

Maintaining vigilant attention relies on different neural regions, amongst which evidence from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies seem to converge on a mostly right-lateralized cortico-subcortical network (Langner & Eickhoff, 2013). This right-lateralization is especially prominent for tasks where the appearance of the target is unpredictable (Langner & Eickhoff, 2013). Furthermore, studies of patients with lesions across the right hemisphere have shown its importance in maintaining sustained attention (Malhotra et al., 2009; Molenberghs et al., 2009; Singh-Curry & Husain, 2009), observing larger vigilance decrements within (Brosnan et al., 2022) and across task blocks (Koski & Petrides, 2001) when compared to other lesions sites or healthy controls. A perfusion fMRI study has shown that the right fronto-parietal attentional network becomes less active during a vigilance task, with consequent vigilance decrements (Lim et al., 2010). Lastly, higher integrity of white matter connections between the right frontal and parietal

cortices is associated with improved sustained attention performance in children (Klarborg et al., 2013). This evidence suggests that optimal functioning of the right fronto-parietal network seems to be imperative for vigilance performance.

In light of the palpable consequences of the vigilance decrement, different studies have tried mitigating the vigilance decrement through a variety of approaches such as caffeine consumption (Repantis et al., 2021; Sanchis et al., 2020), physical exercise (Sanchis et al., 2020), or non-invasive brain stimulation (Clayton, Yeung, & Kadosh, 2018; Dubravac & Meier, 2020; Loffler et al., 2018; Luna et al., 2020; Nelson et al., 2014; Roe et al., 2016; Roy et al., 2015; Wagner et al., 2020). Despite varying results, overall, transcranial direct current stimulation (tDCS) seems to be a promising tool to aid in vigilance performance (Al-Shargie et al., 2019) in healthy (Gan et al., 2022; McIntire et al., 2014; Nelson et al., 2014) and different clinical populations (Begemann et al., 2020; Gaynor et al., 2020). Specifically, Luna et al. (2020) found that anodal high-definition tDCS (HD-tDCS) over the right dorsolateral prefrontal cortex (rDLPFC) and the right posterior parietal cortex (rPPC) exclusively mitigated the EV decrement, whereas AV was unaffected by stimulation (Luna et al., 2020). Furthermore, the authors observed that the increment of alpha power with time-on-task, which is usually reported as a neurophysiological indicator of the vigilance decrement (Benwell et al., 2019; Boksem et al., 2005b), was specifically reduced by anodal HD-tDCS over the rPPC .

This increase of alpha power with time-on-task (Benwell et al., 2019; Boksem et al., 2005b; Compton et al., 2019; Craig et al., 2012) possibly reflects increased inhibition of task-irrelevant processes (Clayton et al., 2015b). However, a more specific approach to reflect vigilance performance and task-engagement could be the combination of several frequency bands within one index. Several indices have been proposed, such as the engagement index (EI), which comprises the ratio of frontal theta to parietal alpha (Kamzanova et al., 2014), the multiplicative inverse of alpha (Coelli et al., 2018), or the task load index (TLI), corresponding to the ratio of parietal beta to the sum of parietal alpha and theta (Pope et al., 1995), among many others (Harty & Cohen Kadosh, 2019; Hussain et al., 2021). Nonetheless, among these indices, there is currently no consensus on their reliability,

especially when switching between different contexts or tasks; nor have they been reliably linked to the effects of neuromodulation.

The current study

This study aimed to further demonstrate the effectiveness of anodal HD-tDCS over the rPPC to mitigate the vigilance decrement by replicating the findings of Luna et al. (2020) and extending the analysis of the effects of anodal HD-tDCS on oscillatory frequencies. Following pre-registered hypotheses, design, and data analysis plans (see https://osf.io/ncbw9/wiki/), we proposed that anodal HD-tDCS over the rPPC would: (i) mitigate the behavioural decrement of EV, (ii) not modulate the AV component, and (iii) reduce the alpha power increment in the right parietal region. Additionally, delta, theta, beta, and gamma power across time-on-task were also analysed.

Materials and Methods

Participants

A power analysis, conducted with G*Power 3.1.9.7. (Faul et al., 2007) on the effect size (η^2_p = .05) observed in the critical Block (1-6) × Group (sham vs. parietal stimulation) interaction with α = .05 and 1-β = .95 (Luna et al., 2020), provided an estimated minimum sample of 22 participants per group. We decided to collect 30 participants per group as in the original study.

All sixty participants (43 women, age: M = 23.4, SD = 4.08) met the safety criteria for magnetic resonance imaging (MRI)[1] and tDCS (Antal et al., 2017), were right-handed, had normal or corrected-to-normal vision, no neurological or psychiatric conditions, signed an informed consent form and received monetary compensation (10 €/hour). Participants were randomly assigned to either receive anodal (n = 30, 22 women, age: M = 22,7, SD = 3,47) or sham (n = 30, 21 women, age: M = 23.42, SD = 4,57) HD-tDCS over the rPPC. This study is part of two larger research projects approved

[1] As part of a larger research project, MRI data were collected from all participants prior to completing the main experiment. The data and results from this procedure are beyond the scope of this report, as this data has been collected as part of a larger research project across several experiments in order to achieve an adequate sample size for the analyses of interest.

by the Ethical Committee of the University of Granada (536/CEIH/2018 and 1188/CEIH/2020), and concordant with the ethical standards of the 1964 Declaration of Helsinki (last update: Brazil, 2013).

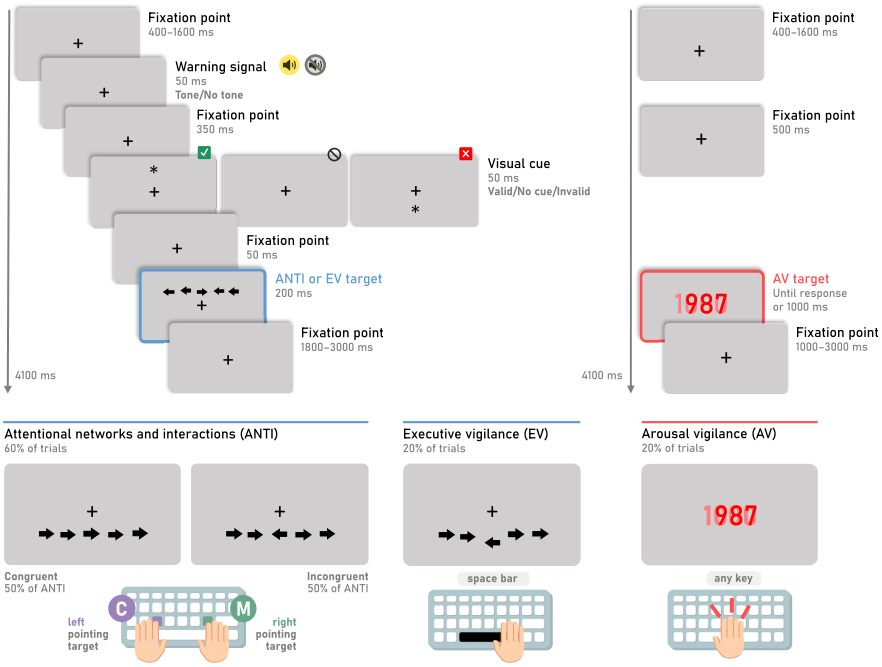


Fig. 6.1. The ANTI-Vea task. *Upper left*: procedure for ANTI or EV trials. ANTI trials measure performance in the alerting network via an auditive warning signal present in 1/2 of trials, the orienting network via a visual cue that can be—from left to right in the figure—valid (at the location of the target), neutral (no cue) or invalid (at the opposite location of the target) present for 1/3 of trials each, and the executive network via the congruency of the target arrow in regards to the flankers. EV trials measure the detection of infrequent critical signals when the target arrow is vertically displaced. *Upper right*: procedure for AV trials, in which the arousal vigilance decrement is measured by responding to a millisecond counter. Note that the countdown is red in the real task environment. *Bottom panels*: proportion and correct responses for each type of trial.

Apparatus and Stimuli

Behavioural measures

Behavioural measures of attentional networks and vigilance components were obtained through the ANTI-Vea task (Luna et al., 2018b), which was used by Luna et al. (2020) (see **Fig. 6.1**). The ANTI-Vea task measures the independence and interactions of classic attentional functions (i.e., phasic

alertness, orienting, and executive control) along with the executive and arousal vigilance decrements. For more details on stimuli, timing, and procedure, see **Appendix A** from the **Supplementary Material** or Luna et al. (2018).

HD-tDCS setup and EEG recordings

The HD-tDCS protocol and EEG signal recording were applied through the wireless Starstim® system with 8 channels and controlled through the NIC v2.0.6 software (Neuroelectrics®, Barcelona, Spain). Eight hybrid NG Pistim electrodes (with a 12 mm Ag/AgCl sintered pellet and a circular contact area of 3.14 cm^2) were placed into a neoprene headcap with 39 predefined positions based on the international 10-10 EEG system. A dual (common mode sense and driven right leg) reference EarClip electrode (with two Ag/AgCl pellets and a contact area of 0.5 cm^2) was connected to the left participant's earlobe.

HD-tDCS was applied through a 4 × 1 setup, comprised of one central anode with 4 surrounding return-electrodes distributed in a ring-like array, allowing for more focal stimulation and diminished shunting of the electrical current (Alam et al., 2016; Datta et al., 2009). Stimulation was applied (with a duration of ~28 min) over the right posterior parietal cortex (rPPC): placing the anode over P4 and the surrounding cathodes over CP2, CP6, PO4, and PO8. Using a single-blind procedure, anodal (1.5 mA) or sham (0 mA) protocols were applied depending on the experimental group. The sham protocol used two ramps (30 sec of ramp up and 30 sec of ramp down) at the beginning and the end of the stimulation period. In the active protocol, 30 sec of ramp up at the beginning and 30 sec of ramp down at the end of the stimulation period were set. **Fig. 6.2.A** depicts the electrode setup and a simulation of the resulting voltage field (extracted from the NIC software, Neuroelectrics®).

EEG recordings were collected from six electrodes, shown in **Fig. 6.2.B**: a frontal region over AF4, F4, and FC2, and a parietal region over CP2, P4, and PO8, in two distinct steps, prior to and after the stimulation. The signal was registered with a sampling rate of 500 Hz, a bandwidth of 0–125 Hz, and a notch filter at 50 Hz.

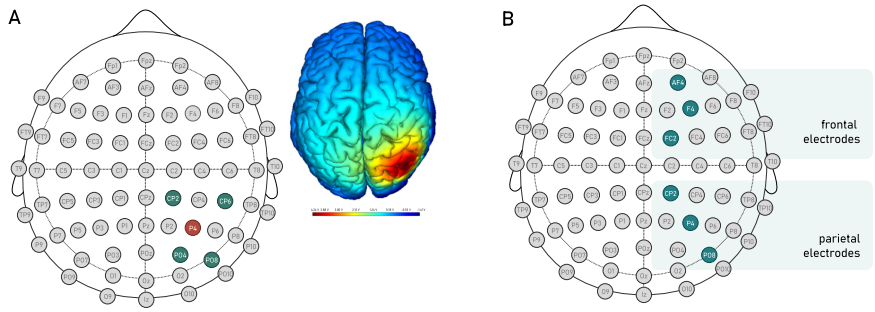


Fig. 6.2. (A) Anodal HD-tDCS 4 × 1 setup with the anode over P4 (black electrode) and current returning through CP2, CP6, PO4, and PO8 (grey electrodes), obtaining the simulated voltage field shown on the right. **(B)** EEG recordings were collected from six electrodes (black electrodes: CP2, P4, and P08 in the parietal region, and AF4, F4, and FC2 in the frontal region) before and after the stimulation period in both anodal and sham HD-tDCS groups.

EEG data were pre-processed with the EEGLAB toolbox v2020.0 (Delorme & Makeig, 2004) for MATLAB R2019a (The Math-Works, Inc), selecting a 210-second epoch from the original recording (avoiding contamination by the ramp-up/ramp-down), applying high-pass (0.5 Hz) and low-pass (45 Hz) filters, and performing Independent Component Analysis (ICA) to identify and reject artifacts. The remaining artifacts were identified and excluded through visual inspection of each epoch (after which the average length of epochs was 209.6-seconds for pre-stimulation and 208.9-seconds for post-stimulation). Mean power (i.e., squared signal filtered by each frequency band's boundary) was computed for all standard frequencies. Boundaries were based on vigilance literature: delta: 0.5-3.8 Hz, theta: 4-7.5 Hz, alpha: 7.5-12.5 Hz, beta: 13-30 and, gamma: 30-45 Hz (Bearden et al., 2004; Boksem et al., 2005b; Clayton et al., 2015b; Clayton, Yeung, & Kadosh, 2018; Donoghue et al., 2021a; Hoedlmoser et al., 2011; Kamzanova et al., 2012; Kim et al., 2017; Luna et al., 2020; Moessinger et al., 2021; Reteig et al., 2019b; Schmidt et al., 2009; Smith et al., 2001). To further examine the effects of anodal HD-tDCS over other oscillatory frequencies than alpha, EEG data from Luna et al. (2020) was re-analysed as in the present study.

Procedure

The procedure is illustrated in **Fig. 6.3**. Eligible participants (fulfilling MRI and tDCS inclusion criteria) completed an online survey at home with self-

reported questionnaires from a larger research project, inquiring about general health, lifestyle, mindfulness, and mind-wandering practices. Each session began with an MRI scan, after which participants were sat in another, dimly lit room for the ANTI-Vea experiment. Participants completed the practice blocks. Then, electrode setup and calibration were completed before commencing with the experimental task. Anodal or sham HD-tDCS was applied from the 2nd to the 6th experimental block, whereas EEG recordings were acquired in the 1st (pre-stimulation) and 7th (post-stimulation) blocks. In addition, participants self-reported their fatigue state at three times across the session: before the practice blocks, and before and after the experimental blocks (which are also beyond the report's scope). At the end, all participants completed the transcranial Electrical Stimulation survey, screening for their subjective experience and any possible adverse sensations perceived during stimulation (Fertonani et al., 2015).

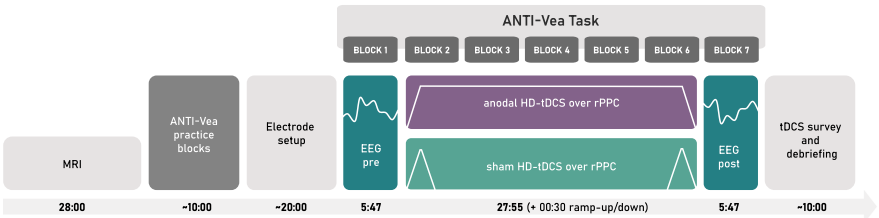


Fig. 6.3. Procedure for the experimental session. The bottom arrow shows the exact or approximate (those with a preceding tilde [~] symbol) duration in minutes for each step of the procedure.

Statistical analyses

Behavioural data

Data were analysed as in Luna et al. (2020), following our pre-registered analysis plan (osf.io/ncbw9/wiki/). Data analysis of ANTI trials is reported in **Appendix A**. For EV and AV trials, data was analysed from the 1st to the 6th block, computing Hits (percentage of correct responses to displaced targets) for EV, and standard deviation (SD) of RT to the countdown for AV. Each index was included as a dependent variable in separate mixed ANOVAs[2], with Blocks (1st to 6th) as a within-participant factor and Group as

[2] Note that for all reported ANOVAs, degrees of freedom were adjusted with Greenhouse-Geisser correction when the sphericity assumption was violated (i.e., $p < .05$ in Mauchly's test).

a between-participant factor. To assess any possible differences in baseline performance, one-way ANOVAs were computed for the 1st block considering Group as a between-participant factor. Lastly, as in Luna et al. (2020), polynomial contrasts were performed to analyse the linear component of Hits or SD of RT across blocks by Group. These analyses are standard to analyse ANTI-Vea scores (Luna, Barttfeld, et al., 2021; Luna, Roca, et al., 2021). Further statistical analyses and results for the remaining EV and AV indices are described in **Appendix C**.

EEG Data[3]

Mean power in each frequency band was analysed through five mixed ANOVAs with Period (pre-/post-stimulation) and Region (parietal/frontal) as within-participant factors, and Group (anodal HD-tDCS/sham HD-tDCS) and Study (Study 1: Luna et al., 2020/Study 2: current study) as between-participant factors.

Results[4]

Blinding efficacy

The intensity of self-reported discomfort/sensations associated with stimulation (Fertonani et al., 2015) was not significantly different across Group, F(1, 58) = 1.26, p = .266, ηp2 = .02, nor were there any group differences in each reported sensation: itching, warmth/heat, pinching, metallic/iron taste or fatigue with anecdotal to moderate evidence against group-differences (see **Appendix B**, **Table B.1** in the **Supplementary Material** for statistical details). Importantly, there were no group differences in the participant's guessed estimation of their assigned group (U = 474, p = .709), as 43% of participants from the sham HD-tDCS group and

[3] In Study 1 (Luna et al., 2020), seven participants were excluded: five (all from the anodal HD-tDCS group) due to issues during data acquisition, and two (from the sham group) due to a noisy EEG signal. In Study 2, three participants were excluded due to a noisy EEG signal (one from the sham group and two from the anodal HD-tDCS group).

[4] Demographic data of the participant sample did not differ significantly between groups, as evidenced by two ANOVA's that considered Group (sham HD-tDCS or anodal HD-tDCS) as independent variable and Age, $F(1, 58) = 1.87$, $p = .176$, $\eta_p^2 = .03$, or Sex, $F < 1$, as dependent variables.

36% from the stimulation group believed having received active stimulation, further supporting the efficacy of the present single-blinding procedure.

HD-tDCS effects on the EV and AV decrement

The EV decrement was observed as a significant decrement across Blocks in Hits, $F(4.02, 233) = 11.77$, $p < .001$, $\eta_p^2 = .17$. The Block × Group interaction was not significant, $F(4.02, 233) = 1.58$, $p = .180$, $\eta_p^2 = .03$. To further examine whether the modulation of HD-tDCS reported by Luna et al. (2020) was replicated, the linear component was analysed, which was statistically significant both in the sham, $F(1, 58) = 29.18$, $p < .001$, $\eta_p^2 = .33$, and in the anodal HD-tDCS group, $F(1, 58) = 7.01$, $p = .011$, $\eta_p^2 = .10$,. Critically, as in Luna et al. (2020), these linear decrements were marginally different between groups, $F(1, 58) = 3.79$, $p = .056$, $\eta_p^2 = .06$[5], as can be seen in **Fig. 6.4.A**. To further determine whether anodal HD-tDCS on the rPPC mitigates the linear decrement in hits, additional Bayesian ANOVAs were conducted including the Slope of Hits (calculated from 1st to 6th Blocks for each participant) as the dependent variable and Group (anodal or sham HD-tDCS) as a between-participant factor. The Bayesian ANOVA showed only weak evidence ($BF_{10} = 1.261$) in favour of the effect of Group on the Slope of Hits across blocks. However, given that the present study was designed as a replication of a previous study with a similar design and procedure (Luna et al., 2020), an additional Bayesian ANOVA was conducted to test how considering the evidence of the original study (Luna et al., 2020) would affect the current evidence regarding the modulation of anodal HD-tDCS on the rPPC over the Slope of Hits. For this purpose, we calculated a replication Bayes factor (Ly et al., 2019; Verhagen & Wagenmakers, 2014) on the above-mentioned Bayesian ANOVA (Slope of Hits by Group), using the BF of the original study as a prior ($BF_{10} = 1.63$) and the BF of the combined dataset from both studies ($BF_{10} = 7.96$). Using these parameters, the updated Bayesian

[5] Note that the reported results include Blocks 1-6 as per our pre-registered plan for analyses. However, for clarity, the same analyses performed considering all task blocks (1-7) show a significant decrement across Blocks for Hits, $F(5.09, 278) = 15.20$, $p < .001$, $\eta_p^2 = .21$. As in the analysis for Blocks 1-6, now including Block 7, the Block × Group interaction is also not significant, $F(5.09, 278) = 1.45$, $p = .210$, $\eta_p^2 = .02$. However, both the sham, $F(1, 58) = 47.66$, $p < .001$, $\eta_p^2 = .45$] and anodal HD-tDCS, $F(1, 58) = 15.06$, $p < .001$, $\eta_p^2 = .21$, groups showed a significant linear decrement. Importantly, this linear decrement was significantly different between groups, $F(1, 58) = 4.57$, $p = .037$, $\eta_p^2 = .07$. Therefore, when all seven blocks are taken into account, the effect of stimulation on executive vigilance is even more evident.

ANOVA showed a BF for the current study with moderate evidence (Jeffreys, 1961) in favour of this replication (BF_{10} = 4.87).

The AV decrement was observed as a significant increment of SD of RT across blocks, $F(3.70, 214.68) = 5.86$, $p < .001$, $\eta_p^2 = .09$, with a significant linear component, $F(1, 58) = 16.71$, $p < .001$, $\eta_p^2 = .22$. Most importantly, as depicted in **Fig. 6.4.B** and observed in Luna et al. (2020), the linear change across blocks was not significantly different across groups, $F(3.70, 214.68) = 1.31$, $p = .268$, $\eta_p^2 = .02$.

Note that, as depicted in **Fig. 6.4**, for both EV and AV indices there were no group differences at baseline (1st block; both Fs < 1).

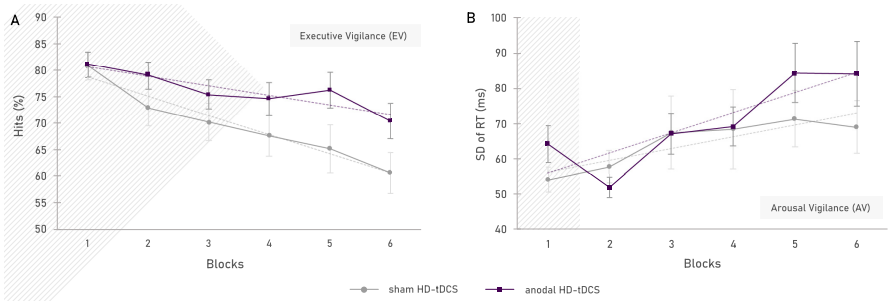


Fig. 6.4. **(A)** Executive vigilance decrement (shown as a reduction in Hits across blocks), as a function of HD-tDCS condition (sham HD-tDCS or anodal HD-tDCS). The shaded area represents the pre-stimulation period (baseline) for both groups (1st block). Dotted lines represent the linear trend for each group in that score across blocks. Error bars represent the standard error of the mean (SEM). **(B)** Arousal vigilance decrement (shown as an increment in the SD of RT across blocks).

HD-tDCS effects on EEG measures

For the sake of clarity, only significant interactions related to Group (anodal/sham HD-tDCS) and Period (pre-/post-stimulation) will be reported here. For results on the remaining frequency bands, see **Appendix D** in the **Supplementary Material**.

Alpha power was not significantly different across Group or Study (both Fs < 1). There were significant main effects of Region, $F(1,109) = 77.08$, $p < .001$, $\eta_p^2 = .41$, and Period, $F(1, 109) = 78.77$, $p < .001$, $\eta_p^2 = .42$, neither of which interacted significantly with Study (both Fs < 1). Furthermore, the Period × Region interaction was also significant, $F(1, 109) = 5.27$, $p = .024$, $\eta_p^2 = .05$. Critically, as depicted in **Fig. 6.5**, the three-way Period × Region × Group

interaction was significant, $F(1, 109) = 5.27$, $p = .050$, $\eta_p^2 = .04$, and not modulated by Study ($F < 1$), indicating that the parietal alpha power increment with time-on-task was reduced in the anodal HD-tDCS group (change from pre- to post-stimulation: $M = 1.12$, $SEM = 0.18$), as compared to the sham group ($M = 2.03$, $SEM = 0.40$), $F(1, 109) = 4.26$, $p = .041$, $\eta_p^2 = .04$.

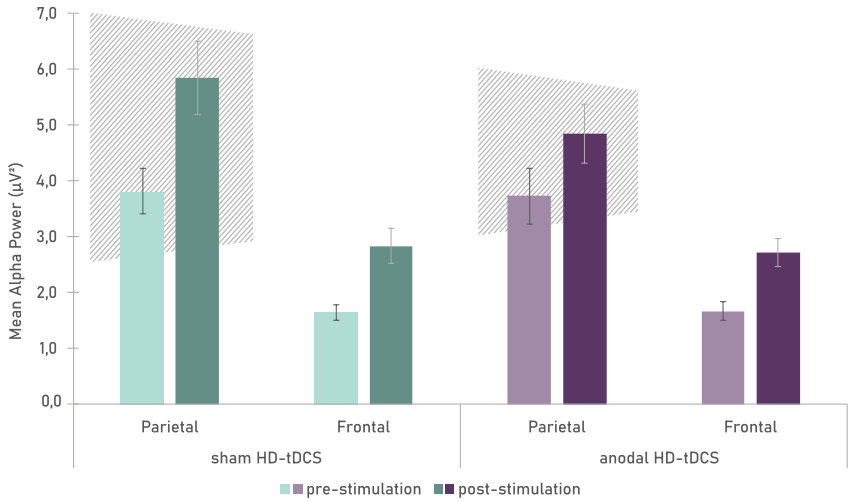


Fig. 6.5. Mean alpha power by Group (sham/anodal HD-tDCS) and Region (Parietal/Frontal). The alpha power increment from pre-stimulation (baseline) to post-stimulation is mitigated in the parietal electrodes (see Fig.2.b) in the anodal HD-tDCS group as compared to the sham group, as highlighted by the shaded areas. Error bars represent SEM.

Gamma power was not significantly different across Group [$F(1, 109) = 1.47$, $p = .228$, $\eta_p^2 = .01$], Regions, $F(1, 109) = 2.13$, $p = .147$, $\eta_p^2 = .02$, nor Study ($F < 1$). The main effect of Period, $F(1, 109) = 55.97$, $p < .001$, $\eta_p^2 = .34$, not significantly modulated by Study, $F(1, 109) = 1.01$, $p = .317$, $\eta_p^2 = .01$, showed that gamma power increased with time-on-task. The Region × Period, $F(1, 109) = 34.40$, $p < .001$, $\eta_p^2 = .24$, and Period × Group, $F(1, 109) = 12.39$, $p < .001$, $\eta_p^2 = 0.10$, interactions were significant. Importantly, the triple Period × Region × Group interaction, $F(1, 109) = 6.11$, $p = .015$, $\eta_p^2 = .05$, as shown in **Fig. 6.6**, was significant, reflecting that the frontal gamma power increment with time-on-task was larger in the anodal HD-tDCS group ($M = 0.13$, $SEM = 0.02$) than in the sham group ($M = 0.5$, $SEM = 0.01$), $F(1, 109) = 6.11$, $p = .015$, $\eta_p^2 = .05$.

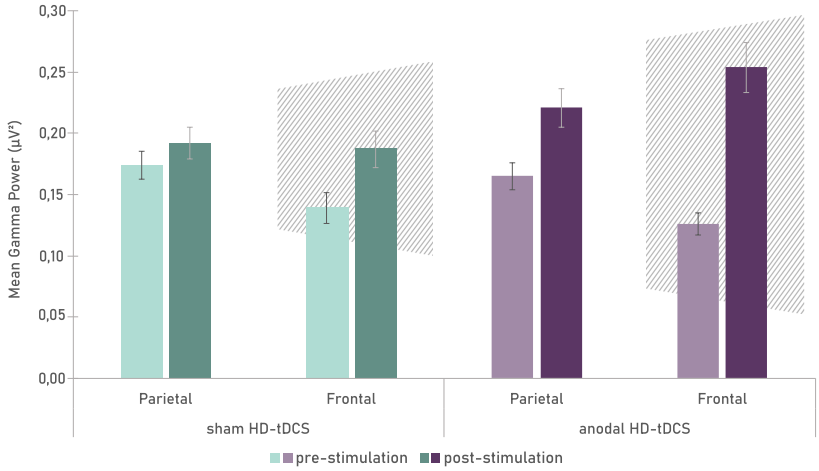


Fig. 6.6. Mean gamma power by Group and Region. In both regions, although primarily in the frontal electrodes (as highlighted by the shaded areas), the gamma power increment from pre-stimulation (baseline) to post-stimulation is increased by anodal HD-tDCS as compared to the sham group. Error bars represent SEM.

Exploratory analyses: HD-tDCS effects on the EV decrement and its association with the $Alpha_{parietal}/Gamma_{frontal}$ Index

To delve deeper into the related behavioural-neurophysiological-neuromodulatory effects of anodal HD-tDCS, an index combining parietal alpha power and frontal gamma power was computed: $Alpha_{parietal}/Gamma_{frontal}$. This index was calculated for the pre- and post-stimulation periods and analysed in a mixed ANOVA with Period as a within-participant factor, and Group and Study as between-participant factors. A significant Period × Group interaction, $F(1, 109) = 16.51$, $p < .001$, $\eta_p^2 = .13$, not modulated by Study ($F < 1$), was observed. Indeed, as shown in Fig. 7.a, this effect was clearly replicated across Study 1, $F(1, 54) = 7.6$, $p = .008$, $\eta_p^2 = .12$, and Study 2, $F(1, 55) = 8.96$, $p = .004$, $\eta_p^2 = .14$, in two partial ANOVAs for each Study. The replication BF for this analysis (using the Slope of Hits to obtain the BF of the combined dataset ($BF_{10} = 266.45$) and the BF of Study 1 ($BF_{10} = 9.74$) as a prior), updated the evidence for the Block × Group interaction ($BF_{10} = 5.51$) to showing very strong evidence in favour of this result ($BF_{10} = 48.35$). For further information on these analyses see **Table E.1.** of **Appendix E**. For both studies, the $Alpha_{parietal}/Gamma_{frontal}$ Index decreased by Period in the

anodal HD-tDCS group, $F(1, 55) = 11.02$, $p = .002$, $\eta_p^2 = .17$, but increased in the sham group, $F(1, 56) = 6.16$, $p = .016$, $\eta_p^2 = .10$.

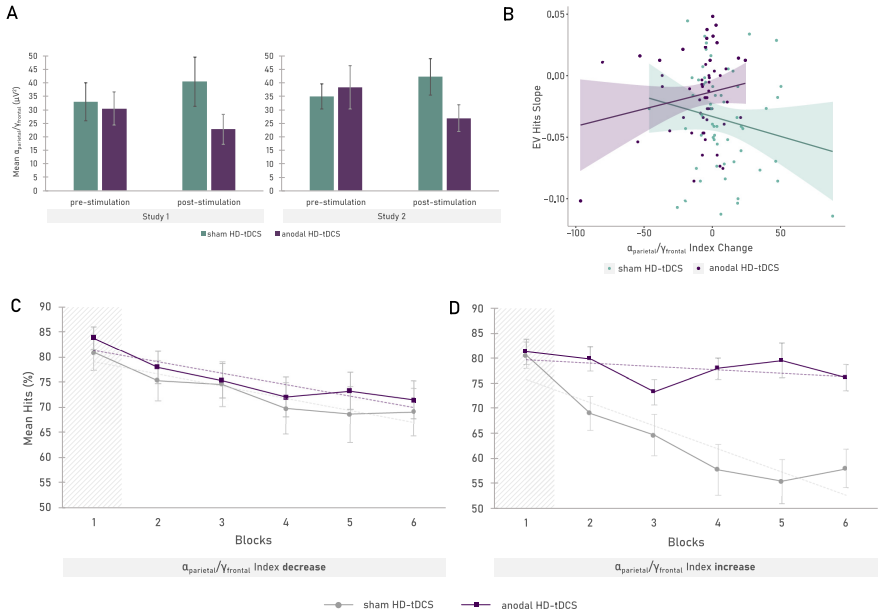


Fig. 6.7. **(A)** Pre-/post-stimulation $Alpha_{parietal}/Gamma_{frontal}$ Index. Data are shown separately for each study, in order to observe the clear replication across studies of an increment of the index with time-on-task in the sham group, whereas the index decreases in the HD-tDCS group. Error bars represent SEM. **(B)** Relationship between the $Alpha_{parietal}/Gamma_{frontal}$ Index Change and behavioural EV changes (slope of hits), depending on the stimulation group (anodal HD-tDCS in black and sham HD-tDCS in grey). **(C)** EV decrement across blocks by stimulation condition for participants with a decrease of the $Alpha_{parietal}/Gamma_{frontal}$ Index. The shaded area represents the pre-stimulation period for both groups. Error bars represent the SEM. **(D)** EV decrement across blocks by stimulation condition for participants with an increase in the $Alpha_{parietal}/Gamma_{frontal}$ Index.

To further explore the effects of the changes of this index on the effect of anodal HD-tDCS on the behavioural EV decrement, the $Alpha_{parietal}/Gamma_{frontal}$ Index Change was added as a covariate in EV analyses. Namely, an ANCOVA was performed with Hits as the dependent variable, Blocks (1st to 6th) as a within-participant factor, with Group (sham/anodal HD-tDCS) and Study (Study 1/2) as between-participant factors, and with the $Alpha_{parietal}/Gamma_{frontal}$ Index Change as a covariate. Importantly, the ANCOVA showed that the critical interaction of Block × Group × Alpha/Gamma Index Change was significant, $F(4.14, 434.682) = 3.5$, $p = .007$, $\eta_p^2 = .03$, and not modulated by Study ($F < 1$). As can be seen in **Fig.**

7.B, in the sham HD-tDCS group, an increase in the Index is associated with worse performance in EV, whereas in the anodal HD-tDCS group, an increase in the Index, is associated with a mitigated EV decrement (less negative Slope of Hits). To explore this modulation in further depth, the anodal HD-tDCS and the sham HD-tDCS group were split-half divided by their median in the change from pre- to post-stimulation in the $Alpha_{parietal}/Gamma_{frontal}$ Index, obtaining participants with an index decrease (below the median) and participants with an index increase (above their group median). A new mixed ANOVA was conducted with Hits as the dependent variable, Blocks (1^{st} to 6^{th}) as a within-participant factor, and the $Alpha_{parietal}/Gamma_{frontal}$ Change Group (decrease/increase), Group (sham/anodal HD-tDCS), and Study (Study 1/2) as between-participant factors. The three-way Block × Group × $Alpha_{parietal}/Gamma_{frontal}$ Change Group interaction was also significant, $F(4.31, 452.75) = 3.00$, $p = .011$, $\eta_p^2 = .03$, and not modulated by Study ($F < 1$). However, the replication BF for this analysis (using Slope of Hits instead of Blocks to test the Stimulation Group × $Alpha_{parietal}/Gamma_{frontal}$ Change Group interaction, using the BF of the combined dataset ($BF_{10} = 6.89$), and the BF of Study 1 ($BF_{10} = 12.10$) as a prior), still showed that for the current study on its own there's no evidence in favour of the effect (original $BF_{10} = .050$, updated $BF_{10} = .57$). Given the moderate evidence for the results on the combined dataset, and the significant results triple interaction both with the continuous and the dichotomized change in the $Alpha_{parietal}/Gamma_{frontal}$ index, two partial ANOVAs were conducted separately for participants with a decrease/increase of the index, with Blocks (1^{st} to 6^{th}) of Hits in EV trials as a within-participant factor and Group (sham/anodal HD-tDCS) as a between-participant factor. The Block × Group interaction was significant for the increase group, $F(4.15, 224.3) = 6.37$, $p < .001$, $\eta_p^2 = .11$, but not for the decrease group ($F < 1$). Further supporting this dissociation, polynomial contrasts showed that the linear decrement was not significantly different between stimulation conditions (Group) in the $Alpha_{parietal}/Gamma_{frontal}$ decrease group ($F < 1$; see Fig. 7.c), (although both sham, $F(3.73, 96.86) = 4.19$, $p = .004$, $\eta_p^2 = .14$, and anodal HD-tDCS groups, $F(4.13, 111.52) = 4.27$, $p = .003$, $\eta_p^2 = .14$, had a significant linear decrement with time-on-task), whereas for the $Alpha_{parietal}/Gamma_{frontal}$ increase group there was a significant difference in the linear decrement between stimulation conditions, $F(1, 56) = 17.01$, $p <$

.001, η_p^2 = .23. As depicted in **Fig. 7.D**, a pronounced EV decrement across Blocks in the sham group was observed, $F(3.91, 113.27) = 12.86$, $p < .001$, η_p^2 = .31, compared to a non-significant change of Hits across blocks in the anodal HD-tDCS group, $F(3.48, 94.02) = 1.85$, $p = .134$, $\eta_p^2 = .06$. This seems to indicate, critically, that the modulation of HD-tDCS on EV performance is related to changes in neural oscillations through this specific index, whereas other indices reported in the literature were not significantly modulated by HD-tDCS in our current data[6].

Discussion

The aim of the present study was to investigate the modulatory effects of HD-tDCS on behavioural and oscillatory frequencies related to the vigilance decrement, specifically (i) replicating prior findings of a mitigatory effect of anodal HD-tDCS over the rPPC on the EV decrement and (ii) further investigating the relationship among the EV decrement, oscillatory frequencies, and their modulation by HD-tDCS. The effects of HD-tDCS on vigilance components observed by Luna et al. (2020) were replicated as per our pre-registered hypotheses: anodal HD-tDCS over the rPPC specifically mitigated the EV but not the AV decrement. Regarding EEG data, we replicated the finding of Luna et al. (2020) of a reduced alpha power increment in the rPPC by anodal HD-tDCS and also observed that frontal gamma power increments with time-on-task were further increased by stimulation. A combined index of the frequency bands modulated by anodal HD-tDCS (i.e., alpha and gamma) was used to relate behavioural and electrophysiological findings. We observed that the $\text{Alpha}_{\text{parietal}}/\text{Gamma}_{\text{frontal}}$ Index increased with time-on-task in the sham group, whereas it decreased in the anodal HD-tDCS group. Lastly, we observed that participants with a

[6] As a case in point, for two EEG indices reportedly related to the vigilance decrement (Coelli et al., 2018; A. T. Kamzanova et al., 2014), such as the engagement index (EI, ratio of $\beta/(\alpha+\theta)$ from parietal electrodes), and the task load index (TLI, ratio of frontal-θ/parietal-α), we observed a significant effect of Period (pre-/post-stimulation) for EI, $F(1, 109) = 20.31$, $p < .001$, $\eta_p^2 = .16$, which was not significant for TLI, $F(1, 109) = 2.37$, $p = .126$, $\eta_p^2 = .02$. There were no significant Period × Group interactions for either EI or TLI (both $F < 1$). More importantly, there was no link between these indexes and behavioural outcomes, as Blocks (1-6) for Hits in EV trials did not interact significantly with the Change in either index (selecting participants above or below their group median of the pre-post change rate), see EI ($F < 1$), and TLI, $F(4.28, 449.01) = 1.26$, $p = .285$, $\eta_p^2 = .01$. The triple interaction of Block × Change Group × Group was also not significant for EI, $F(4.24, 445.08) = 1.40$, $p = .232$, $\eta_p^2 = .01$, nor for TLI, $F(4.28, 449.01) = 1.40$, $p = .231$, $\eta_p^2 = .01$.

decrease in the index showed a standard EV decrement, regardless of the stimulation condition. However, participants with an increase in the index showed a pronounced EV decrement in the sham group, which was mitigated in the anodal HD-tDCS group.

Currently emerging studies using neuromodulation to understand and boost cognitive functions (Coffman et al., 2014a; Dedoncker et al., 2016) are being met with similarly growing criticism substantiated by the technique's contradictory results (Horvath et al., 2016) or undetectable neurophysiological effects (Horvath et al. 2015, see Antal et al. 2015 for a rebuttal). Several methodological countermeasures to these critiques (Filmer et al., 2020) were considered in the present study: (i) the use of a reliable and widely used task measuring attentional and vigilance functioning (Luna, Roca, et al., 2021), (ii) the use of HD-tDCS, which targets a more specific cortical area, ensuring more predictable outcomes (Alam et al., 2016; Masina et al., 2021), (iii) the collection of EEG data to improve the understanding of stimulation effects on neural mechanisms, and iv) the use of online stimulation, which has demonstrated more beneficial effects than offline stimulation (Martin et al., 2014).

To the best of our knowledge, this is the first study to replicate (N = 60) an effective anodal HD-tDCS procedure that seems to mitigate the EV decrement by stimulating the rPPC. Previous research has observed some null or opposite findings in mitigating the vigilance decrement (Gan et al., 2022; Lanina et al., 2018; McIntire et al., 2014; J. Nelson et al., 2015; J. T. Nelson et al., 2014), which might be explained by factors such as the inconsistency of tDCS procedures, behavioural tasks, sample sizes (N = 10-16 per stimulation condition), and cortical areas stimulated across studies. For instance, anodal tDCS over frontal regions during extended wakefulness but not caffeine has shown to improve performance in the Mackworth Clock Test (more akin to EV measures; Mackworth 1948), whereas both caffeine and tDCS improved performance in the Psychomotor Vigilance Test (more akin to AV measures; Lim and Dinges, 2008, see McIntire et al. 2014). Although null inhibitory effects in a visual search task have been reported with cathodal tDCS over the right and left PPC (Lanina et al., 2018), these could be partially explained by the use of offline stimulation. Adding more complexity to the understanding of the effect of stimulation, Roe et al. (2016)

reported non-linear results, as tDCS over the PPC degrades attentional functioning in a highly demanding task, whereas they reported null effects of the technique under low or medium demand conditions. Additionally, many tDCS studies target frontal areas but without consistent results (Gan et al., 2022; Gaynor et al., 2020; Jacoby & Lavidor, 2018; J. Nelson et al., 2015; J. T. Nelson et al., 2014), and other studies using sustained attention tasks study the effect of tDCS on mind-wandering (Coulborn et al., 2020; Filmer et al., 2021), where the mind-probes used in these experiments, render the results difficult to compare to the current results, as those probes could partially restore attentional performance (Arrabito et al., 2015; Helton & Russell, 2017).

Recent discussions on models and neural correlates of vigilance, seem to agree that vigilance is supported by an interconnected set of brain areas (Clayton et al., 2015b; Langner & Eickhoff, 2013), which could partially explain the non-converging results of the above-mentioned tDCS interventions on vigilance performance with different protocols and montages. Although the present outcomes seem to support an effective procedure to mitigate the EV decrement by anodal HD-tDCS over the rPPC, future studies could explore other protocols and/or target brain areas as potential procedures to effectively modulate vigilance performance. While some studies have been attempting to narrow down specific regions involved in vigilance maintenance (Bearden et al., 2004; Brosnan et al., 2018; Craig et al., 2012; Kim et al., 2017; Langner & Eickhoff, 2013; Luna et al., 2020; Wagner et al., 2020); further studies –and especially replication studies, and studies using active control sites– are needed to better understand if and how vigilance performance can be modulated by electrical stimulation, and which areas are should be specifically targeted.

The effects of tDCS on alpha power reported by Luna et al. (2020) were also replicated here: anodal HD-tDCS over the rPPC reduced the alpha power increment with time-on-task. Similar results have been observed by Linnhoff et al. (2021), where the occipital alpha power increase with time-on-task was reduced via anodal tDCS over the left DLPFC. Furthermore, we observed that gamma power in the frontal area also increased with time-on-task which, interestingly, was further increased by anodal HD-tDCS over the rPPC. This pattern of gamma oscillations may be related to the indirect

activation of the locus coeruleus (LC) via peripheral nerve stimulation (van Boekholdt et al., 2021), which has shown to induce gamma activity in the prefrontal cortex (Neves et al., 2018). Combining the mean power of these two frequency bands in the regions where the broadest change with time-on-task was observed in a new index ($Alpha_{parietal}/Gamma_{frontal}$) allowed us to observe a summarized modulatory effect of tDCS on neural oscillations. In particular, in the sham group, the $Alpha_{parietal}/Gamma_{frontal}$ Index increased (i.e., increment of alpha and a decrease of gamma power) from pre- to post-stimulation, whereas it decreased in the anodal HD-tDCS group (i.e., reduced alpha power increment and/or augmented gamma power increment).

Critically, the effects of HD-tDCS on alpha and gamma power, combined in the $Alpha_{parietal}/Gamma_{frontal}$ Index, were further associated with behavioural performance with time-on-task. Participants with a decrease in the $Alpha_{parietal}/Gamma_{frontal}$ Index had a slight EV decrement, which did not differ between stimulation conditions. However, participants with an increase in the $Alpha_{parietal}/Gamma_{frontal}$ Index presented a prominent EV decrement in the sham condition, which was mitigated via anodal rPPC HD-tDCS. It must be noted that the split-dichotomous design applied here is not exempted from some methodological limitations. Categorizing participants into two groups based on the change in the proposed index homogenizes participants within each group and thus, reduces inter-individual variability (MacCallum et al., 2002). Given these limitations and the fact that these results were exploratory, they should be interpreted cautiously. Furthermore, the reliability of this new index should be further tested through different tasks and task-load conditions.

To our knowledge, this index has not been reported earlier in the vigilance literature relating to tDCS or oscillatory frequencies. However, this pattern of alpha and gamma oscillations throughout the task in response to stimulation is directly linked to the behavioural modulation by HD-tDCS over the EV decrement and fits coherently with the oscillatory frequencies model of sustained attention proposed by Clayton et al. (2015). The oscillatory frequencies model of sustained attention proposes that a reduced alpha power increment would reflect a reduced need for inhibiting task-irrelevant processes and that the augmented gamma increment,

heightened the excitation of task-relevant processes (Clayton et al., 2015b). Moreover, posterior alpha and gamma activity has been linked to the processing of top-down feedback and bottom-up feed-forward processes, respectively, aiding in predicting the appearance of visual stimuli (Michalareas et al., 2016). Furthermore, gamma power has shown to be phase-locked to alpha activity in posterior regions (Osipova et al., 2008), which is thought to aid in the rhythmic regulation of attention.

In a broader sense, our results underscore the idea that stimulation *"seems to act where it is needed",* in alignment with other findings where, for example, stimulation effects on sustained attention are maximized in participants with worse behavioural performance at the task's baseline (Brosnan et al., 2018; Gan et al., 2022). This may also explain why protocols similar to the one used in this study, such as HD-tDCS over the right temporoparietal junction, lead to different effects on neural oscillations (Donaldson et al., 2019). This contradictory pattern of findings may be particularly observed when stimulation is applied offline and not related to any task prior to or after stimulation, giving the excitatory effect of stimulation *"nowhere to act"*. Lastly, while our results show that anodal HD-tDCS modulates alpha and gamma power (and therefore, their combined index), and the change over time in these combined frequencies is related to the effect of neuromodulation on the vigilance decrement, further research is needed to understand the possible causal relationship between these variables. Therefore, future research should explore this bidirectional effect (the effect of stimulation on neural oscillations and the predictive power of neural oscillations on stimulation outcomes) separately, for example by measuring the power of oscillatory frequencies and applying tDCS in separate sessions to further refine whether individual oscillatory profiles can be identified and related to task performance and stimulation outcomes.

Conclusion

The findings of the present study present a twofold contribution: i) they replicate the previously reported mitigation of the EV decrement through anodal HD-tDCS over the rPPC (Luna et al., 2020); and ii) importantly, this behavioural effect is related to the pre/post-task change in a proposed

$Alpha_{parietal}/Gamma_{frontal}$ Index, where participants with an increase in this index seem to significantly benefit from the anodal HD-tDCS stimulation. Research including neurophysiological measures in studies of tDCS interventions over the vigilance decrement is still quite scarce (Annarumma et al., 2018) and requires further exploration. Within this gap, the replicated modulatory effect of HD-tDCS on the EV decrement and its association with a changing pattern in neural oscillations over time opens up the possibility of finding a neural marker that might act as a predictor of stimulation outcomes.

Supplementary Material

Appendix A. The ANTI-Vea Task: procedure, analysis, and ANTI results

A.1. ANTI-Vea task procedure

The ANTI-Vea is an adapted version of the classical attentional networks task (Fan et al., 2002), which comprises three embedded subtasks. In the ANTI trials (60% of the total), the independence and interaction (Callejas et al., 2004) of the classical attentional networks (alerting, orienting, and executive control) is measured as in the ANTI task of Callejas et al. (2004). Participants complete a flanker task where the direction of the target (i.e., a central arrow) has to be selected (pressing the *c*-key for left-pointing arrows, and *m*-key for right-pointing arrows) regardless of the direction of the flankers (i.e., the surrounding arrows). At the same time, independent measures of vigilance components are recorded. EV trials (20% of total) measure executive vigilance as in signal-detection tasks such as the Sustained Attention to Response Task (SART; Manly and Robertson 2005), the Mackworth Clock Test (MCT; Mackworth 1948), or the Continuous Performance Test (CPT; Conners 2000). Participants must detect an infrequent and large vertical displacement of the target of the flanker task by pressing the space bar. Lastly, to measure arousal vigilance (AV), in the remaining 20% of trials, a red countdown has to be stopped as fast as possible by pressing any key, as in the Psychomotor Vigilance Test (PVT; Lim and Dinges 2008).

A.2. Behavioural analysis of ANTI trials

For ANTI trials (where participants had to respond to the direction of the target arrows independently of the flankers), data were collapsed in the stimulation period (blocks 2nd to 6th). Trials with incorrect responses (6.52%) and trials with reaction times (RT) below 200 ms (0.49 %) or above 1500 ms (0.36%) were excluded. Then, two separate mixed ANOVAs were conducted with RT or the percentage of errors as the dependent variable, including the following three within-participant factors: warning signal (with 2 levels:

tone/no tone), visual cue (with 3 levels: valid cue/invalid cue/no cue) and executive control (with 2 levels: congruent/incongruent), and Group as a between-participant factor.

The main effects usually reported with the ANTI and ANTI-Vea tasks (Callejas et al., 2004; Luna et al., 2018b) were replicated. For Warning Signal, responses were faster, $F(1, 58) = 90.61$, $p < .001$, $\eta_p^2 = .61$, and more accurate $F(1, 58) = 12.31$, $p < .001$, $\eta_p^2 = .18$, for trials with tone (RT: $M = 575$ ms, $SE = 11.95$; Errors; $M = 5.3\%$, $SE = 0.7$), than those with no tone (*RT*: M = 606 ms, $SE = 11.95$; Errors: $M = 7\%$, $SE = 0.7$). As in Luna et al. (2020), for Visual Cue, the cueing effect was only observed with mean RTs, $F(2, 116) = 68.59$, $p < .001$, $\eta_p^2 = .54$, but not for Errors ($F < 1$), with faster responses in trials with valid cues (M = 571 ms, $SE = 11.97$), than no cues ($M = 594$ ms, $SE = 11.97$), and the slowest responses for invalid cues ($M = 607$ ms, $SE = 11.97$), reflecting attentional benefits [no cue - valid cue, $F(1, 59) = 50.29$, $p < .001$, $\eta_p^2 = .46$ and costs [invalid cue - no cue, $F(1, 59) = 136.96$, $p < .001$, $\eta_p^2 = .70$, of visual cueing. Differently to Luna et al. (2020), where the congruency effect was found for both mean RTs and errors, in the current study the effect of Congruency was only significant for mean RTs, $F(1, 58) = 88.23$, $p < .001$, $\eta_p^2 = .60$, but not for errors, $F(1, 58) = 2.51$, $p = .119$ $\eta_p^2 = .04$, with faster responses in congruent ($M = 574$ ms, $SE = 11.97$) than incongruent trials ($M = 607$ ms, $SE = 11.97$).

Furthermore, regarding the two-way interactions typically reported with this task: Warning Signal × Visual Cue was significant for mean RT, $F(2, 116) = 8.71$, $p < .001$, $\eta_p^2 = .13$, but not for errors ($F < 1$), reflecting a larger cueing effect for trials in the tone condition; Visual Cue × Congruency was only significant for mean RT, $F(2, 116) = 7.29$, $p = .001$, $\eta_p^2 = .11$, but not for errors, $F(2, 116) = 1.27$, $p = .285$, $\eta_p^2 = .02$, reflecting larger congruency effects on invalid cue compared to no cue or valid cue conditions; and Warning Signal × Congruency was neither significant for RT, $F(1, 58) = 3.24$, $p = .077$, $\eta_p^2 = .05$, nor for errors ($F < 1$).

A.3. HD-tDCS effects on ANTI trials (phasic alertness, orienting, and executive control and its interactions)

Anodal HD-tDCS did not significantly modulate any of the three ANTI components for mean RTs (see **Table A.1**) or the percentage of errors (**Table A.2**), as shown by non-significant interactions of Group with either Visual Cue (RT: $F < 1$; errors: $F < 1$), Congruency, (RT: $F < 1$, errors: $F(1, 58) = 1.59$, $p = .212$, $\eta_p^2 = .03$), or Warning Signal (RT: $F < 1$; errors: $F(1, 58) = 1.01$, $p = .318$, $\eta_p^2 = .02$). This last pattern of results differs from the results observed by Luna et al. (2020), where both rPPC-HD-tDCS and DLPFC HD-tDCS reduced phasic alertness on errors (i.e., the difference between the no tone and tone conditions of Warning Signal).

HD-tDCS did not significantly modulate any two-way interactions (for RTs, all Fs > 1 and $p > .500$, and for errors, all Fs < 3.4 and $p > .070$). The three-way interaction of Warning Signal × Visual Cue × Congruency was also not significantly modulated by Group, RT ($F > 1$) and errors $F < 2.4$, $p = .097$.

Table A.1. Mean correct RT in milliseconds (ms) for Warning Signal (No Tone/Tone), Visual Cue (Invalid/No Cue/Valid), and Congruency (Congruent/Incongruent), as a function of HD-tDCS group. The SE of the mean is shown between parentheses.

		No Tone			Tone		
		Invalid	No Cue	Valid	Invalid	No Cue	Valid
rPPC HD-tDCS	Congr.	614 (18)	620 (19)	585 (20)	588 (17)	574 (18)	556 (17)
	Incongr.	652 (18)	641 (17)	607 (17)	633 (17)	605 (17)	584 (17)
sham HD-tDCS	Congr.	578 (19)	594 (18)	558 (20)	557 (17)	540 (17)	527 (16)
	Incongr.	624 (18)	608 (18)	593 (19)	611 (19)	571 (15)	560 (16)

Table A.2. Mean percentage of errors for Warning Signal (No Tone/Tone), Visual Cue (Invalid/No Cue/Valid), and Congruency (Congruent/Incongruent), as a function of HD-tDCS group. The SE of the mean is shown between parentheses.

		No Tone			Tone		
		Invalid	No Cue	Valid	Invalid	No Cue	Valid
rPPC HD-tDCS	Congr.	7.70 (1.33)	6.70 (1.37)	6.00 (1.35)	6.30 (1.39)	4.20 (1.33)	5.20 (0.91)
	Incongr.	5.20 (1.26)	8.70 (1.24)	8.20 (1.31)	5.00 (1.31)	4.20 (1.02)	3.70 (0.99)
sham HD-tDCS	Congr.	8.20 (1.52)	8.30 (2.23)	8.00 (1.81)	6.50 (1.20)	5.00 (1.42)	7.50 (1.72)
	Incongr.	7.70 (1.50)	5.30 (1.15)	4.70 (1.08)	5.20 (0.95)	5.50 (1.64)	4.80 (1.44)

Appendix B. Subjective Sensations associated with tDCS

As this subjective sensation data did not follow a normal distribution (p < .001 in all conditions), we performed the Mann-Whitney U test (N = 60) to test for the blinding efficacy, completed by a Bayesian independent sample test showing that there is anecdotal to moderate evidence for an absence of group-differences (see **Table B.1**).

Table B.1. Sensations between the anodal and sham HD-tDCS groups.

Sensation	U	p	BF_{01}	Error %
Itching	529.00	.216	2.953	0.003
Pain	449.50	1.000	3.721	0.003
Burning	540.00	.132	1.651	0.008
Warmth/Heat	469.50	.696	3.234	0.003
Pinching	480.00	.402	2.907	0.003
Metallic/Iron taste	*	/	/	/
Fatigue	455.50	.922	3.738	0.003

* No outcome as the variance for this variable is equal to 0 after grouping it based on the Stimulation Condition.

Appendix C. Complementary analyses for EV and AV

C.1. Statistical analyses for remaining EV and AV indices

The remaining indices of EV and AV were also computed with data from the 1st to the 6th block. For EV, in addition to Hits, we computed False Alarms (FA, percentage of space bar presses in ANTI trials), sensitivity (A′), and response bias (B″). For further details on the use of non-parametric indices of Signal-Detection Theory, see Luna et al. (2018) and Stanislaw & Todorov (1999). For AV, complementary to SD of RT, we computed mean RT in AV trials. The same analyses reported in the main text were performed for these indices as dependent variables: separated mixed ANOVAs with Blocks (1st-6th) as a within-participant factor and Group as a between-participant factor. In addition, separate one-way ANOVAs were computed for the 1st block considering Group as a between-participant factor to check for differences at baseline. Lastly, for each index' Block × Group interaction, polynomial contrasts were conducted to test the significance of the linear component across blocks by Group.

C.2. Results for EV and AV trials

Regarding EV (see **Fig. C.2.1**), the main effect of Group was not significant for B′′ ($F < 1$) and FA ($F < 1$). There was a significant main effect of Group for A′, $F(1, 58) = 4.14$, $p = .047$, $\eta_p^2 = .70$), with slightly higher sensitivity in the anodal HD-tDCS group ($M = 0.91$, $SE = 0.01$) than in the sham HD-tDCS group ($M = 0.89$, $SE = 0.01$). We observed a significant decrement across Blocks in FA, $F(5, 290) = 7.21$, $p < .001$, $\eta_p^2 = .11$, and a significant increment in B′′, $F(4.06, 235.33) = 10.53$, $p < .001$, $\eta_p^2 = .15$. The decrement was not significant for A′, $F(4.11, 238.20) = 1.87$, $p = .114$, $\eta_p^2 = .03$. None of the Block × Group interaction were observed as significant: FA ($F < 1$), A′, $F(4.11, 238.20) = 1.18$, $p = .322$, $\eta_p^2 = .02$, or B′′ ($F < 1$). Polynomial contrasts of the linear component showed that the linear decrement was significant for FA in the sham HD-tDCS, $F(1, 58) = 7.93$, $p = .007$, $\eta_p^2 = .12$, and the anodal HD-tDCS group, $F(1, 58) = 10.15$, $p = .002$, $\eta_p^2 = .15$, but not significantly different from each other ($F < 1$). For A′, the linear decrement was significant in the sham HD-tDCS, $F(1, 58) = 6.67$, $p = .012$, $\eta_p^2 = .10$, but not in the anodal HD-tDCS group ($F < 1$), and also not significantly different between groups [$F(1, 58) = 2.65$, $p = .109$, $\eta_p^2 = .04$.

Lastly, for B'', the linear decrement was significant both in the sham HD-tDCS, $F(1, 58) = 3.52$, $p < .001$, $\eta_p^2 = .19$, and the anodal HD-tDCS group, $F(1, 58) = 2.80$, $p = .002$, $\eta_p^2 = .16$; but not significantly different between groups ($F < 1$).

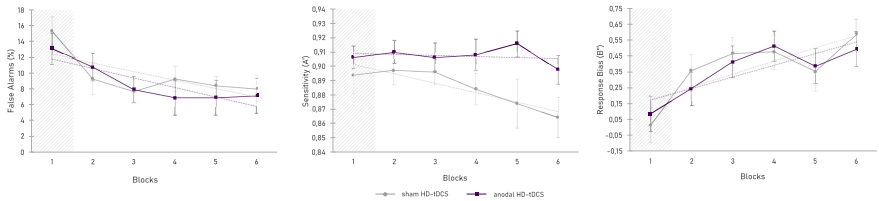


Fig. C.2.1. Executive Vigilance decrement for FA, A' and B'', as a function of HD-tDCS condition (sham HD-tDCS or anodal HD-tDCS). The shaded area represents the pre-stimulation period (baseline) for both groups. Error bars represent the SEM.

For AV (see **Fig. C.2.2**), the main effect of Group for mean RT was not significant ($F < 1$). Mean RT significantly increased across blocks [$F(3.14, 182.15) = 7.01$, $p < .001$, $\eta_p^2 = .11$], with a significant linear component [$F(1, 58) = 13.75$, $p < .001$, $\eta_p^2 = .19$]. As for SD of RT, this linear decrement of mean RT was not significantly different between anodal HD-tDCS and sham HD-tDCS groups, [$F(3.14, 182.15) = 1.01$, $p = .391$, $\eta_p^2 = .02$].

Note that for all EV and AV indices in Appendix B, there were no group differences at baseline (all Fs < 1).

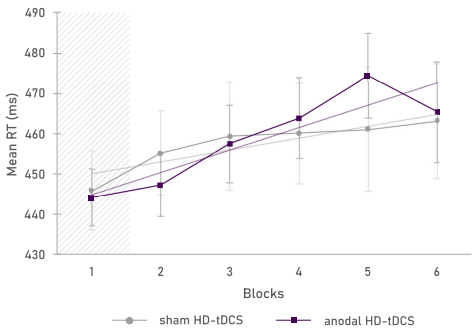


Fig. C.2.2. Arousal vigilance decrement as an increment of mean RT, as a function of HD-tDCS condition (sham HD-tDCS or anodal HD-tDCS). The shaded area represents the pre-stimulation period (baseline) for both groups. Error bars represent the SE of the mean.

Appendix D. HD-tDCS effects on delta, theta, and beta power

D.1. Delta Power

Delta power was not significantly different between Group ($F < 1$), whereas it was for Study, $F(1, 109) = 8.05$, $p = .005$, $\eta_p^2 = .07$. There was a main effect of Region, $F(1, 109) = 36.55$, $p < .001$, $\eta_p^2 = .25$, and Period, $F(1, 109) = 23.79$, $p < .001$, $\eta_p^2 = .18$; neither of which significantly interacted with Study ($F < 1$), nor with Group: Region × Group, $F(1, 109) = 3.46$, $p = .066$, $\eta_p^2 = .03$, Period × Group ($F < 1$). The three-way interaction between Period × Region × Group was also not significant ($F < 1$).

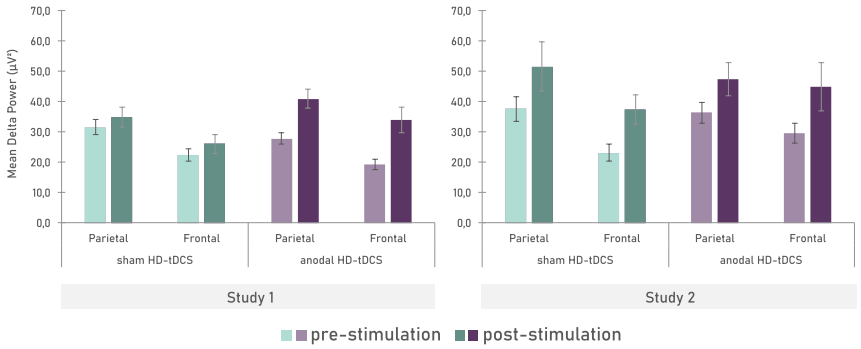


Fig. D.1. Mean delta power by Group (sham/anodal HD-tDCS) and Region (Parietal/Frontal). Data are shown separately for each study: Study 1 (Luna et al., 2020) and Study 2 (current study). Error bars represent SEM.

D.2. Theta Power

Theta power was not significantly different between Group nor Study (both *F*s < 1). The main effect of Region was not significant, $F(1, 109) = 3.34$, $p = .070$, $\eta_p^2 = .03$, whereas there was a main effect of Period, $F(1, 109) = 37.75$, $p < .001$, $\eta_p^2 = .26$, with theta power increasing from the pre-stimulation to post-stimulation, which did not significantly interact with Group, $F(1, 109) = 1.65$, $p = .201$, $\eta_p^2 = .02$, nor Study ($F < 1$). The three-way interaction between Period × Region × Group, was also not significant ($F < 1$). The Region × Group × Study interaction was significant, $F(1, 109) = 6.84$, $p = .010$, $\eta_p^2 = .06$: theta power was higher in the anodal HD-tDCS group in the frontal region, as demonstrated by the significant interaction of Region × Group in Study 1, $F(1, 54) = 7.49$, $p = .008$, $\eta_p^2 = .12$; which was not observed as significant in Study 2 ($F < 1$).

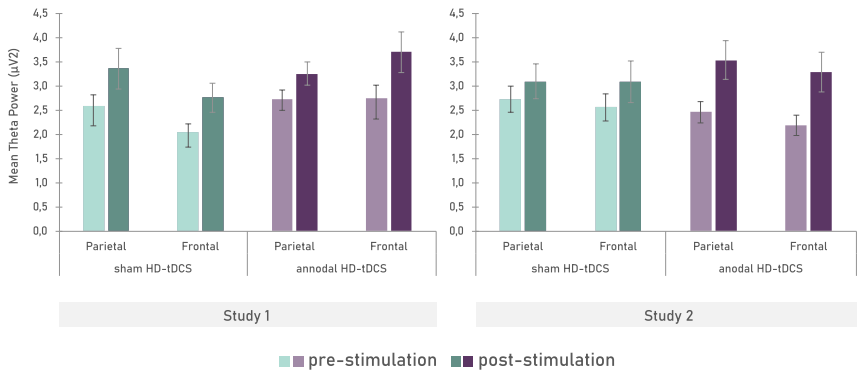


Fig. D.2. Mean theta power by Group (sham/anodal HD-tDCS) and Region (Parietal/Frontal). Data are shown separately for each study: Study 1 (Luna et al., 2020) and Study 2 (current study). Error bars represent SEM.

D.3. Beta Power

Beta power was not significantly different between Group ($F < 1$), but it was across Study, $F(1, 109) = 4.68$, $p = .033$, $\eta_p^2 = .04$. There was a significant main effect of Region, $F(1, 109) = 31.54$, $p < .001$, $\eta_p^2 = .22$, and Period, $F(1, 109) = 80.14$, $p < .001$, $\eta_p^2 = .42$, neither of which significantly interacted with Group or Study (both $Fs < 1$). Thus, beta power consistently increased from pre- to post-stimulation, with larger increments over the parietal than the frontal electrodes, as evidenced by the significant Period × Region interaction, $F(1, 109) = 34.20$, $p < .001$, $\eta_p^2 = .24$, which was nevertheless significantly modulated by Study, $F(1, 109) = 8.15$, $p = .005$, $\eta_p^2 = .07$.

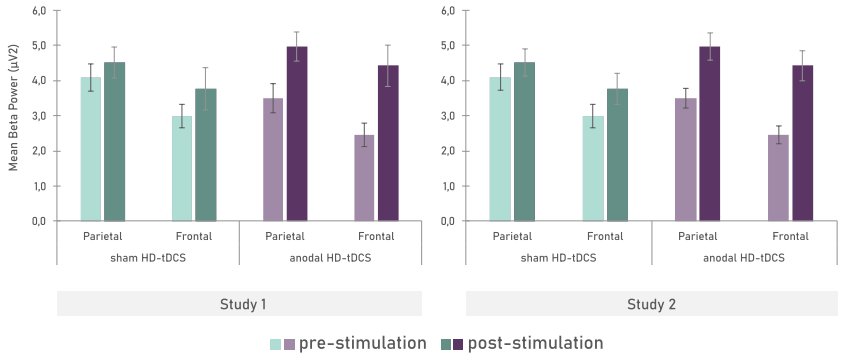


Fig. D.3. Mean beta power by Group (sham/anodal HD-tDCS) and Region (Parietal/Frontal). Data are shown separately for each study: Study 1 (Luna et al., 2020) and Study 2 (current study). Error bars represent SEM.

Appendix E. Bayesian Analyses to complement results regarding the $Alpha_{parietal}/Gamma_{frontal}$ index

E.1. Neurophysiological effects of HD-tDCS: how the $Alpha_{parietal}/Gamma_{frontal}$ index is related to the stimulation condition.

We completed a Bayesian repeated measures ANOVA with Period (pre-/post-stimulation) as a within-participant factor, and Group (sham/anodal HD-tDCS).

Table E.1. Effect of Period × Group on the $Alpha_{parietal}/Gamma_{frontal}$ Index

	Study 1			Study 2			Study 1 + 2		
Models	BF_{10}	Error %	BF_{incl}	BF_{10}	Error %	BF_{incl}	BF_{10}	Error %	BF_{incl}
Period	0.213	4.686	0.428	0.226	0.984	0.624	0.159	0.969	11.116
Stimulation	0.679	2.460	0.849	0.468	1.787	0.879	0.646	0.731	16.065
Period × Group	5.511	1.150	1.447	9.738	1.120	2.315	266.441	0.941	57.008

Updated BF for Study 2 taking evidence from Study 1, BF_{10} = 48.345 (very strong evidence).

E.2. Neurophysiological effects in relation to the effect of HD-tDCS on the executive vigilance (EV) decrement.

To test how the effect of anodal HD-tDCS on the EV decrement is modulated by the $Alpha_{parietal}/Gamma_{frontal}$ index, we completed a Bayesian ANOVA on the Slope of Hits (calculated across blocks 1, with the (Stimulation) Group and the Alpha/Gamma Group (decrease/increase) as between-participant factors.

Table E.2. Effect of Group × $Alpha_{parietal}/Gamma_{frontal}$ Change Group (decrease/increase), on Slope of Hits (blocks 1-6).

	Study 1		Study 2		Study 1 + 2	
Model	**BF_{10}**	**Error %**	**BF_{10}**	**Error %**	**BF_{10}**	**Error %**
Null model	1.000		1.000		1.000	
Stimulation Group	2.032	0.002	1.285	0.005	9.979	0.001
Alpha/Gamma Group	0.308	0.009	0.270	0.007	0.223	0.005
Group + Alpha/Gamma Group	0.617	0.841	0.335	1.615	2.091	1.500
Group + Alpha/Gamma Group + Group * Alpha/Gamma Group	7.459	4.669	0.166	1.160	14.407	1.061
Group * Alpha/Gamma Group	12.097	4.744	0.495	1.989	6.891	1.838

Updated BF for Study 2, BF_{10} = 0.570 (no evidence in favour of H1)

Chapter 7

A Helping Hand to High Demand: Cognitive Load-Dependent Effects of HD-tDCS on the Executive Vigilance Decrement

The contents of this chapter are currently under review as:

Hemmerich, K., Lupiáñez, J., & Martín-Arévalo, E. (2024) HD-tDCS mitigates the executive vigilance decrement only under high cognitive demands.

Abstract

Maintaining vigilance is essential for many everyday tasks, but over time, our ability to sustain it inevitably decreases, potentially entailing severe consequences. High-definition transcranial direct current stimulation (HD-tDCS) has proven to be useful for studying and improving vigilance. This study explores if/how cognitive load affects the mitigatory effects of HD-tDCS on the vigilance decrement. Participants (N = 120) completed a modified ANTI-Vea task (single or dual load) while receiving either sham or anodal HD-tDCS over the right posterior parietal cortex (rPPC). This data was compared with data from prior studies (N = 120), where participants completed the standard ANTI-Vea task (triple load task), combined with the same HD-tDCS protocol. Against our hypotheses, both the single and dual load conditions showed a significant executive vigilance (EV) decrement, which was not affected by the application of rPPC HD-tDCS. On the contrary, the most cognitively demanding task (triple task) showed the greatest EV decrement; importantly, it was also with the triple task that a significant mitigatory effect of the HD-tDCS intervention was observed. The present study contributes to a more nuanced understanding of the specific effects of HD-tDCS on the vigilance decrement considering cognitive demands. This can ultimately contribute to reconciling heterogeneous effects observed in past research and fine-tuning its future clinical application.

Introduction

Transcranial direct current stimulation (tDCS) provides the possibility to modulate cortical excitability of specific brain regions (A. Liu et al., 2018; Nitsche et al., 2008), which can potentially modify a broad range of cognitive functions (Antal et al., 2022; Coffman et al., 2014b; Davis & Smith, 2019; Kuo & Nitsche, 2012), including attentional functioning (Reteig et al., 2017). Applying tDCS to improve and/or maintain performance gains special relevance in contexts where the targeted function is central to a broad range of tasks and degrades quickly over time. This is the case of vigilance, which requires sustaining the focus of attention over long time periods, and remaining alert to detect specific yet unpredictable stimuli (Parasurman et al., 1987). Using tDCS to mitigate this inevitable decrement of vigilance over time has proven to serve as a fruitful intervention (Brosnan et al., 2018; Dai et al., 2022; Roe et al., 2016; Roy et al., 2015). Specifically, anodal high-definition (HD) tDCS over the right posterior parietal cortex (rPPC, Hemmerich et al., 2023; Luna et al., 2020) has shown to mitigate the decrement of executive vigilance (EV), understood as the ability to monitor and execute a specific response to infrequent but relevant stimuli (Luna et al., 2018a, p. 20). Whereas it has shown no effect in mitigating the decrement in arousal vigilance (AV), understood as the ability to maintain a basic state of activation that allows responding to any stimuli of the environment in a fast and relatively automatic manner (Luna et al., 2018a).

A lateralization of sustained attention processes towards the right hemisphere has been established in neuroimaging studies (Langner & Eickhoff, 2013; Lim et al., 2010; Pardo et al., 1991; Stevens et al., 2005), as well as through lesion studies (Koski & Petrides, 2001; Molenberghs et al., 2009). More specifically, lesion studies have identified the rPPC as a hub for spatial attention as well as vigilance (Malhotra et al., 2009), whereas, on a functional level, the rPPC shows a heightened hemodynamic response to infrequently presented targets (Stevens et al., 2005), maintaining current task goals active as well as responding to (internal or external) novel stimuli (Singh-Curry & Husain, 2009). This has led to considering the rPPC as a "convergence node" between the ventral attentional network and the default mode network (DMN), more associated with self-generated thoughts or mind-wandering (Giacometti Giordani et al., 2023).

Furthermore, imaging data from healthy participants suggests that the superior and inferior parietal cortices (constituting the rPPC) are densely interconnected forming a "structural core" (Hagmann et al., 2008) that in turn is highly connected to other neural regions. This positions the rPPC as a highly relevant target for tDCS, given its functional relevance, as well as the potential benefit of tDCS effects spreading through relevant networks (Cosmo, Ferreira, et al., 2015; Rosenberg et al., 2016). Considering the relevance of the rPPC in vigilance processes, the higher spatial precision achieved in the stimulated area by HD-tDCS, as compared to conventional tDCS (Alam et al., 2016; Edwards et al., 2013; Kuo et al., 2013), is of special benefit for more precisely targeting this region.

To understand the underlying mechanisms of the vigilance decrement and its mitigation, one must consider that it may occur due to a complementary or alternative set of causes. Overload theories (resource-depletion hypothesis) assert that the vigilance decrement occurs due to the consumption of attentional resources with time-on-task due to the demanding nature of vigilance tasks (Grier et al., 2003; Warm et al., 2008a), with the associated experience of stress (Dillard et al., 2019; Grier et al., 2003; Szalma et al., 2004; Warm et al., 2008b). Other accounts (underload theories) posit that the underwhelming nature of vigilance tasks, more associated with boredom (Danckert & Merrifield, 2018; Yakobi et al., 2021), ultimately leads to a gradually more mindless execution of the task (Smallwood & Schooler, 2006, 2015). These theories can be tested empirically by manipulating cognitive demands (i.e., the number of simultaneous tasks to perform and therefore, task instructions to hold in working memory). Overload theories pose that increasing task demands would lead to a greater vigilance decrement, which has indeed been observed under normal conditions (Epling et al., 2016; J. Head & Helton, 2014; Smit et al., 2004b) and found to be accentuated by sleep deprivation (Chua et al., 2017). Underload theories, on the other hand, predict that lowering cognitive demands would lead to a less engaged and more mindless performance, steering thoughts away from the task's goal (Risko et al., 2012), producing the vigilance decrement (Ariga & Lleras, 2011). Further support for underload theories stems from self-reported high mindlessness predicting worse performance in a vigilance task where targets appear with low frequency (Manly, 1999), reports of task-induced physiological

disengagement (i.e., parasympathetic activation and reduced cardiac reactivity) (Pattyn et al., 2008), and activation of DMN structures with time-on-task (Salihu et al., 2022). Given this disparity of results, Thomson et al. propose the resource-control account, wherein resources are constant, but executive control declines with time-on-task causing the progressive shift of attentional resources from task-related towards task-unrelated thoughts (mind-wandering) (Thomson, Besner, et al., 2015). This account considers that other factors than task demand can modulate the vigilance decrement: observing results such as a mitigated vigilance decrement with increased perceptual variability of the task's target (Thomson, Smilek, et al., 2015), where higher difficulty demanding more resources is countered by higher engagement, possibly posing a smaller toll on executive control. Among other theories on the vigilance decrement (for a review see: Fortenbaugh et al., 2017), some accounts represent passive fatigue and active fatigue (Saxby et al., 2013) as two extremes on an inverse U-shaped function (Yerkes & Dodson, 1908) between performance and cognitive load (McWilliams & Ward, 2021) or arousal (Esterman & Rothlein, 2019). These models incorporate both underload and overload as two extremes, between which we may attain a middle-ground of optimal performance (Esterman & Rothlein, 2019; McWilliams & Ward, 2021). As a case in point, Luna, Barttfeld, et al. (2022)created three load conditions (single task, dual task, and triple task) using the ANTI-Vea task (Luna, Barttfeld, et al., 2021; Luna et al., 2018a) and observed that the single and triple task groups showed a significant EV decrement, which was mitigated in the dual task group (Luna, Barttfeld, et al., 2022). This further reinforced the view that the EV decrement, present with under and over-demand, is mitigated with intermediate cognitive demands.

The current understanding of how cognitive demands affect the vigilance decrement is still unclear given the disparity of findings (Ariga & Lleras, 2011; Epling et al., 2016; J. Head & Helton, 2014; Pattyn et al., 2008; Smit et al., 2004b), and the current lack of models that explain diverging results. This is further obscured by the contradictory findings when using tDCS to modulate these effects (Borragán et al., 2018; Filmer, Griffin, et al., 2019; Roe et al., 2016). A better understanding of cognitive load-dependent effects and their interaction with tDCS effects is needed for a better translation of these results towards applied fields. Critically, a more

systematic modulation of task demands and stimulation parameters is required in order to define (i) which conditions lead to a greater vigilance decrement, and (ii) critically, under which conditions the vigilance decrement can be mitigated or reduced. The potential impact of these results can branch into (i) providing a small step towards research parameters to follow for understanding and mitigating the vigilance decrement, shedding some light on the currently often contradictory findings, (ii) adapting real-life contexts to optimize performance in human factor applications where the potential negative consequences of the vigilance decrement are greatest (e.g., air traffic control or security screening (Kharoufah et al., 2018; Yin et al., 2019)), and (iii) provide the basis for constructing more efficient intervention or rehabilitation strategies for attention deficits such as those encountered in Attention Deficit and Hyperactivity Disorder (ADHD) (Pievsky & McGrath, 2018) or as a sequelae of stroke(Brosnan et al., 2022), with better informed decisions on when to use compensatory strategies (e.g., reduce task demands to adapt to a lower threshold of what would be considered overdemanding) or restitutive approaches (e.g., training program where threshold of overdemand is increased with tDCS) during rehabilitation. In order to obtain a better roadmap for these outlined applications, further replications and, specifically, more systematic manipulations of cognitive load and tDCS is needed, which was the objective of the present study.

The present study

In the present study, we applied the task manipulations performed by Luna et al. (2022), measuring vigilance in a single and dual task (Luna, Barttfeld, et al., 2022), in combination with HD-tDCS over the rPPC, following the same stimulation protocol as Hemmerich et al. (2023). Further comparisons were made with data from the original triple task studies (standard ANTI-Vea, of two previously collected samples (Hemmerich et al., 2023; Luna et al., 2020). This will allow (i) the replication of prior findings of cognitive load-dependent effects on the vigilance decrement (Luna, Barttfeld, et al., 2022), and (ii) further understanding of whether/how these are affected by HD-tDCS. Given the specificity of HD-tDCS on the EV and not the AV effects (Hemmerich et al., 2023; Luna et al., 2020), and the differences in EV decrements depending on cognitive load (Luna, Barttfeld, et al., 2022), we

preregistered the following hypotheses (osf.io/9wfbx) regarding behavioural outcomes: (i) we expected a mitigated EV decrement (significantly reduced linear decrement of hits across task blocks in EV trials) in the anodal HD-tDCS group compared to the sham group performing the single load task, replicating the findings from Luna, Barttfeld, et al. (2022) in the sham group, and expecting the same beneficial effect of HD-tDCS in the anodal group that had been observed under higher cognitive load (Hemmerich et al., 2023), (ii) no EV decrement (no linear decrement) in the dual load task, expecting to replicate the findings from Luna, Barttfeld, et al. (2022), and therefore, no expected differences between stimulation conditions, and (iii) no modulation of AV performance (i.e., linear increment of SD of RT across blocks) in any load or stimulation group (replicating the specificity observed for the stimulation intervention for EV) (Hemmerich et al., 2023; Luna et al., 2020).

Methods

Participants

Participants (N = 120) were randomly assigned to perform a single or dual version of the ANTI-Vea task while receiving either sham or anodal HD-tDCS. The sample size of 30 participants per experimental condition matched those of prior studies with the standard ANTI-Vea with a priori estimated sample sizes (Hemmerich et al., 2023; Luna et al., 2020). See **Table 7.1** for demographic data.

Table 7.1. Sample sizes and demographic data for each experimental condition.

Task Load	Stimulation Group	*N*	Sex	Age
Single Task	Anodal HD-tDCS	$n = 30$	21 female	$M = 22.03$, $SD = 2.80$
	Sham HD-tDCS	$n = 30$	19 female	$M = 24.03$, $SD = 4.13$
Dual Task	Anodal HD-tDCS	$n = 30$	20 female	$M = 22.30$, $SD = 4.13$
	Sham HD-tDCS	$n = 30$	14 female	$M = 23.30$, $SD = 3.99$
Total sample		**$N = 120$**	74 female	$M = 22.92$, $SD = 3.82$

Note. No differences between the four groups were observed neither for Sex, $\chi^2(3, N = 120) = 4.09$, $p = .252$, nor for Age, $F(3, 116) = 1.76$, $p = .158$.

All participants met the safety inclusion criteria for tES (Antal et al., 2017; Rossi et al., 2009) and magnetic resonance imaging (MRI), had normal or corrected-to-normal vision, were right-handed, and had no known neurological or psychiatric conditions. Participants signed an informed consent form and received monetary compensation for their participation (10€/hour). This study was approved by the Ethical Committee of the University of Granada (2442/CEIH/2021 and 1188/CEIH/2020), in accordance with the 1964 Declaration of Helsinki (last update: Brazil, 2013).

Apparatus and Stimuli

Behavioural Measures

Participants performed modified versions of the ANTI-Vea Task (as shown in **Fig. 7.1.B**), where all trials of the standard task (Luna et al., 2018a) were presented, but task instructions and responses were coded differently. The ANTI-Vea task is an adapted version of the classical attentional networks task (Fan et al., 2002), that includes independent measures of the executive and arousal vigilance components. For this purpose, the task is comprised of three types of trials (ANTI, EV, and AV) that are presented in pseudorandomized order. All ANTI-Vea versions used in this study were run for 7 blocks (560 trials in total). The ANTI trials (60% of total trials) allow measuring the functioning of the classical attentional networks (alerting, orienting, and executive control Callejas et al., 2004; Petersen & Posner, 2012). These trials present a flanker task where the direction of the target (i.e., a central arrow) must be detected (pressing the *c*-key for left-pointing arrows, and *m*-key for right-pointing arrows) regardless of the direction of the flankers (i.e., surrounding arrows). The EV trials (20% of the total) prompt participants to detect an infrequent and large vertical displacement of the target of the flanker task, by giving an alternative response (pressing the space bar). This sub-task would be akin to signal-detection tasks such as the Mackworth Clock Test (MCT, Mackworth, 1948). Lastly, AV trials (remaining 20% of trials) feature a red countdown (instead of the stimuli from ANTI or EV trials), which has to be stopped as fast as possible by pressing any key from the keyboard, akin to the Psychomotor Vigilance Test (PVT, Lim & Dinges, 2008). For a more detailed description of the standard

task and its parameters, please refer to: Luna et al. (2018), and Luna et al. (2021).

General task instructions across the different load conditions were given for participants to keep their gaze on the fixation point ("+") in the centre of the screen and to respond as fast and as accurately as possible. Then, instructions diverged according to the manipulation of cognitive load, to reflect the correct response for each type of trial as depicted in **Fig. 7.1.A**. While maintaining perceptual load constant, the manipulation of task instructions and response coding resulted in: (i) a **single task**, which required participants to respond only to EV trials, and (b) a **dual task**, in which participants had to respond to both EV and AV trials. These two groups were then further compared with data from (iii) a **triple task**, where participants had to respond to ANTI, EV, and AV trials (standard ANTI-Vea), collected from two previous studies (Hemmerich et al., 2023; Luna et al., 2020) (N = 120).

HD-tDCS setup

HD-tDCS was applied with a Starstim 8® device and hybrid NG Pistim Electrodes (Ag/AgCl, contact area: 3.14 cm^2) controlled through NIC v20.6 software (Neuroelectrics®, Barcelona). Five of the electrodes, placed in a neoprene headcap, were set up in a 4 × 1 ring-like array, targeting the rPPC by placing the central anode over P4, and the four surrounding cathodes over CP2, CP6, PO4, and PO8 (see **Fig 7.1.B** and **Fig. 7.1.C**). Using a single-blind procedure, anodal (1.5 mA) or sham (0 mA) HD-tDCS was applied according to random group allocation, from the 2nd to the 6th task block (see **Fig 7.1.D**). The sham protocol consisted of two ramps (30 s ramp-up and 30 s ramp-down) at protocol onset and offset. The anodal protocol consisted of an initial ramp-up (30 s) followed by active stimulation (~28 minutes), and a ramp-down (30 s) at offset. In this study, electroencephalographic (EEG) signal was recorded during the 1st task block serving as a baseline, and during the 7th block, serving as a post-stimulation measure. Further details regarding this step are beyond the scope of this report as EEG data will not be presented.

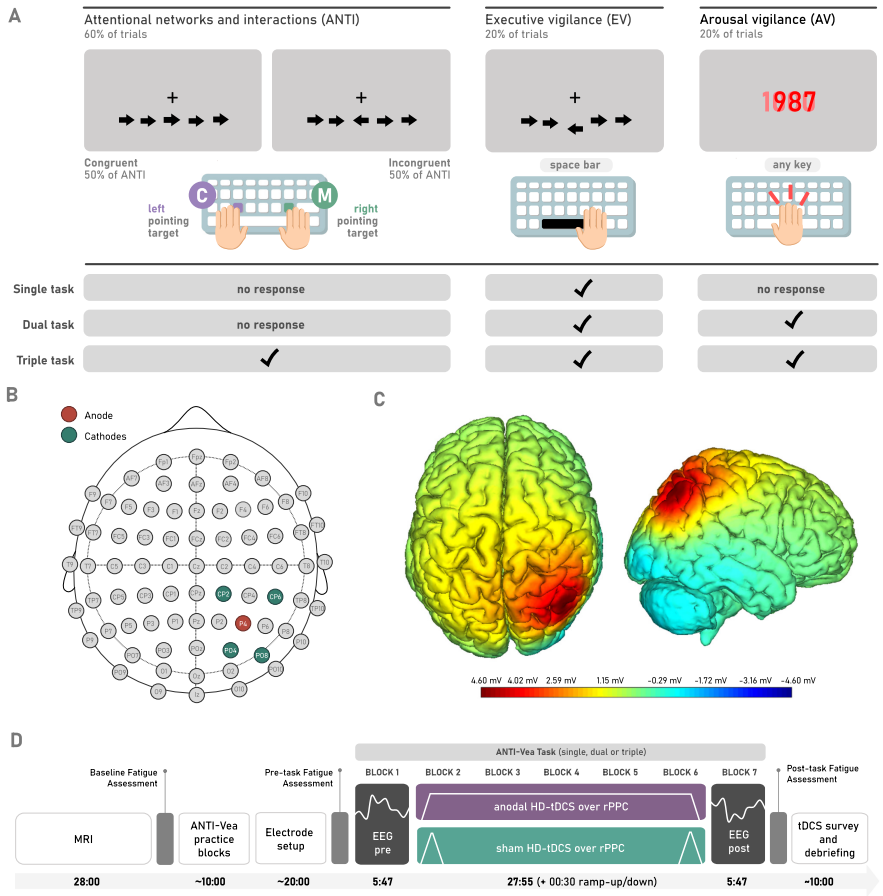


Figure 7.1. ANTI-Vea Task procedure, electrode setup and resulting E-field simulation, and experimental procedure. **(A)** ANTI, EV, and AV targets of the ANTI-Vea task. The bottom table shows which target(s) participants are instructed to respond to (with a check) for the single, dual, and triple tasks. Note that perceptual load is maintained constant across all task conditions, as only instructions and response coding are modified. Note that both hands are placed over the keyboard at all times, using the left hand to press the "C" key and the right hand for the "M" key, whilst the "spacebar" key and the key chosen by the participant for AV trials can be pressed by any finger/hand (and must thus not be necessarily held constant). **(B)** Electrode setup for HD-tDCS: the anode is placed over P4 (red), and the surrounding cathodes over CP2, CP4, PO4, and PO8 (green), following the same protocol as (Hemmerich et al., 2023) (2023) **(C)** Simulated voltage field obtained from the stimulation protocol from a top and right-hemisphere view. (**D**) Experimental procedure, where the bottom arrow shows the exact or approximate (preceded with a tilde) duration of each step, in minutes. Each fatigue assessment took less than a minute.

Fatigue assessment

Subjective mental and physical fatigue ratings were assessed throughout the experiment: baseline, pre-task, and post-task (see procedure or **7.Fig. 1.D**). Responses were recorded through a visual analogue scale: a horizontal line ranging from minimum (left side of the screen) to maximum fatigue (right side). The assessment order for fatigue type was counterbalanced across participants but kept constant for each participant's session, following the procedure of Luna, Barttfeld, et al. (2022).

Procedure

As in (Hemmerich et al., 2023), the experimental session began with an MRI scan (~28 minutes), mainly focused on acquiring diffusion-weighted imaging data. This data is being collected as part of a larger research project and will not be covered in the present report. Participants then sat in a separate, dimly lit room to complete the experiment. First, participants completed the baseline fatigue assessment and the ANTI-Vea's practice blocks (adapted for each load condition). After electrode set-up, participants completed the pre-task fatigue assessment. Then the experimental task started, during which stimulation was applied from the 2nd to the 6th experimental block. Right after the completion of the last (i.e., 7th) experimental block, the post-task fatigue assessment and the transcranial Electrical Stimulation Survey (Fertonani et al., 2015) were completed.

Statistical Analyses

Following the preregistered plan of analysis, we analysed EV and AV data from baseline (1st block) to the final active or sham stimulation block (6th), following prior HD-tDCS studies (Hemmerich et al., 2023; Luna et al., 2020). Following the standard approach to ANTI-Vea scores(Luna et al., 2018a), we computed EV indices [Hits (percentage of correct responses), False Alarms (FA), Sensitivity (A'), and Response Bias (B")] and AV indices [mean RT and standard deviation of RT (SD of RT)]. For EV data, we compared baseline differences in EV indices between stimulation groups using an ANOVA. Then, each index was included in an ANOVA as a dependent variable, with Blocks (1st-6th) as a within-participant factor and Stimulation Group (anodal

or sham HD-tDCS) and Task Load (single or dual) as between-participant factors, followed up by partial ANOVAs for each Task Load level. Polynomial contrasts were used to analyse the linear component of each index across Stimulation Group for each Task Load level. Then, the single and dual task data, combined as a *not-triple* condition, were re-analysed jointly with triple-task data studies (Hemmerich et al., 2023; Luna et al., 2020), combined as a *triple* condition, repeating the above-described analyses (with Updated Task Load) on two balanced samples (n_{triple} = 120, $n_{not\text{-}triple}$ = 119). Lastly, results for AV data are reported first considering only low-load conditions (i.e., only dual task) and then comparing low and high-load conditions (i.e., dual vs triple task, using data from the present study and data from (Hemmerich et al., 2023), to achieve comparable sample sizes in each group).

Note that for all reported ANOVAs, degrees of freedom are reported with Greenhouse-Geisser correction when the sphericity assumption was violated (i.e., p > .05 in Mauchly's test). Additionally, across results, equivalent Bayesian tests are reported to further test the validity of our inferences, as a supplement to non-significant frequentist results. Note Bayes Factors in favour of the null hypothesis (BF_{01}) provided for polynomial contrasts on the linear decrement correspond to independent or one sample t-tests completed on the Slope across Blocks (1^{st}-6^{th}). Lastly, methods and Results for Subjective Mental and Physical Fatigue are reported in **Appendices E-H** of the **Supplementary Material**.

Results

Blinding Efficacy

The total amount of self-reported discomfort/sensations associated with stimulation (Fertonani et al., 2015) was significantly different between the Stimulation Groups, U = 2190, p = .037, with higher discomfort reported in the sham (M = 2.43, SD = 2.08) than in the anodal (M = 1.68, SD = 1.85) group. This difference seems to be mainly driven by the significantly higher intensity reported for *pinching* in the sham group (M = 0.38, SD = 0.80) than in the anodal group (M = 0.03 SD = 0.18), U = 2166, p = .001, without any differences for the remaining sensations (all p's > .136, see **Appendix A of the Supplementary Material** for further statistical details). The higher

discomfort reported in the sham group likely led to a higher estimation of belonging to the active stimulation group in the sham (62 %) than in the anodal group (42 %). However, the guessed active group allocation was not statistically different between Stimulation Groups, $\chi^2(2, N = 120) = 4.85$, $p = .088$. Taken together with the evidence for group differences in total discomfort ($BF_{10} = 1.07$) and pinching ($BF_{10} = 0.93$) being anecdotal (Lee & Wagenmakers, 2014) at most, leads us to conclude that blinding was still effective in the present study.

EV decrement under lower cognitive demands: single vs. dual cognitive load conditions

Following standard filtering for ANTI-Vea data (Luna, Barttfeld, et al., 2021), outliers (defined based on accuracy < 50% in EV and/or AV trials), excluded one participant (sham-single) from further analyses. There were no significant differences in EV Hits at baseline (Block 1) between the sham and anodal HD-tDCS groups for the single task condition, $F(1, 57) = 2.07$, $p = .156$, $\eta_p^2 = .04$ ($BF_{01} = 1.60$), or the dual task condition, $F < 1$ ($BF_{01} = 3.73$). Similarly, no differences between the Stimulation Group at baseline (Block 1) were observed for EV A' in the single task condition, $F(1, 57) = 1.92$, $p = .172$, $\eta_p^2 = .03$ ($BF_{01} = 1.70$), or the dual task condition, $F(1, 58) = 1.20$, $p = .278$, $\eta_p^2 = .02$ ($BF_{01} = 2.31$),

Regarding EV Hits, The Blocks × Stimulation Group × Task Load mixed ANOVA performed on Hits only showed a significant main effect of Blocks, $F(3.72, 428.18) = 24.27$, $p < .001$, $\eta_p^2 = .17$. However, no interactions were significant: Blocks × Stimulation Group, $F < 1$, Blocks × Task Load, $F < 1$, Blocks × Stimulation Group × Task Load, $F < 1$ (all $BFs_{01} > 38.27$), as shown in **Fig. 7.2.A**[1]. A polynomial contrast showed that all groups (joint analysis across experimental conditions) had a significant linear decrement across time, $F(1, 115) = 51.98$, $p < .001$, $\eta_p^2 = .31$. Importantly, in regard to our hypotheses, polynomial contrast showed the expected significant linear decrement of Hits across Blocks in the sham conditions of the single task, $F(1, 57) = 8.42$, $p = .005$, $\eta_p^2 = .13$, which, against our hypotheses was also

[1] Note that the reported results span Blocks 1-6, as per our pre-registered plan for analyses. Nonetheless, for clarity, repeating the analyses over Blocks 1-7 yielded the same result. For low-load conditions (single and dual task), the effect of Block remains significant, $F(4.19, 481.69) = 23.55$, $p < .001$, $\eta_p^2 = .17$, without significant interactions (all Fs < 1).

observed in the sham condition of the dual task, $F(1, 58) = 12.72$, $p < .001$, $\eta_p^2 = .18$. These linear decrements were not significantly different between the two Task Load conditions, $F < 1$ ($BF_{01} = 3.25$).

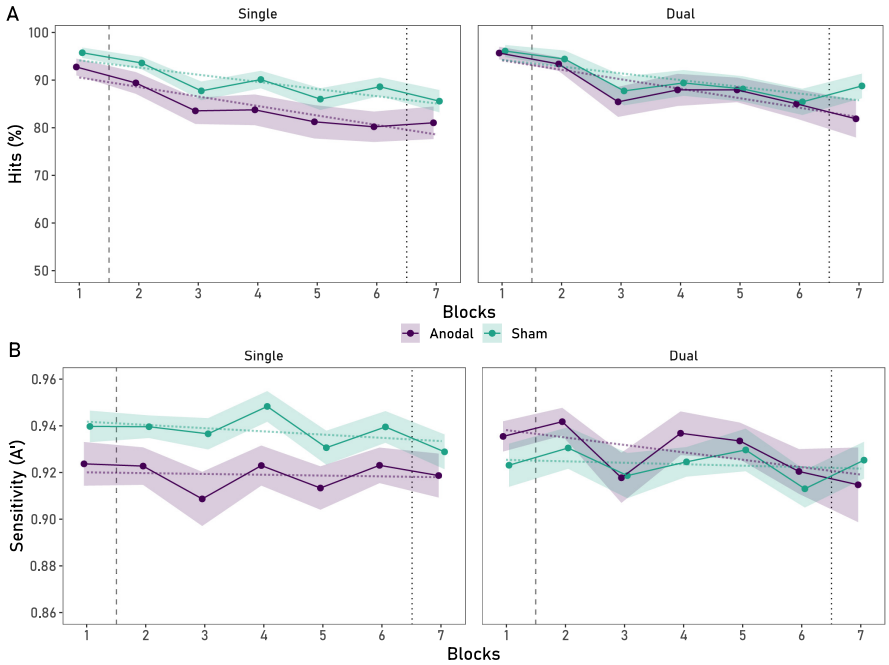


Figure 7.2. (A) Mean % of Hits in EV trials across Blocks for single and dual cognitive load conditions. A linear decrement across Blocks was observed across all conditions. **(B)** Sensitivity (A') in EV trials across Blocks for the single and dual cognitive load conditions. An effect of Blocks on A' is observed regardless of the stimulation condition, although the linear component was not significant, whilst the single task condition shows a lower mean A' (averaged across Blocks) in the anodal compared to the sham condition. *Note.* The dashed vertical line represents the onset of the stimulation protocol. The dotted line represents the offset of the stimulation protocol. The shaded ribbons represent the standard error of the mean (SEM).

Regarding sensitivity (A') for EV trials, although a main effect of Blocks, $F(4.34, 499.11) = 2.48$, $p = .031$, $\eta_p^2 = .02$, was observed, polynomial contrasts show no significant linear decrement across Blocks (across all conditions), $F(1, 115) = 1.39$, $p = .240$, $\eta_p^2 = .01$ ($BF_{01} = 4.89$). More importantly, the effect on Blocks did not interact with Stimulation Condition, $F < 1$ ($BF_{01} = 127.80$), Task Type, $F(4.34, 499.11) = 1.58$, $p = .174$, $\eta_p^2 = .01$ ($BF_{01} = 12.90$), or an interaction of both $F < 1$ ($BF_{01} = 55.47$), as depicted in **Fig. 7.2.B**. As can be observed from **Fig. 7.2.B**, while the linear decrement is not different across conditions, in the

Single Task condition, a difference in overall Hits and A' can be observed. For mean % Hits (across Blocks 1st-6th) the difference between stimulation conditions did not reach significance, $t(57) = -1.88$, $p = .065$ ($BF_{01} = 0.88$), whereas a significantly lower mean A' (across Blocks 1-6) is observed in the sham single task condition ($M = .94$, $SD = .03$), compared to the anodal single task condition ($M = .92$, $SD = .03$), $t(57) = -2.76$, $p = .008$. Refer to **Appendix B of the Supplementary Material** for further results on the remaining EV indices (FA and B").

EV decrement under effects of increased cognitive load: single and dual cognitive load conditions vs. triple load

Baseline (i.e., 1st Block) Hits for EV trials were significantly lower for the triple task condition ($M = 82$ %, $SD = 15$), compared to the single ($M = 94$ %, $SD = 8$) and dual (M = 96 %, $SD = 7$) conditions, $F(2, 234) = 37.60$, $p < .001$, $\eta_p^2 = .24$. However, and importantly, within the triple task condition, there were no significant differences between Stimulation Groups, $F < 1$ ($BF_{01} = 3.85$). Similarly, no baseline differences were observed for EV A', $F < 1$ ($BF_{01} = 5.01$).

The ANOVA performed on Hits in EV trials with Blocks as a within participants variable and Stimulation Group and Updated Task Load (triple/not-triple) as between-participant factors, reflected a main effect of Block, $F(4.31, 513.24) = 21.42$, $p < .001$, $\eta_p^2 = .15$, which interacted significantly with Stimulation Group, $F(4.31, 513.24) = 3.69$, $p = .005$, $\eta_p^2 = .03$. Importantly, the three-way Blocks × Stimulation Group × Updated Task Load interaction was significant, $F(4.24, 999.51) = 2.97$, $p = .017$, $\eta_p^2 = .01$[2]. Polynomial contrasts completed on the grouped (triple vs. not-triple) data showed that the linear decrement between the anodal and sham conditions was not different for the not-triple condition, $F < 1$ ($BF_{01} = 4.09$), whereas it was for the triple task condition, $F(1, 119) = 8.62$, $p = .004$, $\eta_p^2 = .07$. Bayesian analyses further showed that there was moderate evidence ($BF_{10} = 5.66$) for this mitigated EV decrement in the triple task anodal group, as can be seen in **Fig. 7.3** (right), compared to extreme evidence ($BF_{01} = 145.25$) against a significant

[2] For transparency, to complement the pre-registered analyses over Blocks 1-6, repeating the same analyses across Blocks 1-7, yields the same results: the main effect of Block, $F(5.01, 1181.07) = 44.78$, $p < .001$, $\eta_p^2 = .16$, and the critical three-way Block × Stim × Updated Task Type interaction remain significant, $F(5.01, 1181.07) = 2.91$, $p = .013$, $\eta_p^2 = .01$.

interaction in the not-triple task condition, as shown in **Fig. 7.3** (left). Lastly, there was a significant difference in the linear decrement observed between sham conditions between the not-triple and triple tasks, $F(1, 117) = 7.99$, $p = .006$, $\eta_p^2 = .06$, reflecting, the significantly greater EV decrement under high compared to lower load conditions. In contrast, the anodal not-triple and triple conditions' linear decrement were not significantly different from each other, $F(1, 119) = 1.02$, $p = .316$, $\eta_p^2 = .01$ ($BF_{01} = 3.17$), which indicates that HD-tDCS in the triple task conditions seems to mitigate the vigilance decrement up to the performance level observed for the single or dual task conditions.

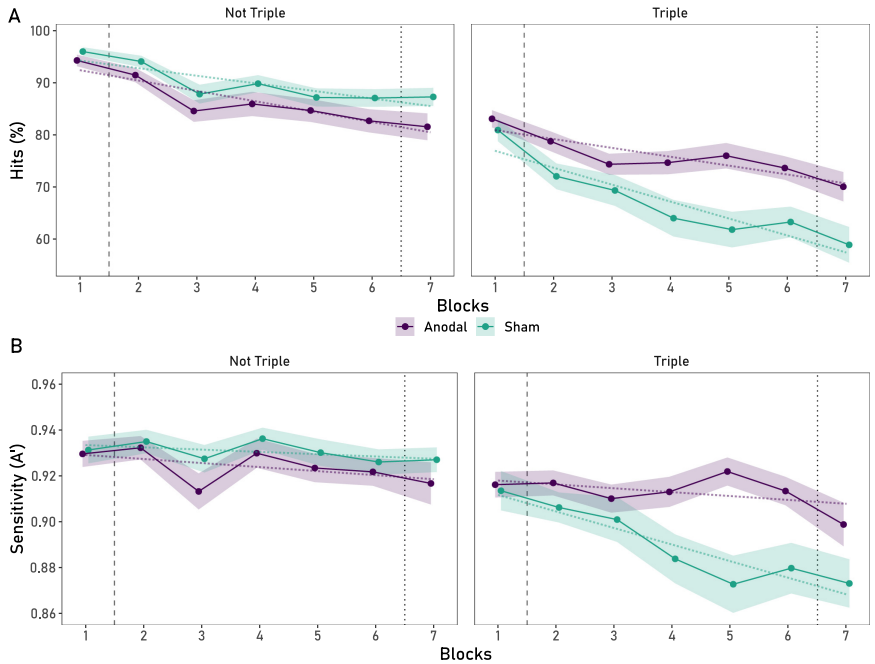


Figure 7.3. (A) Mean % of Hits and in EV trials across blocks combined for the single and dual task conditions (low-load, left), and triple task condition (high-load, right). The above-reported linear decrement in low load conditions, without an effect of HD-tDCS stands in contrast with a significantly lower linear decrement in the anodal compared to the sham HD-tDCS condition of the triple task. **(B)** Sensitivity (A') in EV trials across Blocks for the low-load condition (left) and the high-load condition (right). In the sham triple task condition, a much steeper decrement of A' is observed, compared to the non-significant linear component in the triple anodal condition, which is comparable to both low-load conditions. *Note.* The dashed vertical line represents the onset of the stimulation protocol. The dotted line represents the offset of the stimulation protocol. The shaded ribbons represent the SEM.

Notably, Sensitivity (A') also decreased significantly across Blocks, $F(4.59, 1084) = 3.82$, $p = .003$, $\eta_p^2 = .02$, and was modulated by Stimulation Condition, $F(4.59, 1084) = 2.72$, $p = .022$, $\eta_p^2 = .01$, but not by Updated Task Load, $F(4.59, 1084) = 2.05$, $p = .08$, $\eta_p^2 = .01$ ($BF_{01} = 16.71$). Importantly, the triple interaction was significant, $F(4.59, 1084) = 2.82$, $p = .019$, $\eta_p^2 = .01$. Polynomial contrasts reflected a significant linear decrement in A' in the triple task sham group, $F(1, 119) = 23.36$, $p < .001$, $\eta_p^2 = .16$, significantly different from the linear decrement in the triple task anodal group, $F(1, 119) = 12.11$, $p < .001$, $\eta_p^2 = .09$, where, notably, no significant linear decrement was observed, $F < 1$ ($BF_{01} = 7.01$), as can be seen in **Fig. 7.3.B**. See **Appendix C of the Supplementary Material** for further results on the remaining indices for EV trials (FA and B").

AV decrement: dual vs. triple load conditions

For the dual task AV data there were no significant baseline differences between the two Stimulation Groups on SD of RT, $F < 1$ ($BF_{01} = 3.64$). As predicted, there was a significant AV decrement, shown as an increment in the SD of RTs to AV trials across Blocks, $F(3.39, 196.87) = 4.86$, $p = .002$, $\eta_p^2 = .08$, which was not modulated by HD-tDCS, $F < 1$ ($BF_{01} = 16.26$)[3]. Polynomial contrasts further showed that whilst there was no significant linear increment in the sham group, $F(1, 58) = 3.23$, $p = .077$, $\eta_p^2 = .05$ ($BF_{01} = 0.54$), it was significant for the anodal group, $F(1, 58) = 7.90$, $p = .007$, $\eta_p^2 = .12$. Importantly, the linear increment was not significantly different between Stimulation Groups, $F < 1$ ($BF_{01} = 3.07$), as shown in **Fig. 7.4**.

Finally, an ANOVA performed on SD of RT, contrasting the dual and triple conditions, showed a significant AV decrement (increment of SD of RT) across Blocks, $F(4.02, 466.80) = 9.32$, $p < .001$, $\eta_p^2 = .07$. However, this did not interact with Stimulation Condition, $F(4.02, 466.80) = 1.35$, $p = .249$, $\eta_p^2 = .071$ ($BF_{01} = 21.70$), or Task Load, $F(4.02, 466.80) = 11.62$, $p = .167$, $\eta_p^2 = .01$ ($BF_{01} = 12.10$), nor was there a significant triple interaction, $F < 1$ ($BF_{01} = 15.09$), as can

[3] To complement the pre-registered analyses over Blocks 1-6, if the same analyses are repeated over Blocks 1-7, the same results are observed: comparing the AV (SD of RT) across the dual and triple tasks also showed a significant effect of Blocks, Block: $F(4.11, 476.88) = 11.23$, $p < .001$, $\eta_p^2 = .09$, but no significant interactions (p's ≥ .145).

be seen in **Fig. 7.4**. Refer to **Appendix D of the Supplementary Material** for further AV results (Mean RT in AV trials).

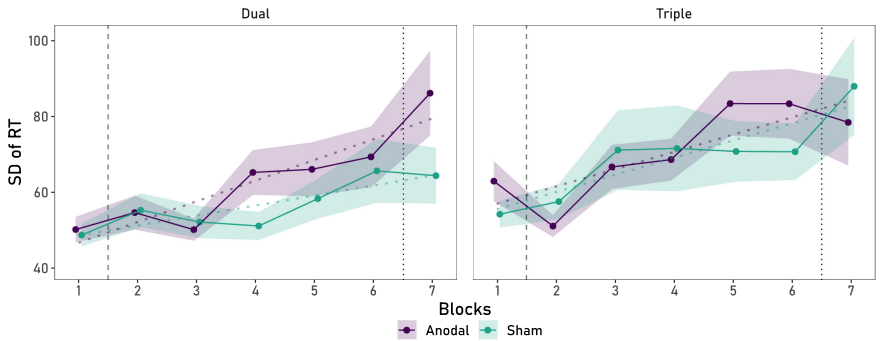


Figure 7.4. AV decrement (increment of SD of RT with time-on-task) as a function of stimulation condition for the dual task (left) and the triplet ask condition (right). No differences between the linear increment of SD of RT across Blocks were observed between Stimulation Groups of either task condition. *Note.* The dashed vertical line represents the onset of the stimulation protocol. The dotted line represents the offset of the stimulation protocol. The shaded ribbons represent the SEM.

Discussion

This study aimed at investigating the influence of cognitive load and HD-tDCS, as well as their interaction, on the EV decrement. To this end, we manipulated task load (single or dual) and HD-tDCS application over the rPPC (sham vs. active). Contrary to our preregistered hypotheses, we observed no differences between the EV decrement in the single and dual task conditions and no modulation of this decrement by HD-tDCS. As expected, neither cognitive load nor HD-tDCS modulated the AV decrement. Importantly, when contrasted with prior results using a triple task, we are able to expand evidence on the specific effect of rPPC HD-tDCS on the executive component of vigilance studies (Hemmerich et al., 2023; Luna et al., 2020): the mitigatory effect of HD-tDCS is only evident under conditions of high cognitive demand.

Against our pre-registered hypothesis, we did not replicate the findings of Luna, Barttfeld, et al. (2022), as the single and dual load conditions both showed a significant EV decrement with time-on-task, without any differences across load conditions. Some studies report similar null effects comparing single and dual tasks (Grier et al., 2003; Stearman & Durso, 2016), or no vigilance decrement at all regardless of the load condition (Epling et

al., 2019; Moray & Haudegond, 1998). However, most of the literature is either skewed towards underload (observing larger decrements with lower task demands (Ariga & Lleras, 2011) or higher engagement (Pop et al., 2012)) or overload theories (observing greater vigilance decrements with increased task demands by adding a secondary task (Epling et al., 2016; J. Head & Helton, 2014; Smit et al., 2004b) or increasing instruction complexity (Stearman & Durso, 2016), without any clear consensus. One possible explanation for our diverging results is that single and dual tasks yielded conditions that were qualitatively not sufficiently different and therefore processed similarly. Under these low to medium load conditions, available resources may suffice to (somewhat successfully) complete the task and mind-winder in parallel (maintaining the same level of performance across slightly differing demand conditions). This could be explained by the *resource-control account*, as executive control decreases with time-on-task, gradually tipping the balance from task-related towards task-unrelated thoughts (Thomson, Besner, et al., 2015). The single and dual tasks may operate at a relatively low "tipping point". Importantly, the EV decrement has been recently linked with the loss of executive control with time-on-task in the standard ANTI-Vea (triple task) (Luna, Tortajada, et al., 2022). Future research systematically manipulating task demands in a within-participants design could explore: (i) whether executive control measures and the EV decrement are related when task demands are reduced, and (ii) how each load level influences the presence of task-unrelated thoughts.

Contrary to the expected mitigated EV decrement in the single group receiving active HD-tDCS and no effect of HD-tDCS on EV performance in the dual group, we observed no mitigatory—or detrimental—effect of stimulation in either the single or dual task condition. Similar results have been observed with the Sustained Attention to Response Task (SART) comparable to our single task condition: prefrontal tDCS did not affect target accuracy (Filmer, Griffin, et al., 2019), and anodal or cathodal tDCS over the right inferior parietal cortex (rIPL) did not affect error rates or RTs (Coulborn et al., 2020). Similarly, another study reports null effects of anodal tDCS over the left PFC in a dual working memory task (Borragán et al., 2018). However, there are also some reports of detrimental effects of higher doses of both anodal and cathodal tDCS over the rIPL on accuracy in the SART (Filmer et al., 2021), and beneficial effects on accuracy with anodal HD-tDCS

over the left dorsolateral prefrontal cortex (DLPFC) regardless of the task demand condition of a standard and a modified SART (Martínez-Pérez et al., 2023). Lastly, it has been suggested that prefrontal tDCS may modulate sustained attention by affecting its higher-order sub-processes, rather than simple target detection (Reteig et al., 2017), which could partially explain the absence of effects of tDCS in low demanding conditions.

In contrast to the null effect of HD-tDCS on the EV decrement in the low and medium load conditions, the mitigatory effect of rPPC HD-tDCS was only observed in the most demanding condition (triple task). The EV decrement in the sham triple-task condition was more pronounced than under single and dual load, which was mitigated in the HD-tDCS condition. Similar results have been observed with anodal tDCS over the right DLPFC, leading to improved accuracy under the highest load condition of a working memory task (Figeys et al., 2023), and anodal tDCS over the left DLPFC leading to delayed beneficial effects on multitasking but not on single task performance(Hsu et al., 2015). Other studies also suggest that tDCS over right prefrontal or parietal areas can lead to detrimental effects on task performance under objective (Roe et al., 2016) and subject-specific high load conditions (Vergallito et al., 2018). In contrast, some studies have reported beneficial effects of cathodal tDCS for maintaining or improving performance in high load conditions (Filmer et al., 2013; Weiss & Lavidor, 2012). Studies on the intersection of cognitive load and tDCS are still rather scarce and yield no clear conclusions. While the inconsistencies across the existing literature are partially explained by the variability between stimulation procedures, cognitive processes studied, and tasks used across these different studies, a crucial factor to consider is the conceptualization of cognitive load and how its levels are established. Roe et al. (2016) argue that *"[...] using a load level that overtaxes cognitive capacity, as well as making use of a wider range of load levels (i.e., more than two), is preferable if one's goal is to investigate the interaction between tDCS and cognitive load*" (Roe et al., 2016). Precisely, the high load condition of our study, although complex and demanding, is not overtaxing, as was the case for the high load condition of studies reporting detrimental effects of anodal tDCS (Roe et al., 2016; Vergallito et al., 2018). The effects of tDCS on the vigilance decrement are likely to depend less on the externally imposed and conceptualized levels of cognitive load, but rather on the specific demand

they impose on each individual, and the specific neural state they induce (Miniussi et al., 2013). Therefore, as illustrated in **Fig. 7.5**, high but manageable cognitive demands could lead to beneficial effects of anodal tDCS, as observed in the present study, where increasing neural excitability may further excite task-relevant processes. However, we hypothesize that when further increasing demands to a level where task performance cannot be maintained, the effects of anodal tDCS would be detrimental, as increasing the excitability of overtaxed neural circuits is likely to disrupt task performance. This might also explain facilitatory effects of cathodal tDCS in tasks with high demand (Filmer et al., 2013; Weiss & Lavidor, 2012), where inhibitory processes could reduce over-demand. Lastly, in the lower load conditions (single and dual task), a ceiling effect of the modulatory effects of HD-tDCS may be taking place.

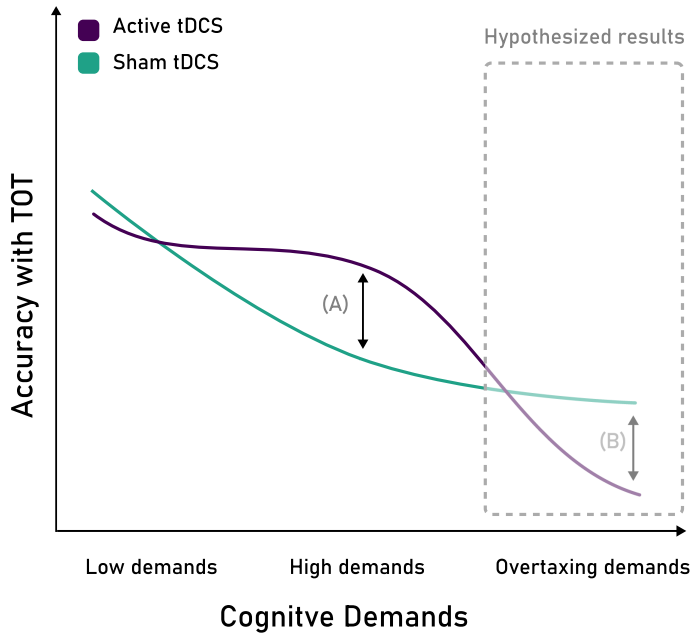


Figure 7.5. Observed and hypothesized interaction of cognitive demands and HD-tDCS over rPPC on the accuracy performance with time-on-task (TOT), with lower values depicting a greater EV decrement. **(A)** Beneficial effect of active HD-tDCS over the rPPC, mitigating the EV decrement, as observed in the present study. **(B)** Further increasing task demands to a level that is overtaxing, would potentially lead to even worse EV performance, which could be further deteriorated by the application of active tDCS –as conceptualized and observed by Roe et al. (2016).

Another relevant result of the present study is the finding that performance gains, namely, the improved accuracy in target detection for EV trials, were due to improved sensitivity (i.e., ability to discriminate signal from noise), and not due to shifts in the response bias (i.e., the adoption of a more liberal response criterion, which would merely increase hits at the cost of increasing false alarms). While some studies do report similar results (Coffman et al., 2012; Falcone et al., 2012), signal detection theory measures are not discussed in most studies exploring the effect of tDCS on vigilance, and opposite findings have also been reported showing greater sensitivity declines in less demanding tasks (Caggiano & Parasuraman, 2004). Thus, whilst requiring further replication, for now, our results highlight that when HD-tDCS mitigates the EV decrement (in high demand conditions), it does so by improving performance in a precise manner.

Taken together, our results further point to the fact that underlying mechanisms driving EV performance are not being properly explored with the tools at hand. As suggested above, a better understanding of what is causing the vigilance decrement, as would do, for example, collecting thought probes throughout the task, would help further understand the present results. Although future challenges still lie in the fact that the presence of mind-wandering is not a fool-proof sign of underload, as the presence of mind-wandering does not always predict performance costs (Thomson et al., 2013), nor does the manipulation of task demands always lead to different mind-wandering rates (Martínez-Pérez et al., 2023). Future research could bridge this gap by including, not only thought-probes in vigilance tasks but also including other more objective measures of engagement, such as eye movements (Krasich et al., 2018). Finally, given that the vigilance decrement can be shaped by a myriad of different factors (Mackie, 1987), future research should refine their approach in studying cognitive load dependent effects on vigilance, in which considering individual differences should be a key factor.

However, despite the above-mentioned limitations and open questions, the present findings can tentatively inform future decisions in research and clinical settings. The cognitive-load dependent effects of HD-tDCS on the EV decrement as observed in the present study underline the importance of considering cognitive load as an essential factor in: (i) predicting stimulation

outcomes, and (ii) tailoring the interactions of demands and tDCS individually. Regarding the first point, whilst future research is needed to understand the generalizability of these results, our data suggests that in areas where a tDCS intervention is to be applied but cognitive demands cannot be modified or adapted, a prediction (based on behavioural data) could be made as of how successful a tDCS intervention would actually be. If the task is overdemanding, the intervention is likely to not adequately induce plastic changes towards the desired outcomes, whereas, if the task is under-demanding, a ceiling effect might hamper any real efficacy of the stimulation as well. While prior to such applications, further research would be needed, this consideration could be a first step in more precisely delineating the intervention and, potentially, offer a broad guideline that could avoid devoting resources to null findings. Regarding the second point, when the cognitive demands can be individually assessed and adjusted to an optimal level, the efficacy of interventions focused on the rehabilitation of attentional functions could be greatly improved. In a clinical setting, attention deficits such as those elicited by ADHD (Pievsky & McGrath, 2018) or as a sequelae of a stroke (Brosnan et al., 2022), could lead to the subjective and individual experience of high cognitive demands or even result in an over-taxing of resources in context that are considered to be of low demand under normal circumstances. Given that the threshold of what is considered overdemanding is not even uniform among healthy participants (Borragán et al., 2018; Vergallito et al., 2018), it will likely be even more heterogenous in these clinical populations. Therefore, instead of externally imposing a fixed demand, individually tailoring demand levels of cognitive training tasks to individual capacity (Borragán et al., 2018; Vergallito et al., 2018) and gradually increasing task demands, for online use in a tDCS intervention may ensure that the neuroplastic effect of tDCS actually reinforces effective task-resolution and learning processes (Miniussi et al., 2013) as a restitutive approach to regain attentional functioning.

Conclusions

According to our results, the EV decrement does not seem to be modulated by cognitive load under relatively undemanding conditions (towards improved performance in the dual load group, as was reported by Luna,

Barttfeld, et al. (2022). Indeed, both single and dual load conditions showed a similar vigilance decrement across time. Under these conditions (single and dual cognitive load), additionally, HD-tDCS does not affect EV performance. However, under conditions with higher demand (i.e., triple task) there is a steeper vigilance decrement compared to lower load conditions, which was mitigated via anodal HD-tDCS over the rPPC. This study highlights the fact that task demands should be an important factor in considering the efficacy of a tDCS intervention on vigilance performance. This will allow a better understanding of the vigilance decrement in itself and facilitate a more effective translation of these results into clinical settings.

Supplementary Material

Appendix A. Blinding Efficacy

As total and individual subjective sensation data did not follow a normal distribution ($p < .001$ for Shapiro-Wilk test in all conditions), we performed a Mann-Whitney test to test for the blinding efficacy, followed up with a Bayesian Mann-Whitney test, showing that there is only anecdotal evidence for group differences in the total discomfort and pinching that was reported.

Table A.1. Sensations between the anodal and sham HD-tDCS groups.

Sensation	U	p	BF_{10}
Total Discomfort	2190	0.037	1.067
Itching	1968	0.336	0.28
Pain	1923	0.137	0.303
Burning	2001	0.170	0.292
Warmth/Heat	1883.5	0.574	0.241
Pinching	2166	0.001	0.926
Metallic/Iron taste	1801.5	0.989	0.255
Fatigue	1649	0.143	0.304

Appendix B. Additional results for EV trials: single vs. dual load

Single vs. Dual Load Conditions (N = 119 after behavioural filter)

False Alarms (**FA**) for EV trials showed a significant decrement across Blocks, $F(5, 575) = 18.73$, $p < .001$, $\eta_p^2 = .14$. This effect did not interact with Stimulation Condition ($F < 1$), Task Type, $F(5, 575) = 1.25$, $p = .284$, $\eta_p^2 = .01$, or an interaction of both ($F < 1$).

The **Response Bias** (**B"**) index of EV trials showed a significant increment across Blocks, $F(4.54, 521.90) = 29.92$, $p < .001$, $\eta_p^2 = .21$, without any significant double or triple interaction with Stimulation Condition or Task Load (all Fs < 1).

Appendix C. Additional results for EV trials: not triple vs triple load

Not triple vs. Triple Load Conditions (N = 240 after behavioural filter)

False Alarms (FA) showed a significant decrement across Blocks, $F(4.65, 1097.98) = 33.01$, $p < .001$, $\eta_p^2 = .12$. This effect did not interact with Stimulation Condition ($F < 1$), or Updated Task Type, $F(4.65, 1097.99) = 1.55$, $p = .175$, $\eta_p^2 = .01$, nor was there a significant interaction of both ($F < 1$).

The **Response Bias (B")** index of EV trials, showed a significant increment across Blocks, $F(4.57, 1078.67) = 44.03$, $p < .001$, $\eta_p^2 = .16$, and the levels of Updated Task Type, $F(1, 236) = 95.28$, $p < .001$, $\eta_p^2 = .29$. This increment did not differ across Stimulation Conditions ($F < 1$). The triple Block × Stimulation Condition × Updated Task Type interaction was also not significant ($F < 1$). However, the Block × Updated Task Type interaction was significant, $F(4.57, 1078.67) = 4.45$, $p = .006$, $\eta_p^2 = .01$. While the overall B" was higher in the Triple ($M = .51$, $SD = .53$), than the Not Triple condition ($M = -.17$, $SD = .56$), the increment with time-on-task, was significantly less steep in the Triple condition compared to the Not-triple condition, $F(1, 119) = 23.36$, $p < .001$, $\eta_p^2 = .16$.

Appendix D. Additional results for AV trials

Mean RT – Only Dual condition.

In the dual task condition, no baseline (1st Block) differences between Stimulation Groups in Mean RT for AV trials were observed, $F < 1$. No significant increment of Mean RT across Blocks was observed, $F(3.41, 197.66) = 1.78$, $p = .145$ ($BF_{01} = 8.24$). The interaction with Stimulation group was also not significant, $F < 1$ ($BF_{01} = 51.59$).

Mean RT – Dual vs. Triple condition.

An ANOVA with Mean RT across Blocks as the dependent variable and Stimulation Group and Task Load (dual vs. triple) as between-subject factors, showed a significant increment of Mean RT across Blocks, $F(3.39, 392.63) = 7.03$, $p < .001$, $\eta_p^2 = .06$. However, interactions with Stimulation Condition, $F(3.39, 392.63) = 1.01$, $p = .397$, $\eta_p^2 = .01$ ($BF_{01} = 63.29$), or Task Load, $F(3.38, 392.63) = 2.16$, $p = .084$, $\eta_p^2 = .02$ ($BF_{01} = 4.68$), were not significant, nor was there a significant triple Block × Stimulation Condition × Task Load interaction $F < 1$ ($BF_{01} = 277.16$).

Appendix E. Analyses for subjective fatigue data

For subjective fatigue (n = 180) we combined data from the present study and a prior study (Hemmerich et al., 2023). As for this data no specific analyses were pre-registered, we carried out the following exploratory analyses. First, an omnibus ANOVA was conducted with Fatigue Type (mental/physical) and Fatigue Moment (baseline/pre-task/post-task) as dependent variables, and Stimulation Group (anodal/sham) and Task Load (single/dual/triple) as between-participant factors. We followed up with post-hoc tests for significant interactions. Then, a post-task–pre-task change score was computed for both fatigue types, which were included in two further ANOVAs with Stimulation Group and Task Load as between-participant factors, and further planned comparisons (testing differences between Stimulation Group for each level of Task Load). Finally, we calculated Pearson correlation coefficients to relate EV and AV performance (Slope of Hits and Slope of SD of RT, respectively) to mental and physical fatigue.

Appendix F. Exploratory analyses on Subjective Fatigue Measures and their relationship to HD-tDCS efficacy

The omnibus ANOVA revealed a main effect of Fatigue Type, $F(1, 173) = 53.51$, $p < .001$, $\eta_p^2 = .24$, as overall mental fatigue ($M = 3.66$, $SD = 2.32$) was higher than physical fatigue ($M = 2.91$, $SD = 1.96$). The significant main effect of Fatigue Moment, $F(1.62, 280.43) = 185.85$, $p < .001$, $\eta_p^2 = .52$, reflected higher overall fatigue levels in the post-task ($M = 4.44$, $SD = 2.45$), compared to baseline ($M = 2.81$, $SD = 1.75$) and pre-task assessments ($M = 2.59$, $SD = 1.77$). Refer to **Appendix G of the Supplementary Material** for a full table of results. The significant Fatigue Type × Fatigue Moment interaction, $F(1.67, 280.43) = 56.37$, $p < .001$, $\eta_p^2 = .25$, showed (via Tukey corrected post-hoc tests) that, without baseline differences between Fatigue Type, [$t(178) = 2.43$, $p = .148$; $M_{mental} = 2.97$, $SD = 1.89$; $M_{physical} = 2.66$, $SD = 1.62$], mental fatigue was incrementally higher than physical fatigue at pre-task [pre task: $t(178) = 3.02$, $p = .003$; $M_{mental} = 2.79$, $SD = 1.88$, $M_{physical} = 2.41$, $SD = 1.65$], and post-task [$t(178) = 12.19$, $p < .001$, $M_{mental} = 5.22$, $SD = 2.35$, $M_{physical} = 3.67$, $SD = 2.33$].

The Fatigue Moment × Stimulation Group × Task Load interaction was marginally significant, $F(3.24, 280.43) = 2.47$, $p = .057$, $\eta_p^2 = .03$. We explored this marginal triple interaction separately for each Fatigue Type, using the post-task–pre-task change, as baseline and pre-task fatigue did not differ significantly (both p's > .321). The ANOVA on **physical fatigue change** revealed a significant Stimulation Group × Task Load interaction, $F(2, 173) = 4.16$, $p = .017$, $\eta_p^2 = .05$. Planned contrasts showed that physical fatigue increments for the dual task load were higher in the sham group ($M = 1.87$, $SD = 1.81$) as compared to the anodal group ($M = 0.87$, $SD = 1.66$), $t(173) = 2.33$, $p = .021$, as shown in **Fig. G.1.A** However, the single task condition showed a marginally significant opposite pattern, $t(173) = -1.70$, $p = .090$, with lower physical fatigue in the sham ($M = 0.86$, $SD = 1.51$) compared to the anodal group ($M = 1.60$, $SD = 1.91$). The triple task condition showed no significant differences between stimulation conditions ($t(173) = -0.23$, $p = .816$). Additionally, the ANOVA on the pre-post task change for **mental fatigue** showed no main effects nor interaction (all F's < 1).

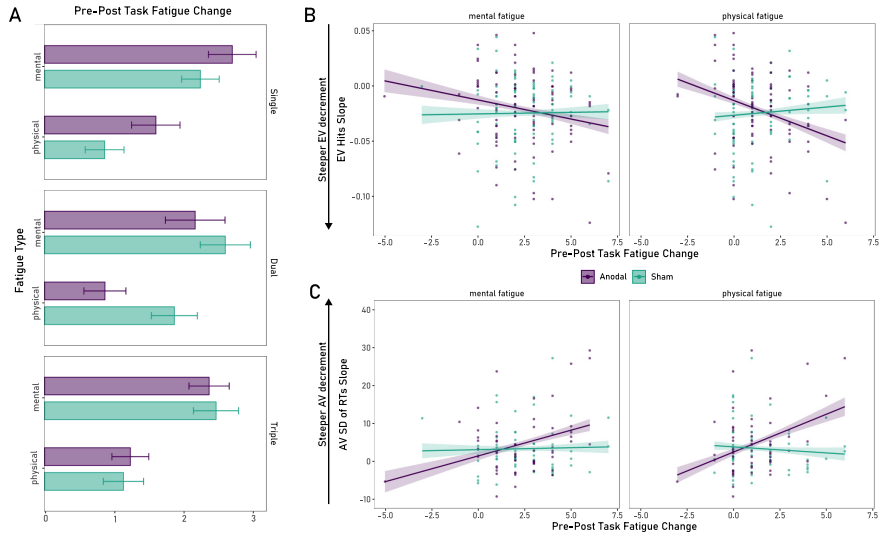


Figure G.1. Subjective Fatigue and its interaction with the EV and AV decrements. **a)** Mental and physical fatigue reported as a function of Task Load and Stimulation Group. **b)** Relationship between the Hits Slope (EV decrement) and the change in pre-post task fatigue for mental (left) and physical (right) fatigue. **c)** Relationship between SD of RT (AV decrement) and the change in pre-post task fatigue. Note that in this last plot: only the dual and triple task conditions are included (as no AV observations are included in the single task).

Note that, whilst prior analyses steps show some differences between load conditions, the tendency of all correlations between fatigue and performance follow the same pattern for each Task Load × Stimulation Condition combination. Although the most prominent results were observed in the dual task condition (see **Appendix H of the Supplementary Material** for further statistical details), which aligns with the previously observed results, given this overarching pattern, results are combined across Task Load levels to achieve a more adequate sample size for correlations. As can be seen in **Fig. G.1.B**, in the anodal groups a mitigated EV decrement (less negative Slope of Hits) was related to lower fatigue ratings [physical fatigue: $r(90) = -.319$, $p = .002$ ($BF_{10} = 13.34$); marginally for mental fatigue: $r(90) = -.199$, $p = .060$ ($BF_{10} = 0.75$)]; whereas in the sham groups fatigue measures were independent of EV performance [physical: $r(89) = .079$, $p = .461$ ($BF_{01} = 5.77$); mental: $r(89) = .015$, $p = .887$ ($BF_{01} = 7.47$)]. This same pattern was also observed for AV performance (see **Fig G.1.C**): a mitigated AV decrement (lower Slope of SD of RT) was related to lower

fatigue ratings in the anodal groups [physical: $r(60) = .386$, $p = .002$ ($BF_{10} = 14.80$); mental: $r(60) = .327$, $p = .011$ ($BF_{10} = 3.87$)], which was not observed in the sham groups [physical: $r(60) = -.073$, $p = .581$ ($BF_{01} = 5.34$); mental: $r(60) = .020$, $p = .879$ ($BF_{01} = 6.14$)].

Appendix G. Subjective fatigue Results

Table E.1. Mean (SD in grey) subjective fatigue by Fatigue Type, Fatigue Moment, Task Load and Stimulation Condition

		Single Task				Dual Task				Triple Task			
Fatigue Moment	**Fatigue Type**	**Sham**		**Anodal**		**Sham**		**Anodal**		**Sham**		**Anodal**	
Baseline	Mental	2.97	1.94	3.30	2.18	3.10	1.92	2.33	1.71	3.20	1.65	2.90	1.88
	Physical	3.14	1.79	3.10	1.65	2.50	1.64	2.17	1.39	2.77	1.61	2.30	1.51
Pre-task	Mental	2.93	1.81	3.03	2.21	3.03	1.94	2.37	1.61	2.47	1.53	2.93	2.15
	Physical	2.86	1.81	2.67	1.83	2.13	1.41	2.07	1.70	2.37	1.30	2.37	1.81
Post-task	Mental	5.17	2.22	5.73	1.87	5.63	2.67	4.53	2.56	4.93	2.26	5.30	2.44
	Physical	3.72	2.69	4.27	1.86	4.00	2.52	2.93	2.27	3.50	2.01	3.60	2.49

Appendix H. Correlations between subjective fatigue and the slope of the EV and AV decrements, presented individually for each experimental condition.

Table F.1. EV Hits Slope and Mental/Physical Fatigue Change as a function of task and stimulation condition

			EV Hits Slope – Mental Fatigue Change			EV Hits Slope – Physical Fatigue Change		
		N	r	*p*	BF_{10}	r	*p*	BF_{10}
Single task	sham	29	-.302	.111	0.78	.092	.637	0.257
	anodal	30	-.187	.322	0.36	-.315	.090	0.895
Dual task	sham	30	.307	.099	0.83	.157	.408	0.315
	anodal	30	-.138	.466	0.29	-.26	.165	0.569
Triple task	sham	30	-.053	.782	0.24	.011	.953	0.227
	anodal	30	-.287	.125	0.70	**-.374***	**.042***	**1.644**

Table E2. AV SD of RT slope and Mental/Physical Fatigue Change as a function of task and stimulation condition

			AV SD of RT Slope – Mental Fatigue Change			AV SD of RT Slope – Physical Fatigue Change		
		N	r	*p*	BF_{10}	r	*p*	BF_{10}
Dual task	sham	30	**-.327**	**.078**	1.00	-.257	.171	0.556
	anodal	30	**.457***	**.011***	**4.91**	**.494****	**.006****	**9.949**
Triple task	sham	30	**.364***	**.048***	**1.47**	.135	.478	0.289
	anodal	30	.159	.402	0.32	.260	.165	0.571

Chapter 8

Cognitive-load dependent effects of HD-tDCS on the executive vigilance decrement: insights from aperiodic EEG activity

The contents of this chapter are *in preparation* as:

Hemmerich, K., Lupiáñez, J., Martín-Arévalo, E., & Cohen Kadosh, R. Cognitive-load dependent effects of HD-tDCS on the executive vigilance decrement: insights from aperiodic EEG activity.

Abstract

This study aimed to investigate the cognitive-load-dependent effects of high-definition transcranial direct current stimulation (HD-tDCS) on the executive vigilance (EV) decrement and its mediation through aperiodic and periodic electroencephalography (EEG) markers. Given the role of vigilance in critical activities and its susceptibility to decline over time, this research explored whether tDCS could counteract such decrements. Participants (N = 180) received anodal HD-tDCS over the right posterior parietal cortex (rPPC) under varying levels of cognitive load during task performance (single, dual, and triple task), with on-task EEG data collected pre- and post-stimulation. Power spectra were parametrized to disentangle periodic (oscillatory) from aperiodic (non-oscillatory, namely aperiodic exponent and offset) components. HD-tDCS led to a decrease in the aperiodic exponent within the 30-45 Hz frequency range, suggesting an increased excitation/inhibition (E/I) balance. This increment of the E/I balance was associated with a mitigated EV decrement in the high-demand task and an exacerbated EV decrement in the low-demand task, illustrating a potential mechanistic explanation of the cognitive-load dependent effect. However, these results were only significant when considering a directional hypothesis, which underlines the need for further research. Baseline EEG markers did not significantly moderate the effect of tDCS on the EV decrement, indicating that individual differences in baseline neural activity might not predict responsiveness to tDCS as previously thought. The findings of the present study highlight the nuanced interplay between brain state, task demands, and tDCS outcomes. Further research is required to elucidate the mechanisms underlying these observations and to refine stimulation protocols for mitigating the executive vigilance decrement.

Introduction

Transcranial direct current stimulation (tDCS) has the potential to modulate cognitive performance by altering cortical excitability (M.-F. Kuo & Nitsche, 2012). This potential enables the exploration of its effectiveness in maintaining or enhancing attentional functioning (Roy et al., 2015), particularly in the case of vigilance. Vigilance—understood as the ability to detect infrequent but critical stimuli (Mackworth, 1948)—degrades as time-on-task progresses, a phenomenon known as vigilance decrement (Warm et al., 2008a). Essential for numerous daily activities such as driving (Wundersitz, 2019), vigilance is also crucial in work environments that require supervision or detection of threats (Barger et al., 2006; Kharoufah et al., 2018; Krüger & Suchan, 2015). Additionally, vigilance is susceptible to deterioration due to atypical brain development (Pievsky & McGrath, 2018) and acquired brain injury (Catroppa & Anderson, 2005). The potential negative consequences of the vigilance decrement in these different scenarios warrant the in-depth study of tDCS protocols that may help to mitigate it. This examination should extend beyond the behavioural effect of brain stimulation and investigate additional markers. For instance, the use of electroencephalography (EEG) data could provide insights into: (i) neurophysiological markers of task performance and its degradation with time-on-task, (ii) tDCS-dependent changes in neurophysiology that can explain the mechanisms of the effects of tDCS on behaviour, and (iii) potential baseline neurophysiological predictors of tDCS outcomes.

Regarding potential applications of tDCS to mitigate the vigilance decrement, recent studies have shown that anodal high-definition tDCS (HD-tDCS) over the right posterior parietal cortex (rPPC) effectively mitigated the vigilance decrement (Hemmerich et al., 2023; Luna et al., 2020). Interestingly, these studies categorized vigilance into an arousal vigilance (AV) component, associated with the sustenance of fast responses in a relatively automatic manner throughout the task, and an executive vigilance (EV) component, which requires a more deliberate distinction between non-targets and targets prior to responding (Luna, Barttfeld, et al., 2021; Luna et al., 2018a). The effect of tDCS on the AV decrement was measured through the increment of reaction times or their variability with time-on-task, whilst its effect on the EV decrement was measured as a

decrement of the hit rate with time-on-task, which was assessed within the same task (ANTI-Vea task, Coll-Martín et al., 2023; Luna et al., 2018). Notably, these studies observed that the mitigatory effect of tDCS was exclusive to the EV decrement (Hemmerich et al., 2023; Luna et al., 2020). However, one point of nuance must be considered in these results, as the mitigatory effect of tDCS on the EV decrement was dependent on the cognitive load of the task (Hemmerich et al., *under review*). Whilst under low demand conditions, the EV decrement was less pronounced and no effect of tDCS on performance was observed, in a condition of high—but not overtaxing—demand, the EV decrement was more pronounced, but mitigated by tDCS (Hemmerich et al., *under review*). This result can be extended with other research observing detrimental effects of anodal tDCS over the rPPC under overtaxing cognitive load conditions (Roe et al., 2016). These results highlight the intricacies of functional targeting in tDCS, which entails, beyond selecting an anatomically relevant stimulation target, appropriately activating relevant neural connections in the target region via an external task, to further enhance tDCS outcomes (Bikson et al., 2013; Miniussi et al., 2013). In this sense, brain states of under- or over-demand are likely to not interact in a beneficial manner with the external administration of tDCS. Concurrent with this idea, anodal tDCS can have different effects during the process of learning a new task. In the initial stages, where excess neural noise may be prevalent, further enhancement of cortical excitability via tDCS showed no behavioural benefit (Dockery et al., 2009). However, once the task was well-learned, anodal tDCS led to enhanced performance (Dockery et al., 2009). While at the behavioural level, these results already offer relevant insight into the importance of the current brain state and/or task conditions on tDCS outcomes, the use of EEG measures offers the opportunity to validate this idea, particularly by using indices of cortical excitability.

Cortical excitability depends on a delicately balanced homeostatic state—referred to as criticality or self-organized criticality—where in response to an input, an adequate level of excitatory and inhibitory connections shape the correct path to emit an output (Ahmad et al., 2022; Krause et al., 2013). An excess of excitation would lead to a disorganized neural state that at its extreme can be associated with epileptic seizures (Žiburkus et al., 2013), whereas an excess of inhibition would hinder the

input from propagating appropriately (Poil et al., 2012). Therefore, this state of criticality has also been referred to as the excitation/inhibition (E/I) balance. While the E/I balance may be inferred more directly from intracranial recordings, aperiodic parameters extracted from EEG recordings offer a valuable non-invasive approach to exploring global activity across neuronal populations to infer cortical state through macroscopic measures (Ahmad et al., 2022; Gao et al., 2017; Weber et al., 2020). A key to this approach is the fact that when EEG data is represented in the frequency domain (i.e., as a power density spectrum), regardless of the presence of specific peaks in a given frequency, the overall data follow a 1/f-like distribution (akin to "pink noise"), where power is higher in lower frequencies, and decreases with higher frequencies (see **Fig. 8.1.A**). The steepness of this $1/f$-like function or slope can vary slightly and referred to as the aperiodic exponent—the x in the $1/f^x$ function (Donoghue et al., 2021b; Donoghue, Haller, et al., 2020), whereas the intercept of the slope, is referred to as the aperiodic offset (see **Fig. 8.1.B**). Whilst aperiodic parameters in EEG data and their notion as a source of information rather than background noise is not new (Gilden, 2001), a recent interest in this data has facilitated the emergence of new methods of extraction of these measures by parametrizing the power density spectrum (Donoghue, Dominguez, et al., 2020; Donoghue, Haller, et al., 2020; Gerster et al., 2022). The "fitting oscillations and one-over-f" (FOOOF) algorithm developed by Donoghue, Haller, et al. (2020), fits a model (green line in **Fig. 8.1.A**) over the original power density spectrum (grey line in **Fig. 8.1.A**) adjusting to the existing peaks, which then allows fitting the aperiodic exponent (purple dashed line in **Fig. 8.1.A**) to the modelled data. This method allows to disentangle aperiodic activity (purple surface in **Fig. 8.1.B**)—not contained by any predominant temporal scale—from periodic activity (green surface in **Fig. 8.1.B**)—constrained to oscillatory activity in a specific narrowband frequency (He, 2014). With this parametrization, one can inspect changes in power, bandwidth, or centre frequency (point of highest power within an oscillatory peak), devoid of the background aperiodic activity, and on the other hand, inspect specific aperiodic metrics, devoid of the influence of narrowband peaks (Donoghue, Dominguez, et al., 2020; Donoghue, Haller, et al., 2020).

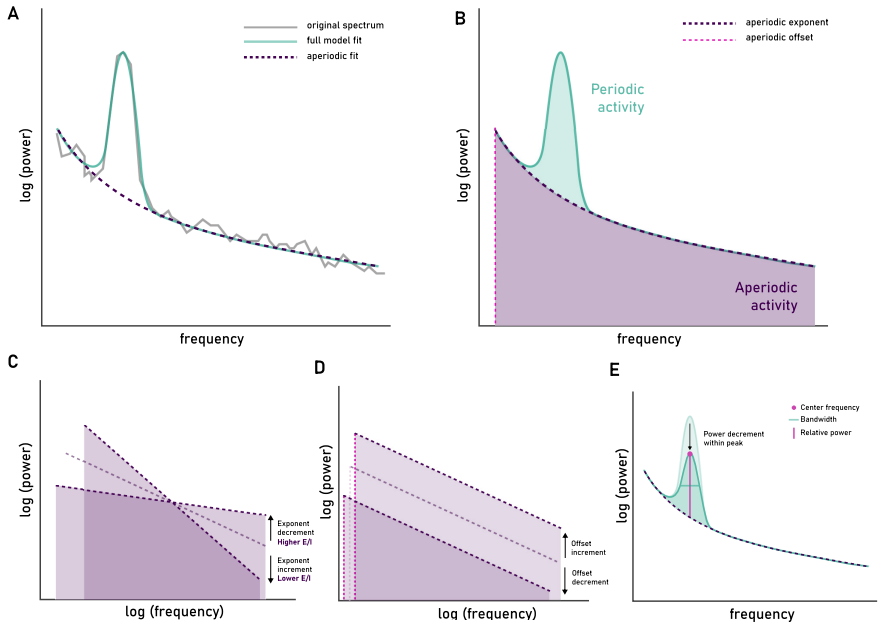


Fig. 8.1. (A) To parametrize the power spectrum, a model (green) is fitted to the real data (grey), obtaining the aperiodic exponent (dark purple dashed line) that is fitted to the modelled data. **(B)** The parametrized power spectrum allows disentangling aperiodic activity (the exponent, *x*, in $1/f^x$, and the offset, *y*-intercept) from periodic activity (peaks identified above the aperiodic exponent, centred around a certain frequency). **(C)** The aperiodic exponent can reflect shifts in the relative power at lower frequencies to power at higher frequencies: an increment of the exponent reflects a steeper spectral slope, and thus a lower E/I balance, whereas a decrement of the exponent, indicates a flatter spectral slope, and thus an increment of the E/I balance. **(D)** The aperiodic offset can reflect broadband shifts of power across the complete frequency spectrum that is being analysed, which might reflect spiking across larger populations of neurons. **(E)** The periodic data comprises the peaks detected above the aperiodic exponent, with each peak identified by its centre frequency, bandwidth, and power.

The idea that the aperiodic exponent can function as a proxy of the E/I balance has been validated with simulations and external manipulations known to alter the ratio of excitation to inhibition. For instance, Gao et al. (2017) developed a computational model demonstrating that the E/I balance can be inferred from the slope of the power density spectrum. Additionally, general anaesthesia administration has been associated with steeper power spectra—indicating a reduced E/I balance —in both animal intracranial (Gao et al., 2017) and human recordings (Lendner et al., 2020). Recent studies have further refined these results, showing that the aperiodic exponent

decreases, producing a flatter power spectrum, from sleep to wakefulness (Lendner et al., 2020), and from rest to performing a task (button-press or visuomotor: He et al., 2010; visuomotor: Podvalny et al., 2015). Furthermore, a recent study has shown that switching between visual and auditory modalities of a detection task was associated with a flattening of spectral slopes (i.e., greater E/I balance) in regions related to the attended modality, especially for visual attention in occipital regions (Waschke et al., 2021). However, Pathania et al. (2021) report opposite findings: a higher exponent (i.e., steeper power spectrum) is observed during a videogame task compared to a rest period, and, importantly, further increased with both time-on-task and task difficulty. Moreover, Ouyang et al. (2020) found that faster processing speed in an object recognition task was predicted by steeper spectral slopes in resting-state EEG (rs-EEG) data recorded prior to the task. Therefore, these findings overall point to the fact that wakefulness and task-engagement are associated with a heightened E/I balance, whereas the reports of a lowered E/I balance may reflect task-specific requirements of increased inhibition.

Additionally, more longitudinal changes in the aperiodic exponent have also been observed during brain maturation (Chini et al., 2022; Rico-Picó et al., 2023) and aging (Voytek et al., 2015). Notably, aperiodic data might prove to be useful in the detection of pathological brain maturation. As a larger aperiodic exponent (i.e., steeper spectral slope) is observed both in infants at risk for developing attention deficit hyperactivity disorder (ADHD) compared to low-risk peers (Karalunas et al., 2022), as well as in medication naïve children with ADHD compared to typically developing peers and peers with ADHD that were medicated (M. M. Robertson et al., 2019). However, these differences seem to revert during development, as a smaller exponent (i.e., flatter spectral slope) is observed in adolescents with ADHD compared to healthy controls (Karalunas et al., 2022; Ostlund et al., 2021) and medicated peers with ADHD (Karalunas et al., 2022). On the other hand, in chronic stroke, a steeper spectral slope is observed (Johnston et al., 2023). These findings highlight that the current brain state evoked by the task, the current state of development of the brain, and potential pathological states must be considered in understanding the aperiodic exponent.

On the other hand, the aperiodic offset can reliably predict neuronal spiking in scalp EEG data, as Manning et al. (2009) have demonstrated. They suggest that some effects, previously attributed to the gamma band, might actually reflect broadband power increases (Manning et al., 2009). The aperiodic offset increases during brain maturation (Rico-Picó et al., 2023), but decreases with older age (Donoghue, Haller, et al., 2020). Compared to the aperiodic exponent, researchers have paid less attention to the aperiodic offset, and its association with specific cognitive processes or on-task/off-task states is less frequent. However, some interesting links have been made with pathological brain maturation. Robertson et al. (2019), for instance, report that medication naïve children with ADHD have a higher aperiodic offset (i.e., higher overall broadband power) compared to healthy controls or medicated peers with ADHD. Furthermore, Turri et al. (2023) observed that adults with dyslexia who have a higher aperiodic offset perform slower when reading a task. While these findings do not directly link to vigilance, they suggest that the aperiodic offset may also hold significant predictive or explanatory power in cognition. Current associations to vigilance have been made more prominently with periodic EEG data (without separating it from aperiodic contributions). Specifically, alpha power has shown to increase with time-on-task (Boksem et al., 2005a; Craig et al., 2012; Hemmerich et al., 2023; Luna et al., 2020), potentially reflecting attenuated information processing (Pershin et al., 2023), or an increased need to inhibit task-irrelevant stimuli (Clayton et al., 2015a). The significance of periodic EEG data in relation to the vigilance decrement emphasizes the need to study it separately from aperiodic EEG data.

The EEG markers mentioned above, namely aperiodic exponent, offset, and alpha power, could provide valuable insights into the mechanisms underlying the effectiveness of tDCS in mitigating the vigilance decrement. To date, no direct evidence of a relationship between aperiodic EEG data predicting tDCS outcomes has been published. However, some promising results have emerged from studies using transcranial random noise stimulation (tRNS). A recent study shows a decrease in the aperiodic exponent in rs-EEG data from pre- to post-stimulation with active compared to sham tRNS (van Bueren et al., 2023). Although this flattening of the spectral slope was not directly associated with behavioural parameters, participants with a low aperiodic exponent during the pre-stimulation rs-

EEG showed improved performance in a mathematical learning task when receiving active tRNS (van Bueren et al., 2023). Sheffield et al. (2020) report similar results of increased tRNS efficacy with a higher aperiodic exponent both before and during the tRNS protocol. Furthermore, an intervention combining tRNS and cognitive training in medication-naïve children with ADHD led to a lower aperiodic exponent after the active intervention when a directional hypothesis based on the prior findings of van Bueren et al. (2023) was adopted (Dakwar-Kawar et al., 2022). The active intervention was associated with decreased ADHD symptom severity scores in a parent-rated questionnaire. However, it was not directly tested whether the effects of tRNS on the aperiodic exponent can be causally attributed to the reduced ADHD symptomatology. In contrast to these findings with the aperiodic exponent, the aperiodic offset has not been explored in much detail regarding brain stimulation outcomes, as it is not reported in most studies.

On the other hand, periodic EEG data has been more directly explored in relation to tDCS applications. Time-on-task induced increments in alpha power are reduced by anodal tDCS over the rPPC (Hemmerich et al., 2023; Luna et al., 2020) and over the left dorsolateral prefrontal cortex (DLPFC, Linnhoff et al., 2021), whereas time-on-task induced increments of gamma power were further increased by anodal tDCS over the rPPC (Hemmerich et al., 2023). Hemmerich et al. (2023) explored the ratio of parietal alpha to frontal gamma power, as an $Alpha_{parietal}/Gamma_{frontal}$ index, to assess changes in EEG from pre- to post-stimulation. A decrement of this index corresponded to a moderate EV decrement, which did not differ across stimulation conditions. Conversely, an increment of this index was linked to a more pronounced EV decrement in the sham condition, which was mitigated in the active stimulation condition. While offering a relevant window into the tDCS-brain-behaviour axis, these results are limited by the fact that narrowband power was extracted without controlling for potential aperiodic contributions (i.e., the results in alpha or gamma power may be confounded by potential shifts in the aperiodic exponent offset). Overall, these findings highlight key areas that require further research: (i) disentangling aperiodic and periodic components in EEG data to inspect their individual contributions and potential interactions along the tDCS-brain-behaviour axis, (ii) exploring how the findings observed with tRNS and the aperiodic exponent translate to transcranial electric stimulation (tES)

techniques, as the effect on cortical excitability may be greater in tRNS as compared to tDCS (Inukai et al., 2016, albeit not consistently, see: Ho et al., 2015); and (iii) investigating the potential causal link between tDCS induced changes in electrophysiology and tDCS induced behavioural changes. This could lead to a better understanding of tES mechanisms and improve the ability to infer causality in tES interventions (Bergmann & Hartwigsen, 2021; Harty et al., 2017).

The present study

The aim of the present study was to further investigate the possible contributions of EEG markers in predicting the efficacy of tDCS in mitigating the EV decrement by parametrising EEG spectra to analyse aperiodic and periodic contributions separately. The rationale, background, and design of this study have been pre-registered on the Open Science Framework (OSF, osf.io/umjc8). However, in the interest of full transparency, it must be noted that this study was designed after data was collected as part of a different study design, and that during analyses some changes were made to the initially pre-registered design.

Therefore, we here detail the pre-registered hypotheses, highlighting the changes and additional hypotheses that were introduced: (i) The first research question set out to explore whether the change from pre- to post-stimulation in the aperiodic exponent would reflect the expected neurophysiological effect of tDCS. We expected to observe increased excitation (indexed as a reduction of the aperiodic exponent) in response to anodal HD-tDCS. Specific hypotheses were made relating to the polarity of the stimulation electrodes. However, data inspection revealed an overall effect of tDCS across electrodes. Therefore, an average across electrodes was used for the following added hypotheses: (a) We expected that the increased excitation resulting from the application of tDCS would explain the beneficial effects of tDCS on the EV decrement observed in the triple task. (b) The change in the aperiodic offset and alpha power were introduced as additional mediators that could potentially explain tDCS outcomes. (ii) A second research question tested whether baseline values of the aperiodic exponent could predict the efficacy of tDCS in mitigating the EV decrement. We expected to replicate prior findings from tRNS studies (Sheffield et al.,

2020; van Bueren et al., 2023) that a higher baseline aperiodic exponent (indicative of a lower E/I balance) would predict greater tDCS efficacy (i.e., a mitigated EV decrement). (a) It was left open in the pre-registration whether/how this effect would be affected by cognitive load. (b) Baseline aperiodic offset and baseline alpha power measures were additionally included as potentially relevant moderators of tDCS effects on the EV decrement. (iii) Furthermore, the pre-registration set out to explore the relationship of these results with subjective reports of fatigue. However, these analyses were not performed as the data showed a non-straightforward relationship with cognitive load and tDCS manipulations (Hemmerich et al., *under review*).

Finally, it was pre-registered that analyses reported in Hemmerich et al. (2023) regarding the pre-post stimulation changes in the $Alpha_{parietal}/Gamma_{frontal}$ index would be repeated with parametrized periodic data and across all cognitive load levels. However, these analyses were not feasible due to insufficient observations of gamma power after parameterization.

Methods

Participants

The total sample was comprised of 180 participants. This data is part of a larger study exploring whether the EV decrement can be mitigated by HD-tDCS applied over the rPPC, and its dependence on cognitive load (Hemmerich et al., 2023, under review). The combination of these two between-participant experimental conditions (Stimulation Condition × Cognitive Load Condition) led to 30 participants per experimental condition. Given that this data was collected as part of prior experiments, sample size calculations are provided in previous reports of this data (see Hemmerich et al., 2023). Participants were selected according to the following inclusion criteria: aged between 18-35 years, right-handed, with normal or corrected to normal vision, no known neurological or psychiatric conditions, and no safety contraindications for receiving tES (Rossi et al., 2009; Rossini et al., 2015) or undergoing magnetic resonance imaging (MRI). All participants gave signed consent and received 10€/hour in exchange for

their participation. This study was embedded in larger research projects (PID2020-114790GB-I00 and B-CTS-132-UGR20) approved by the Ethical Committee of the University of Granada (2442/CEIH/2021 and 1188/CEIH/2020), following ethical standards of the 1964 Declaration of Helsinki (last update: Brazil, 2013).

Behavioural meassures

Participants performed either a single, dual, or triple task in order to manipulate the cognitive load evoked by the task. All three tasks were versions of the ANTI-Vea Task (Coll-Martín et al., 2023; Luna, Barttfeld, et al., 2021). The triple task corresponds to the standard ANTI-Vea task, where 60% of trials consist of a flanker task (ANTI trials), 20% of trials consist of EV trials (where the central arrow between the flankers is vertically displaced and participants need to press an alternate key upon detection), and the remaining 20% of trials are AV trials (where a large red countdown appears in the middle of the screen and participants have to stop it as fast as possible by pressing any key). In the dual and single tasks, the same stimuli were presented, changing only the instructions and coding of correct responses. In the dual task participants had to respond to AV and EV trials, whereas in the single trials, only EV trials had to be responded to (for more details on these task manipulations, see Luna et al., 2022). See **Fig. 8.2.A** for an example of each type of trial.

HD-tDCS procedure

Simultaneous to performing the single, dual, or triple tasks, participants received either anodal or sham HD-tDCS over the right posterior parietal cortex (rPPC). HD-tDCS was applied from the 2nd to the 6th task block (for ~28 minutes), with an intensity of either 1.5 mA (anodal stimulation group, n = 90) or 0 mA (sham group, n = 90) and a ramp-up and ramp-down of 30 seconds. The sham procedure consisted of ramps at the beginning and end of the stimulation period with a stimulation duration of 30 seconds. Stimulation was applied with a Starstim 8 device (Nueroelectrics®, Barcelona), using five of the total eight hybrid NG Pistim Electrodes (with a 12 mm Ag/AgCl sintered pellet, with a circular contact area of 3.14 cm2), set up in a 4 × 1 ring-like array with the central anode over P4, and the four

surrounding cathodes over CP2, CP6, PO4, and PO8 (see **Fig. 8.2.B**), in order to target the rPPC (see **Fig. 8.2.C** for a simulation of the resulting electric field).

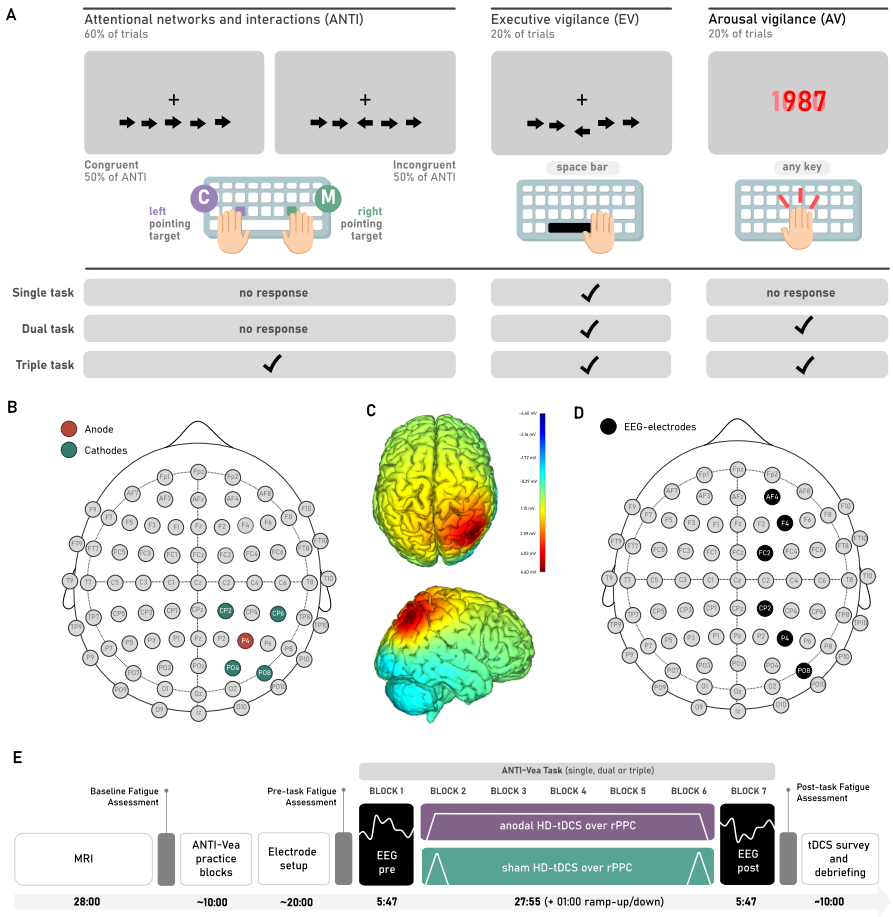


Fig. 8.2. (A) ANTI-Vea task procedure for ANTI, EV, and AV trials, and configuration of single, dual, and triple task versions. **(B)** Electrode setup for HD-tDCS procedure targeting the rPPC. **(C)** Simulated e-field resulting from the HD-tDCS protocol, top and right-view. **(D)** Electrode setup for EEG data collection**. (E)** Procedure of the experimental session.

EEG procedure and pre-processing

EEG was recorded from six electrodes (AF4, F4, FC2, CP2, P4, and PO8), as depicted in **Fig. 8.2.D**. The signal was recorded with a sampling rate of 500 Hz, a bandwidth of 0-125 Hz, and a notch filter at 50 Hz. EEG data was pre-processed with the EEGLAB toolbox v2020.0 and v2021.1 (Delorme & Makeig, 2004) run on MATLAB R2020a (The MathWorks, Inc.). A 210-second epoch was selected from the original recordings (347-second blocks) to avoid any contamination by either the ramp-up or ramp-down. Then high-pass (0.5 Hz) and low-pass (45 Hz) filters were applied. Afterwards, Independent Component Analysis (ICA) was run to identify and reject artifacts (mainly for blinking and eye movements), and visual inspection of the data was used to reject remaining non-periodical artifacts leaving pre-stimulation EEG datasets at an average of 209.30 seconds, and post-stimulation EEG datasets at 208.69 seconds.

For each dataset (pre- and post-stimulation EEG for each of the six EEG electrodes), power density spectra were estimated with Fast Fourier Transform (FFT) using the Welch method, with the *pwelch* function in MATLAB R2020a, with a frequency resolution of 0.5 Hz over 2-second Hann windows with a 1-second overlap. Power spectra were intentionally calculated using a lower frequency resolution, achieving sufficiently smooth spectra in order to avoid fitting peaks to noise (Gerster et al., 2022). The power density spectra were then parametrized into their aperiodic and periodic components using the "fitting oscillations and one-over-f" (FOOOF) v1.1.0 algorithm (Donoghue, Haller, et al., 2020) run in Python v3.9., with the following parameters: peak width limits [1-6], maximum number of peaks [8], minimum peak height [0.2], peak threshold [1.5] and fixed aperiodic mode. These parameters were based on the default settings, adjusted for optimal fit to the data via visual inspection of the model fit and goodness-of-fit measures (GoF): error and R^2.

While it was pre-registered that a frequency range of 1-45 Hz would be used, given the interest in the gamma band (30-45 Hz) explored in a prior study (Hemmerich et al., 2023), the algorithm could not be run over this frequency range, as visual inspection revealed inadequate fits to the original EEG spectrum. A 1-35 Hz frequency range, was the widest range possible that produced an adequate fit between the original data and the model

adjusted by the FOOOF algorithm, supported both by GoF measures (low error and high R^2), as well as visual inspection of each individual power density spectrum after spectral parametrization. See **Appendix A** for an example of the fit and GoF measures for a sample participant at different frequency ranges, and how the fit improves when reducing the upper limit of the frequency range from 45 Hz in 5 Hz intervals. To overcome this limitation, the FOOOF algorithm was run a second time over the 30-45 Hz range (which has been reported as providing reliable outcomes by Lendner et al. (2020). See **Appendix A** for a visual depiction of the fit output over the 30-45 Hz range for an example participant. GoF measures were used to filter out outliers prior to analyses, setting the threshold at 3 standard deviations (SD) error and at 2.5 SD for R^2. Apart from GoF measures, for each dataset (still separate for each participant, recording period, and electrode) we extracted aperiodic parameters: the aperiodic exponent (slope of the exponent fit to the model that was adjusted to each power density spectrum), and the aperiodic offset (intercept at the *y*-axis of the aperiodic exponent slope). This way, the exponent and offset were obtained for each frequency range. For the periodic data (i.e., peaks above the aperiodic exponent), we extracted the centre frequency (CF), power (PW), and bandwidth (BW) for each peak. As can be seen in **Fig. 8.3.A**, in the periodic data extracted from spectra in the 1-35 Hz range, the most common CF from the detected peaks was around 10 Hz, i.e., in the alpha range (7.5-12.5 Hz). To ensure consistency in our analysis, we selected the peak with the highest power value from each electrode and recording period for every participant. This way, a single peak could be used to calculate the post-pre change measures. This approach, as depicted in **Fig. 8.3.B**, reduced the number of peaks uniformly across the alpha band, i.e., preserving the distribution of the original data. Consequently, the total number of observations for alpha power was reduced from 2203 to 1793, retaining 81.39% of the data for further analyses. On the other hand, as can be seen in **Fig. 8.3.C**, in the periodic data extracted from the 30-45 Hz spectra, the most common CF was around 36-39 Hz. However, in the gamma range, many electrodes registered no periodic activity (i.e., peaks above the exponent) at all, yielding an insufficient number of observations for further analyses (all peaks constituted 819, from which 721 remained after leaving only the peak with the highest power for each participant's electrode and recording period).

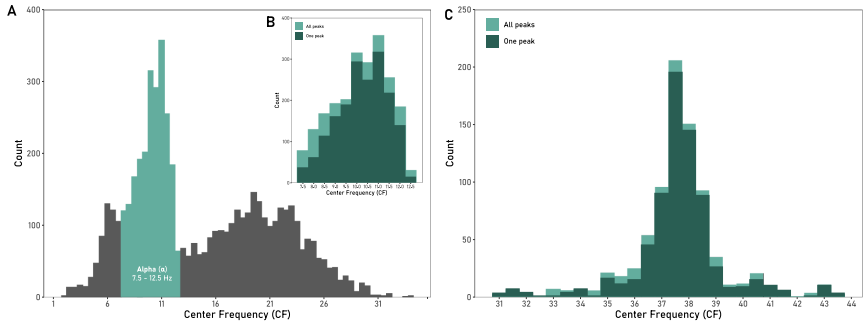


Fig. 8.3. (A) Distribution of Centre Frequencies (CF) at a frequency resolution of 0.5 Hz across all datasets, which depicts at which frequency peaks are most common. **(B)** Distribution of CF within the alpha band (7.5-12.5 Hz) considering all detected peaks (light green) and after reducing the peaks within this narrow-band range to maximum one peak per participant (dark green). **(C)** Distribution of CF within the gamma band (30-45 Hz) considering all detected peaks (light green) and after reducing the peaks within this narrow-band range to maximum one peak per participant (dark green).

Procedure

The experimental session began with an MRI scan (30 min)[1]. After that, participants sat in another dimly lit room to complete the ANTI-Vea task and stimulation. Participants started by reading task instructions (slightly different for the single, dual, and triple task version) and completing several practice blocks. After that, electrodes were set up, and the task was started. During the experimental task, pre-stimulation EEG recordings were completed during the 1st experimental block (5:47 min.). Then anodal or sham HD-tDCS over the rPPC was applied from the 2nd to the 6th experimental block (~28 min.). During the 7th and last experimental block, the post-stimulation EEG measures were recorded (5:47 min.). Subjective assessments of mental and physical fatigue were completed by participants at three points: before the practice block (baseline), before (pre-task), and after the task (post-stimulation). Right after, participants completed a tES Survey, recording their subjective experience during stimulation to test the study's blinding efficacy (Fertonani et al., 2015). The experimental procedure is depicted in **Fig. 8.2.E**.

[1] Note that this data was collected as part of a larger research project and lies beyond the scope of this report.

Data Analysis

Given prior findings of the most prominent results of rPPC HD-tDCS mitigating the EV decrement, and not the AV decrement (Hemmerich et al., 2023; Luna et al., 2020), the former vigilance component was the main measure of interest on a behavioural level in the current study, given that all task-conditions recorded this variable. For the analyses reported in the current study, the EV Slope was calculated, as was done in prior studies (Hemmerich et al., 2023; Luna et al., 2020), taken as an indicator of the EV decrement. The EV Slope was obtained by calculating the regression line for each participant across Blocks 1-6 (i.e., from Baseline up to the halt of active/sham stimulation) for Hits (i.e., correct responses to vertically displaced targets)

For each of the parametrized EEG measures (Aperiodic Exponent and Aperiodic Offset extracted from the 1-35 and 30-45 Hz range, and Alpha Power) we calculated two indices: a Baseline index, filtering out data from the pre-stimulation EEG recordings, and a change-index (Δ), subtracting the pre-stimulation exponent, offset or power value from the post-stimulation value at each electrode for each participant. To test pre-registered hypotheses of electrode-specific effects on the aperiodic indices, each one was introduced as a dependent variable in an ANOVA, with Stimulation Condition and Task Type as between-participant factor and Electrode as a within-participant factor.

Firstly, to test whether the effect of tDCS on the EV decrement was mediated by the pre- to post-stimulation change in either of the aperiodic EEG components (Aperiodic Exponent and Offset from 1-35 and 30-45 Hz range), we introduced the four components as parallel mediators into a model with Stimulation Condition (sham or anodal HD-tDCS over the rPPC) as the predictor, and EV Slope as the outcome measure (see **Fig. 8.4.A-C**). This model corresponds to Hayes' Model 4 (Hayes, 2022), and assessed whether the effect of tDCS on the EV decrement was mediated by the pre- to post change in EEG activity. The model was run separately for each Task Type, as prior behavioural analyses had revealed different direct effects of Stimulation Condition on the EV Slope (Hemmerich et al., *under review*). Furthermore, to address whether the effect of tDCS on the EV decrement was mediated by the pre- to post-stimulation change in Alpha Power, Hayes'

Model 4 was run as specified above, with this single mediator in this case. The model was run separately for periodic data (see **Fig. 8.4.D**) as not all participants showed periodic activity. This ensured running the prior analyses over all available data. For all these analyses, we have used the change score, despite its limitations, as it provides a summarized and simple measure of actual changes in electrophysiology, less dependent on baseline (pre-stimulation) levels.

Secondly, to test whether pre-stimulation EEG measures predict outcomes on EV differently based on the Stimulation Condition, Haye's moderation Model 3 was used. As in the prior models, the direct effect of Stimulation Condition on EV Slope was assessed, testing whether it was moderated by the baseline value of either EEG measure (i.e., pre-stimulation EEG recording), further moderated by Task Type (see **Fig. 8.4.E**). Therefore, these models were run separately with each baseline EEG value as a second moderator.

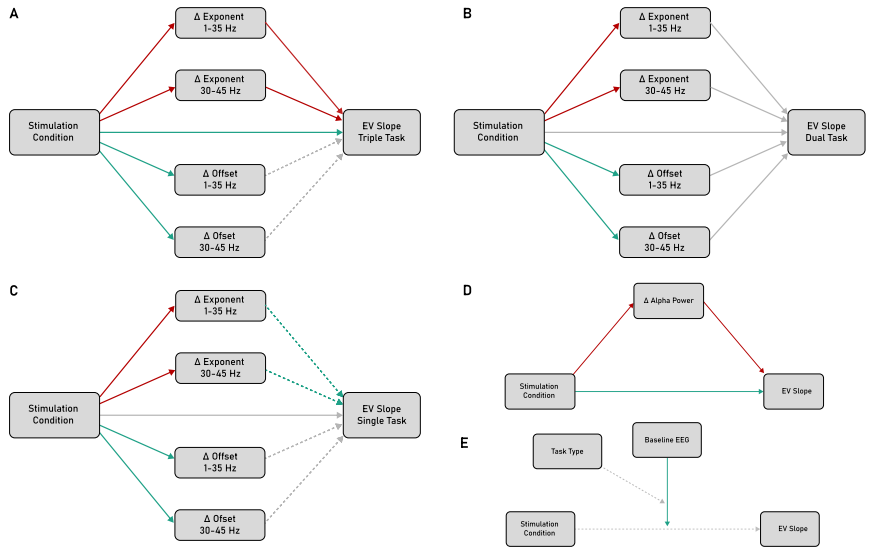


Fig. 8.4. Proposed models for analyses. **(A)** Parallel mediation of aperiodic data in the triple task. **(B)** Parallel mediation of periodic data in the dual task. **(C)** Parallel mediation of periodic data in the single task. **(D)** Simple mediation for Alpha Power. **(E)** Moderation model for baseline EEG data. *Note*. Expected hypotheses (based on pre-registration and updated hypotheses, see *the present study* section) are represented by colours, with negative expected effects in red, positive effects in green, and no expected effect in grey solid lines. Dotted lines represent instances where no fixed hypotheses were established.

All models were run via the PROCESS macro v.4.1.1 (Hayes, 2022) in RStudio. All continuous predictor variables were mean-centred. Percentile bootstrapping was performed using 1000 intervals and a 95% confidence interval (CI). However, for models where specific hypotheses had been made based on prior studies (see expected positive effects in green and negative effects in red in **Fig. 4.**), one-sided or directional hypothesis testing was also performed (using a CI of 90%). A common seed was used to ensure the replicability of analyses. Bootstrapping (robust resampling technique that estimates the sampling distribution of a statistic by resampling with replacement from the observed data), provides advantages in the context of these analyses as it does not rely on assumptions about the shape of the sampling distribution, which makes it particularly useful for small sample sizes or non-normally distributed data (Hayes, 2022), ensuring a more robust analysis. The *modelbt* option was activated in order to obtain bootstrapped CI's for all regression coefficients and not only the direct and indirect effects. Simple paths, direct, indirect, or moderated effects were considered significant when the CI did not include zero. Unstandardized regression coefficients (*b*), standard error (SE), and CI are reported in Tables in the main text and supplementary material.

Results

Outliers and blinding efficacy

From the EEG data, following the above-described criteria for outlier removal (based on GoF measures), 13 datasets were flagged as outliers and discarded (3.67% of total data, i.e., 354 EEG datasets) when the FOOOF algorithm was run over the 1-35 Hz range. No outliers were discarded from the data extracted from the 30-45 Hz range. From behavioural data, one participant was flagged and excluded from further analyses (described in Hemmerich et al., *under review*)

The single-blind procedure was effective (i.e., participants remained naïve as to which stimulation condition they belonged to during the experiment) as described in Hemmerich et al. (2023) for the triple task condition and in Hemmerich et al. (*under review*) for the single and dual task conditions.

Is the effect of anodal HD-tDCS on the EV decrement mediated by aperiodic or periodic measures?

Regarding the direct effect of anodal HD-tDCS on aperiodic indices, we did not find a polarity-specific effect associated with anodal and cathodal electrodes. In fact, the pre-registered ANOVA inspecting either of the aperiodic indices (exponent and offset from the 1-35 and 30-45 Hz range) revealed no significant Stimulation Condition × Task Type × Electrode interaction (all *F*s < 1). Given that the indices did not vary significantly between electrodes in the different experimental conditions (see Figures B1-B4 in Appendix B), the average across electrodes for each index was used for further analyses.

Mediation models with aperiodic data

Results from the parallel mediation models including aperiodic EEG indices extracted from both frequency ranges (1-35 and 30-45 Hz) revealed an interesting pattern for the triple and single task (depicted schematically in **Fig. 8.5.A** and **Fig. 8.6.A**). In the **triple task**, participants in the anodal HD-tDCS group showed a significant decrement of the aperiodic exponent (i.e., increment of E/I) extracted across the 30-45 Hz frequency range, from pre- to post-stimulation (see **Fig. 8.5.B** and **Table 1**). This decrement of the aperiodic exponent was, in turn, negatively associated with EV Slope, reflecting that an increased E/I balance was associated with a mitigated EV decrement (see **Fig. 8.5.C**). This result reflected a significant positive indirect effect of tDCS on EV Slope in the triple task, mediated through Δ Aperiodic Exponent (extracted from 30-45 Hz) when holding all other mediators constant. Anodal HD-tDCS also significantly increased the offset (extracted from the 1-35 Hz range) from pre- to post-stimulation (**Fig. 8.5.D**), which in turn was associated with a more pronounced EV decrement, as reflected by the significant negative indirect effect (see **Fig. 8.5.E** and **Table 8.1**). Furthermore, the *b*-paths for Δ Aperiodic Exponent (1-35 Hz) and Δ Aperiodic Offset (30-45 Hz) were associated with a larger EV decrement (more negative EV Slope), as a pre- to post-stimulation increment of these parameters was associated with a mitigated EV decrement. However, these effects occurred in the absence of an effect of tDCS on these variables (see **Table 8.1**). Lastly, the application of anodal HD-tDCS was associated with a

mitigated EV decrement even when taking into account the indirect effect through the four aperiodic mediators.

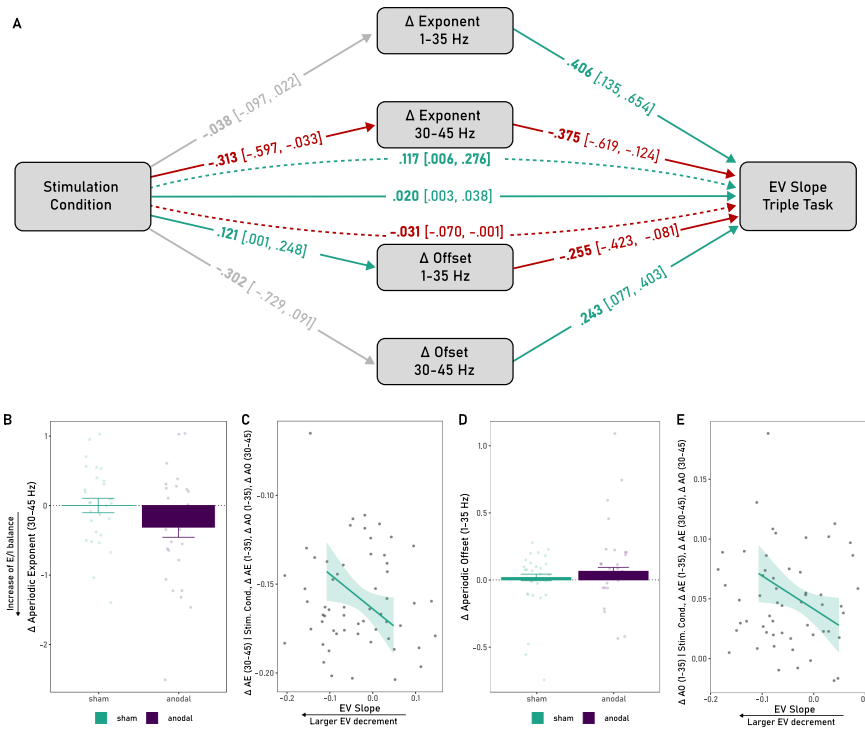


Fig. 8.5. (A) Mediation results for aperiodic EEG data in the **triple task**, where two significant indirect effects (represented with dotted curved lines) were observed. **(B)** A greater negative change in the aperiodic exponent (30-45 Hz) was observed in the group receiving active HD-tDCS; **(C)** which in turn was associated with a mitigated EV decrement. **(D)** Additionally, a significant increment of the aperiodic offset (1-35 Hz) was observed in the group receiving active HD-tDCS compared to the sham group; **(E)** which, in turn, was associated with a more pronounced EV decrement. *Note.* The b-paths represented in panels C and E contain the aperiodic variable of interest, whilst controlling for all remaining variables in the model (Stim. Cond. = Stimulation Condition, AE = aperiodic exponent, AO = aperiodic offset), as calculated in the model.

Table 8.1. Mediation model for aperiodic data in triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a-paths: effect of Stimulation Condition on each mediator						
a_1: Δ Exponent (1-35 Hz)	-0.038	0.037	-0.097	0.022	-0.110	0.034
a_2: Δ Exponent (30-45 Hz)	**-0.313**	**0.171**	**-0.597**	**-0.033**	-0.639	0.015
a_3: Δ Offset (1-35 Hz)	**0.121**	**0.075**	**0.001**	**0.248**	-0.014	0.267
a_4: Δ Offset (30-45 Hz)	-0.302	0.250	-0.729	0.091	-0.783	0.195
b-paths: effect of each mediator on EV Slope						
b_1: Δ Exponent (1-35 Hz)	**0.406**	**0.161**	**0.135**	**0.654**	**0.082**	**0.720**
b_2: Δ Exponent (30-45 Hz)	**-0.375**	**0.151**	**-0.619**	**-0.124**	**-0.672**	**-0.079**
b_3: Δ Offset (1-35 Hz)	**-0.255**	**0.105**	**-0.423**	**-0.081**	**-0.459**	**-0.048**
b_4: Δ Offset (30-45 Hz)	**0.243**	**0.099**	**0.077**	**0.403**	**0.049**	**0.440**
Total and indirect effects (Stimulation Condition > EV Slope)						
c (Total Effect)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c' (Direct effect)	**0.020**	**0.011**	**0.003**	**0.038**	-0.001	0.042
Indirect effects (Stimulation Condition > Mediator > EV Slope)						
a_1b_1: tDCS → Δ Exponent (1-35 Hz)	-0.015	0.017	-0.046	0.008	-0.056	0.013
a_2b_2: tDCS → Δ Exponent (30-45 Hz)	**0.117**	**0.086**	**0.006**	**0.276**	-0.011	0.312
a_2b_3: tDCS → Δ Offset (1-35 Hz)	**-0.031**	**0.021**	**-0.070**	**-0.001**	-0.076	0.003
a_4b_4: tDCS → Δ Offset (30-45 Hz)	-0.074	0.075	-0.216	0.024	-0.254	0.046

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

In the parallel mediation model for the **single task** (shown schematically in **Fig. 8.6.A** and reported in detail in **Table 8.2**), a similar excitatory effect of anodal HD-tDCS was observed, as the Δ Aperiodic Exponent (30-45 Hz) significantly decreased from pre- to post-stimulation (see **Fig. 8.6.B**). However, contrary to what was observed for the triple task, in the single

task, this decrement of the aperiodic exponent was further associated with a steeper EV decrement (see **Fig. 8.6.C**). This effect was reflected in a significant negative indirect effect of tDCS on the EV Slope, mediated through the Δ Aperiodic Exponent (extracted from 30-45 Hz) when holding all other mediators constant. Notably, in the single task a positive indirect effect of tDCS on the EV Slope was observed through the Δ Aperiodic Offset (extracted from 1-35 Hz), as here, anodal HD-tDCS induced an increment of the offset, which in turn was associated with a more pronounced EV decrement (**Fig. 8.6.D** and **8.6.E**). Additionally, significant negative *b*-paths were observed for Δ Aperiodic Exponent (1-35 Hz) and Δ Aperiodic Offset (30-45 Hz), as an increment in both variables was associated with a steeper EV decrement, which was however not attributed to any effect of tDCS on these indices.

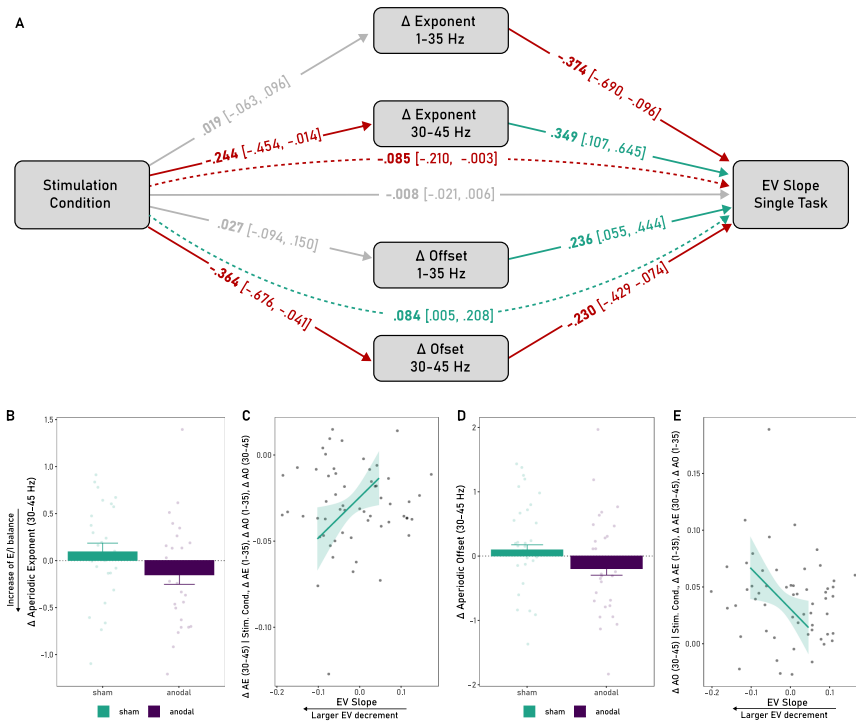


Fig. 8.6. (A) Mediation results for aperiodic EEG data in the **single task**, where two significant indirect effects (represented with dotted curved lines) were observed. **(B)** A greater negative change in the aperiodic exponent (30-45 Hz) was observed in the group receiving active HD-tDCS; **(C)** which in turn was associated with a more pronounced EV decrement. **(D)** Additionally, a significant increment of the aperiodic offset (30-45 Hz) was observed in the group receiving active HD-tDCS compared to the sham

group; **(E)** which, in turn, was associated with a mitigated EV decrement. *Note:* The b-paths represented in panels C and E contain the aperiodic variable of interest, whilst controlling for all remaining variables in the model (Stim. Cond. = Stimulation Condition, AE = aperiodic exponent, AO = aperiodic offset), as calculated in the model.

In contrast to these results, in the dual task, no paths were significant for the parallel mediation model including all aperiodic variables (see **Table C1** in **Appendix C**, for full results).

Table 8.2. Mediation model for aperiodic data in single task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a-paths: effect of Stimulation Condition on each mediator						
a_1: Δ Exponent (1-35 Hz)	0.019	0.049	-0.063	0.096	-0.080	0.117
a_2: Δ Exponent (30-45 Hz)	**-0.244**	**0.135**	**-0.454**	**-0.014**	-0.508	0.010
a_3: Δ Offset (1-35 Hz)	0.027	0.073	-0.094	0.150	-0.113	0.165
a_4: Δ Offset (30-45 Hz)	**-0.364**	**0.196**	**-0.676**	**-0.041**	-0.742	0.006
b-paths: effect of each mediator on EV Slope						
b_1: Δ Exponent (1-35 Hz)	**-0.374**	**0.179**	**-0.690**	**-0.096**	**-0.750**	**-0.043**
b_2: Δ Exponent (30-45 Hz)	**0.349**	**0.161**	**0.107**	**0.645**	**0.061**	**0.713**
b_3: Δ Offset (1-35 Hz)	**0.236**	**0.118**	**0.055**	**0.444**	**0.017**	**0.493**
b_4: Δ Offset (30-45 Hz)	**-0.230**	**0.107**	**-0.429**	**-0.074**	**-0.473**	**-0.044**
Total and indirect effects (Stimulation Condition > EV Slope)						
c (Total Effect)	-0.010	0.008	-0.023	0.003	-0.025	0.006
c' (Direct effect)	-0.008	0.008	-0.021	0.006	-0.024	0.008
Indirect effects (Stimulation Condition > Mediator > EV Slope)						
a_1b_1: tDCS → Δ Exponent (1-35 Hz)	-0.007	0.021	-0.045	0.021	-0.055	0.030
a_2b_2: tDCS → Δ Exponent (30-45 Hz)	**-0.085**	**0.064**	**-0.210**	**-0.003**	-0.242	0.004
a_2b_3: tDCS → Δ Offset (1-35 Hz)	0.007	0.020	-0.022	0.040	-0.031	0.048
a_4b_4: tDCS → Δ Offset (30-45 Hz)	**0.084**	**0.062**	**0.005**	**0.208**	-0.002	0.236

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

In contrast to what is observed in the parallel mediation models, no significant mediation (indirect effects) is observed when each aperiodic variable is introduced separately into single mediation models testing the direct and indirect effects of Stimulation Condition on EV Slope, as summarized in **Fig. 8.7** (see **Tables D1-D8** in **Appendix D** for the full result tables for each model). While the a-paths that were significant in the parallel models remain significant in these individual models, the effects observed in the b-paths, and, as a consequence, the indirect effects, are not observed. This contradictory finding seems to suggest that the relationship between each aperiodic variable and behavioural results only emerges when controlling for the remaining aperiodic variables.

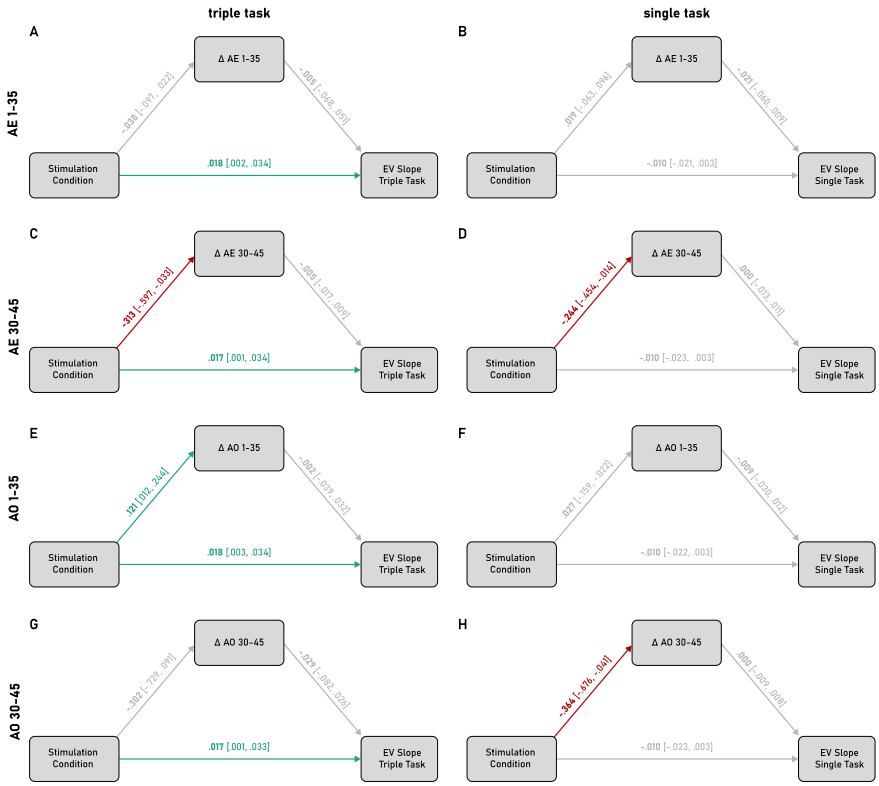


Fig. 7. Single mediation models for the triple (left column) and single (right column), for each aperiodic index introduced as a mediator separately.

Mediation model with periodic data

A parallel mediation model including both Δ Alpha Power and Δ Gamma Power could not be run as too few observations remained in Δ Gamma Power. The mediation model with Δ Alpha Power as a mediator in the triple task (see **Fig. 8.8.A**), revealed a significant negative effect of the Stimulation Condition on Δ Alpha Power. As shown in **Fig. 8.8.B**, the increment of alpha power was significantly reduced in the group receiving anodal HD-tDCS compared to the sham group in the triple task condition, thus replicating previous results exploring alpha power without parametrizing the power spectra (Hemmerich et al., 2023; Luna et al., 2020). The direct effect of Stimulation Condition on EV Slope remained significant (see **Table 8.3**), however, neither the b-path (effect of Δ Alpha Power on EV Slope) nor a mediated effect (indirect effect of Stimulation Condition on EV Slope via the Δ Alpha Power) was observed.

Similarly, in the single and dual tasks alpha power also increased from the pre- to the post-stimulation recording. However as can be seen in **Fig. 8.B**, this was not affected by Stimulation Condition (i.e., the *a*-paths were non-significant). Furthermore, for the single and dual tasks, the b-path, direct or indirect effects were also not significant, when introducing Δ Alpha Power as a mediator in the relationship between Stimulation Condition and EV Slope (for detailed results see **Table E1** and **E2** in **Appendix E** of the **Supplementary Material**).

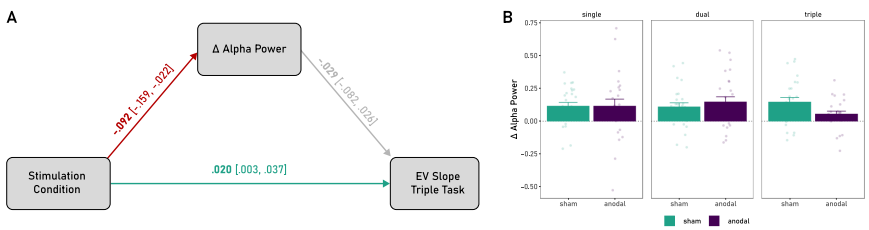


Fig. 8.8. (A) Mediation results for periodic EEG data (alpha power) in the triple task condition. **(B)** A significant *a*-path was observed in the triple task, as the alpha power increment from pre- to post-stimulation was significantly decreased in the triple task condition.

Table 8.3. Mediation model for periodic data in the triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond. > Δ Alpha Power	**-0.092**	**0.043**	**-0.159**	**-0.022**	**-0.175**	**-0.012**
b: Δ Alpha Power > EV Slope	-0.029	0.032	-0.082	0.026	-0.094	0.037
c: Total Effect (Stim. Cond. > EV Slope)	**0.023**	**0.010**	**0.006**	**0.039**	**0.003**	**0.042**
c': Direct effect (Stim. Cond. > EV Slope)	**0.020**	**0.010**	**0.003**	**0.037**	-0.001	0.040
ab: Stim. Cond. → Δ Alpha Power > EV Slope	0.003	0.003	-0.002	0.009	-0.004	0.010

Note. N = 50. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Do baseline EEG parameters determine tDCS outcomes?

Moderation models with aperiodic data

Models including the direct effect of Stimulation Condition on EV, and both Task Type and baseline values of either aperiodic index (exponent and offset from the 1-35 and 30-45 Hz range), revealed no significant moderated moderation (i.e., interaction of Stimulation Condition, Task Type, and baseline; see full results in **tables 8.4-7**). Thus, the effect of tDCS on the EV decrement does not seem to be moderated by baseline EEG aperiodic data.

Table 8.4. Moderation model for periodic data for Baseline Aperiodic Exponent (1-35 Hz)

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
Outcome variable: EV Slope						
Stimulation Condition	-0.007	0.008	-0.021	0.006	-0.023	0.008
Baseline Exponent	0.039	0.039	-0.035	0.093	-0.044	0.109
Stimulation Condition × Baseline Exponent	-0.012	0.056	-0.087	0.098	-0.103	0.118
Dual Task	-0.002	0.007	-0.014	0.009	-0.017	0.012
Triple Task	**-0.020**	**0.009**	**-0.035**	**-0.006**	**-0.038**	**-0.002**
Stimulation Condition × Dual Task	0.011	0.011	-0.009	0.028	-0.013	0.032
Stimulation Condition × Triple Task	**0.025**	**0.013**	**0.004**	**0.047**	**0.000**	**0.051**

Table 8.4 (continued)

Baseline Exponent × Dual Task	-0.050	0.061	-0.163	0.037	-0.192	0.055
Baseline Exponent × Triple Task	-0.077	0.051	-0.151	0.014	-0.165	0.030
Stimulation Condition × Baseline Exponent × Dual Task	-0.002	0.080	-0.132	0.133	-0.159	0.160
Stimulation Condition × Baseline Exponent × Triple Task	-0.004	0.081	-0.153	0.117	-0.180	0.138

Note. N = 175. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table 8.5. Moderation model for periodic data for Baseline Aperiodic Exponent (30-45 Hz)

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
Outcome variable: EV Slope						
Stimulation Condition	-0.011	0.008	-0.023	0.003	-0.026	0.006
Baseline Exponent	**0.011**	**0.005**	**0.000**	**0.017**	-0.003	0.020
Stimulation Condition × Baseline Exponent	-0.004	0.010	-0.019	0.013	-0.023	0.016
Dual Task	-0.005	0.006	-0.015	0.006	-0.018	0.008
Triple Task	**-0.022**	**0.008**	**-0.035**	**-0.007**	**-0.037**	**-0.003**
Stimulation Condition × Dual Task	0.013	0.011	-0.007	0.030	-0.010	0.035
Stimulation Condition × Triple Task	**0.028**	**0.013**	**0.007**	**0.049**	0.004	0.053
Baseline Exponent × Dual Task	**-0.023**	**0.011**	**-0.041**	**-0.006**	**-0.046**	**-0.002**
Baseline Exponent × Triple Task	**-0.023**	**0.011**	**-0.040**	**-0.005**	**-0.046**	**-0.001**
Stimulation Condition × Baseline Exponent × Dual Task	0.021	0.014	-0.001	0.046	-0.008	0.051
Stimulation Condition × Baseline Exponent × Triple Task	0.011	0.017	-0.018	0.036	-0.024	0.042

Note. N = 175. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table 8.6. Moderation model for periodic data for Baseline Aperiodic Offset (1-35 Hz)

	b	SE	95% CI	
			LLCI	ULCI
Outcome variable: EV Slope				
Stimulation Condition	-0.008	0.008	-0.024	0.008
Baseline Offset	0.015	0.020	-0.017	0.069
Stimulation Condition × Baseline Offset	0.004	0.034	-0.059	0.084
Dual Task	-0.004	0.007	-0.019	0.009
Triple Task	**-0.020**	**0.009**	**-0.037**	**-0.002**
Stimulation Condition × Dual Task	0.013	0.011	-0.012	0.034
Stimulation Condition × Triple Task	**0.025**	**0.013**	**0.001**	**0.050**
Baseline Offset × Dual Task	0.017	0.030	-0.055	0.069
Baseline Offset × Triple Task	-0.038	0.034	-0.108	0.028
Stimulation Condition × Baseline Offset × Dual Task	-0.051	0.047	-0.147	0.038
Stimulation Condition × Baseline Offset × Triple Task	-0.020	0.052	-0.131	0.077

Note. N = 175. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table 8.7. Moderation model for periodic data for Baseline Aperiodic Offset (30-45 Hz)

	b	SE	95% CI	
			LLCI	ULCI
Outcome variable: EV Slope				
Stimulation Condition	-0.011	0.008	-0.027	0.006
Baseline Offset	0.007	0.004	-0.003	0.012
Stimulation Condition × Baseline Offset	-0.002	0.006	-0.014	0.011
Dual Task	-0.005	0.007	-0.018	0.009
Triple Task	**-0.022**	**0.009**	**-0.037**	**-0.002**
Stimulation Condition × Dual Task	0.013	0.011	-0.010	0.036
Stimulation Condition × Triple Task	**0.028**	**0.013**	**0.003**	**0.053**
Baseline Offset × Dual Task	-0.014	0.007	-0.028	0.001

Table 8.7 (continued)

Baseline Offset × Triple Task	-0.013	0.007	-0.027	0.001
Stimulation Condition × Baseline Offset × Dual Task	0.013	0.009	-0.005	0.031
Stimulation Condition × Baseline Offset × Triple Task	0.005	0.011	-0.017	0.026

Note. N = 175. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Moderation model with periodic data

Aperiodic baseline data did also not show a significantly moderated moderation (i.e., interaction of Stimulation Condition, Task Type, and Baseline Alpha Power; see **Table 8.8**). The results suggest that the effect of tDCS on the EV decrement does not seem to be moderated by baseline EEG periodic data (using alpha power as a representative of periodic data).

Table 8.8. Moderation model for periodic data for Baseline Alpha Power

	b	SE	95% CI	
			LLCI	ULCI
Outcome variable: EV Slope				
Stimulation Condition	-0.008	0.009	-0.026	0.007
Baseline Alpha Power	0.019	0.020	-0.030	0.049
Stimulation Condition × Baseline Alpha Power	-0.033	0.031	-0.092	0.034
Dual Task	-0.006	0.007	-0.021	0.006
Triple Task	-0.016	0.009	-0.034	0.000
Stimulation Condition × Dual Task	0.015	0.012	-0.007	0.040
Stimulation Condition × Triple Task	0.026	0.014	-0.001	0.055
Baseline Alpha Power × Dual Task	0.035	0.024	-0.005	0.090
Baseline Alpha Power × Triple Task	-0.029	0.042	-0.113	0.046
Stimulation Condition × Baseline Alpha Power × Dual Task	-0.028	0.041	-0.114	0.055
Stimulation Condition × Baseline Alpha Power × Triple Task	0.053	0.058	-0.065	0.171

Note. N = 161. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Discussion

The aim of this study was to explore the potential role of aperiodic and periodic EEG markers that explain the efficacy of tDCS in mitigating the decrement of EV. A recent spike in the interest in aperiodic EEG activity has shown its relevant contribution to task-induced changes in the neural balance between excitation and inhibition (E/I balance, Gao et al., 2017; Lendner et al., 2020), serving as a potential marker to better understand the effects of interventions with tES (Krause et al., 2013; Sheffield et al., 2020; van Bueren et al., 2023). This approach has not been explored in relation to the effects of tDCS on the vigilance decrement. Contrary to the expected electrode-specific effect of HD-tDCS on the aperiodic exponent, an overall reduction in the aperiodic exponent (indicating an increased E/I balance) in the 30-45 Hz range was observed. This decrement of the aperiodic exponent in the 30-45 Hz range, mediated the effect of HD-tDCS on the EV decrement with opposite effects in the triple and single task conditions, explaining respective beneficial and detrimental effects, as schematically summarized in **Fig. 8.9**. However, in each task condition, an opposite mediation effect was observed with the aperiodic offset, which potentially obscures the direct effect. No mediation was observed for the pre-post change in alpha power as a representation of periodic data. Lastly, contrary to what was hypothesized, baseline values in either aperiodic or periodic data did not moderate the effect of the HD-tDCS application over the rPPC on the EV decrement.

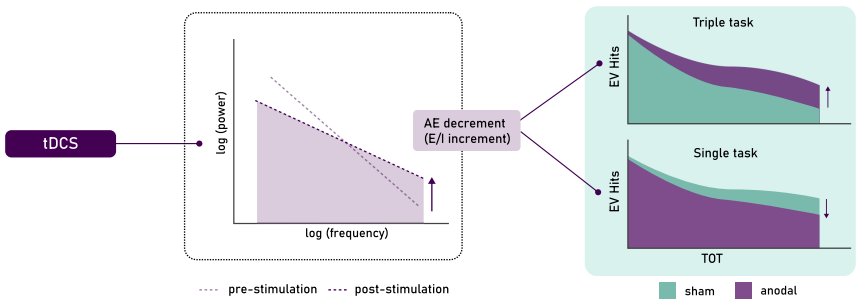


Fig. 8.9. Summary of results of the effect of tDCS on the EV decrement in triple and single task conditions mediated through the decrement of the aperiodic exponent, which reflects an increase of E/I. *Note:* AE = aperiodic exponent.

Regarding the direct effect of the application of the HD-tDCS protocol on aperiodic EEG measures, we had established electrode-specific hypotheses (based on the polarity of the electrodes conforming the HD-tDCS ring), expecting a decrement of the aperiodic exponent to reflect an increase of E/I (flattening of the spectral slope) under the anode and the opposite effect under the cathodes. However, no such specificity was observed in pre-post stimulation changes. Instead, we observed that the overall aperiodic exponent extracted from a higher frequency range (30-45 Hz) more accurately reflected the increment of E/I (flattening of the spectral slope) compared to the exponent extracted from a lower range (1-35 Hz). The non-specific effect as a function of electrode might be explained by the use of an HD-tDCS protocol in the current study. The use of the concentric 4 × 1 stimulation ring has actually shown to produce a skewed e-field in favour of the polarity of the central electrode (Alam et al., 2016), peaking under the central electrode and dissipating towards the surrounding return electrodes (Edwards et al., 2013).

On the other hand, the fact that the aperiodic exponent extracted from the higher frequency range better captured the expected effect on the E/I balance may be due to broadband power measures from higher frequency ranges being less obscured by oscillatory activity in lower frequencies (He, 2014). Notably, a study that served as a relevant foundation for interpreting the aperiodic exponent as an indirect measure of the E/I balance used a relatively similar frequency range (30-50 Hz) to the higher range in the present study (Gao et al., 2017). Furthermore, Lendner et al. (2020) explored different frequency ranges (ranging across 1-20 Hz, 1-40 Hz, and 30-45 Hz fits), and concluded that the aperiodic exponent extracted from the 30-45 Hz range better predicted different states of arousal across wakefulness, anaesthesia, and different sleep stages. Similarly, Pei et al. (2023), compared different aperiodic fits (1-25 and 26-90 Hz) and power measures from canonical frequency bands, and observed that the aperiodic exponent and offset extracted from the higher frequency range showed the greatest association with cognitive load dependent variations in performance.

While the exploration of the direct effect of tDCS on the aperiodic parameters is of great interest, as to further understand the intricate neurophysiological effects of tDCS, the design of the present study is not

optimal for this purpose. Given that the EEG data analysed in the present study was collected during the first and last minutes of the behavioural task, the neurophysiological and task-related effects on EEG cannot be measured independently and are likely to show an interaction. This is further supported by the fact that, whilst the same tDCS protocol induced the same effect in the triple and single tasks aperiodic exponent extracted from the 30-45 Hz range, it did not produce a significant effect in the dual task condition. Therefore, a look into the overall relationship across the tDCS-EEG-behaviour axis might be more appropriate.

The mediation analyses conducted to explore whether any of the aperiodic indices could provide a potential mechanistic explanation of the effects of tDCS on behaviour revealed mixed results. When pitting the different aperiodic indices against each other in a parallel mediation model, to see which one (if any) revealed a potential indirect effect, we observed an opposite pattern between the triple and the single task conditions. As discussed in the prior points, for the triple and single task a significant negative a-path was observed for the aperiodic exponent extracted from the 30-45 Hz range (i.e., a decrement of the aperiodic exponent from pre- to post-task with active tDCS). However, interestingly, this neurophysiological effect had the opposite effect on behaviour in each task condition. In the triple task condition, the decrement of the aperiodic exponent predicted a mitigated EV decrement (i.e., higher E/I was associated with better performance). On the other hand, in the single task condition, the same decrement of the aperiodic exponent predicted a more pronounced EV decrement (i.e., higher E/I associated with worse performance). These results are important as they are supporting a previous theoretical framework that posits that tES needs to drive an optimal change in E/I (Krause et al., 2013), but highlighting that this needs to be tailored to the task at hand.

These results highlight the sensitivity of the effects of tDCS in interaction with task-evoked patterns of brain activity. The triple task, while demanding, is not considered to be overtaxing, and therefore, increasing excitation in task-relevant areas (**Fig. 8.10.A**), may facilitate performance and mitigate the drops in detection accuracy with time-on-task. The single task condition, on the other hand, whilst presenting overall better and less

steep performance decrements with time-on-task, may produce a more mixed pattern of brain activity. If we assume, as proposed by Thomson et al.'s (2015) resource-control account, that available resources are constant, the single task would lead to task-relevant processes to be working in parallel with other non-related operations (i.e., mind-wandering). In that case, further exciting this pattern of activity with tDCS, may further promote task-unrelated thoughts which would lead to the observed detrimental behavioural effects (**Fig. 8.10.B**).

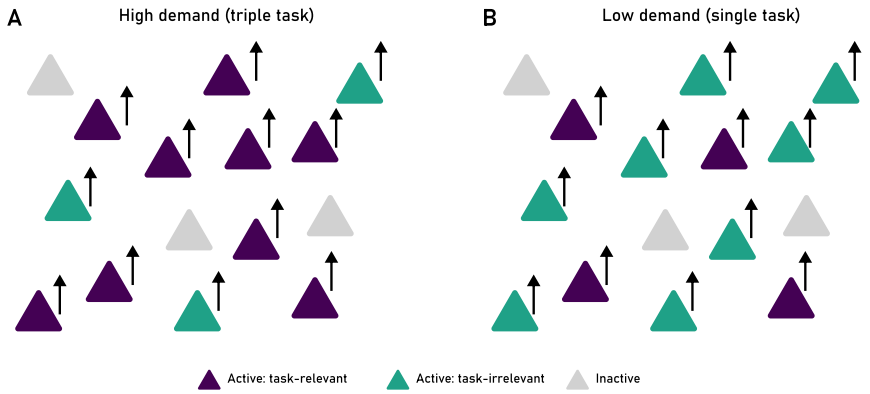


Fig. 8.10. Putative task-dependent effect of tDCS on EV performance mediated by the aperiodic exponent: near-threshold neurons/connections are those that are activated by task-relevant (purple) or task-irrelevant (green) processes, which are more likely to be further excited by the tDCS-induced increment of excitability, compared to inactive neurons (grey). **(A)** In the triple task, a higher cognitive demand engages a larger number of task-relevant neurons/connections, which when further excited by tDCS leads to improved performance. **(B)** The single task can be achieved with a more efficient processing: potentially requiring less active task-relevant neurons/connections for producing adequate performance. Therefore, task-irrelevant areas might be more active, engaging in other non-related activities (such as mind-wandering). If this pattern of activity is further excited by tDCS, the further facilitation of task-irrelevant processes might lead to a detrimental effect on performance.

Such non-linear state-dependent effects of NIBS have been attributed to stochastic resonance, suggesting that processes operating at threshold levels may benefit from an optimal level of noise, compared to conditions of absent or excessive noise (Abrahamyan et al., 2011; Miniussi et al., 2013). While this conceptualization of certain processes benefiting from the input of a certain level of noise to improve information processing has been more popular in considering the effects of transcranial magnetic stimulation, recent evidence points towards its potential application to also understand behavioural outcomes of tDCS (Benwell et al., 2015; Bestmann et al., 2015).

This can be further tied in with the conceptualization of the aperiodic exponent as a measure of noise in underlying neural networks (He et al., 2010; Voytek & Knight, 2015), where a flattening of the spectral slope is an approximation towards the function of white noise. The input of noise via tDCS (i.e., flattening of the spectral slope) observed in the present study, may, in that case, induce an optimal signal-to-noise ratio in the triple task condition based on the underlying activation induced by the task, whereas the addition of noise in the single task interacts in a detrimental manner with ongoing brain activity.

A further interesting finding obtained from the parallel mediation model is that the aperiodic offset shows indirect effects that are, again opposite for the triple and single task, and additionally opposite to the indirect effect observed for the aperiodic exponent within each task type. In the triple task, a negative indirect effect is observed, as active tDCS was associated with an increment of the pre-post stimulation aperiodic offset (extracted from the 1-35 Hz range); which in turn was associated with a steeper EV decrement. This result suggests that in parallel to the beneficial effect of tDCS on performance explained through the aperiodic exponent extracted from the higher frequency range, a detrimental effect is taking place, explained through the increment of the aperiodic offset from the lower frequency range with active tDCS. Given that overall, the active tDCS protocol produces a mitigated EV decrement, the effect on the aperiodic exponent might be stronger, but its efficacy may be reduced due to the additional effects on the aperiodic offset. For the single task, on the contrary, active tDCS was associated with a decrement of the pre-post stimulation aperiodic offset (extracted from the 30-45 Hz range); which in turn was associated with a mitigated EV decrement. Thus, here the contrary opposing indirect effects through aperiodic parameters seem to be more balanced, leading to the slightly detrimental direct effect of tDCS on behaviour that does not reach significance.

The above-outlined interpretation of the parallel mediation results provides a promising explanation for how tDCS effects vary with different tasks and underscores the importance of choosing tasks with the right level of cognitive demand to pair with online tDCS. However, it is important to also consider some limitations to the reliability of these findings, namely,

that results did not replicate when introducing each aperiodic variable separately into a single mediation model. Whilst the a-paths remained significant as to what was observed in the parallel mediation models, the effects of each aperiodic variable on the EV slope, and with it, also the mediated effects of tDCS via these variables, disappeared. Two potential explanations emerge for this discrepancy between the two analysis approaches. First, the way the relationship between the different aperiodic parameters and the behavioural outcomes, as well as the mediated effects, are explored in the parallel mediation model, controls all other variables in each step. Therefore, the presence of potential conflicting effects (as suggested by the opposite effects in the aperiodic exponent and offset) may obscure the role of each variable when investigating its mediating role individually, leading to a suppression effect (MacKinnon et al., 2000). A second alternative explanation to the opposite findings between the parallel and single mediation models is the potential overlap between the different mediators, as the frequency fits are slightly overlapped (over a 5 Hz range) and the exponent and offset may share a certain dependency that could affect the model output. The parallel mediation model operates under the assumption that the mediators do not causally influence each other, whilst they are allowed to correlate (Hayes, 2022).

Contrary to what was observed for aperiodic data, no significant mediation was observed for the pre-post stimulation change in alpha power. Notably, a significantly reduced alpha power increment with time-on-task was observed in the triple task condition, as compared to the single and dual task conditions. This finding in the triple task condition, therefore, replicates prior findings (Hemmerich et al., 2023), observed when analysing alpha power without parametrizing the power spectra (i.e., measuring alpha power including potential shifts in aperiodic data, as compared to only measuring alpha as the peak above the aperiodic exponent). This result further points towards the fact that alpha power is a useful estimator of time-on-task effects in high-demand tasks, likely reflecting an increased need for the inhibition of task-irrelevant information (Clayton et al., 2015a). However, the impact of tDCS on alpha power was not related to behavioural outcomes in the present study, thereby offering no mechanistic insight into the effectiveness or ineffectiveness of the tDCS intervention. The role of alpha oscillations in explaining tDCS efficacy may be found when

considering it as part of an interactive mechanism with other processes but not on its own; as suggested, for example, by the $Alpha_{parietal}/Gamma_{frontal}$ index reported by Hemmerich et al. (2023). Notably, despite an interest in gamma power in relation to these prior findings, this frequency range could not be explored further due to a lack of sufficient observations (i.e., many participants did not have any peaks above the aperiodic exponent in the 30-45 Hz frequency range). This finding may point to the fact that, what was observed as changes in gamma power, may in fact be a shift in broadband power, without any real periodic contribution. This aligns with the potential interpretation of the aperiodic offset as suggested by Manning et al. (2009).

Apart from exploring the pre-post changes in periodic and aperiodic data, in search of a mechanistic explanation, we further explored whether the effect of tDCS on the EV decrement was moderated by baseline values of these periodic and aperiodic variables. Against what was hypothesized, no significant moderation was observed, for either aperiodic component (across both frequency ranges), nor for alpha power in representation of periodic data. The use of baseline measures as a means of predicting individual responsiveness to tDCS has shown promising results, both with behavioural (Brosnan et al., 2018; Gan et al., 2022) and neurophysiological measures (Filmer, Ehrhardt, Bollmann, et al., 2019; Sheffield et al., 2020; van Bueren et al., 2023). The predictions for the present study had been based on promising findings observed with tRNS interventions (Sheffield et al., 2020; van Bueren et al., 2023). The fact that no moderating effects were observed in the present study could, therefore, be explained by the use of a different transcranial electrical stimulation technique, by the outcome being measured on a different cognitive process, the use of on-task baseline data compared to rs-EEG data, or other methodological differences between studies.

While some specific limitations pertaining to the specific findings in the present study have already been discussed above, some more global limitations must be taken into account. First, the type of EEG data used in the present, whilst providing more direct information on task-related processing, is also more difficult to interpret as it does not allow an independent inspection of tDCS-induced changes in neurophysiology, time-on-task effects, and ongoing task processing. Secondly, as indicated

by the results from the present study and prior research (Alnes et al., 2023; Arnett et al., 2022; Lendner et al., 2020), the results might be highly sensitive to the frequency ranges used to extract aperiodic parameters. While the use of two different fits might have been avoided by the use of a "knee" (Gerster et al., 2022) when fitting the data, this yielded highly suboptimal fits to the present data. This highlights that future refinements of parametrization algorithms may aid in more clearly grasping the different spectral components. Third, it must be noted that in order to explore the different hypotheses of the present study, a high number of different models were tested, which increases the likelihood of incurring Type I errors. In line with this prior limitation, it must also be considered that the indirect effects observed in the parallel mediation models were only observed when assuming a directional hypothesis (i.e., using confidence intervals at 90%). Lastly, it must be noted that the use of the offset from the higher frequency range might be controversial as it has not been reported/explored in the above-cited studies that also employ a higher frequency range. Using a smaller and higher frequency range at the same time might increase the correlation between exponent and offset measures, rendering the measures less independent.

Based on the findings outlined in the present study and their limitations, future research is needed to better grasp the intricate but promising relationship between aperiodic EEG data and tDCS-induced effects in vigilance performance. Given the sparse evidence of aperiodic EEG data in the context of tDCS studies, the present findings require further replication, likely requiring larger sample sizes. Future studies would also benefit from the use of both rs-EEG in addition to on-task EEG data, to better explore the role of baseline EEG activity, as well as better understanding the interaction of task-induced and tDCS-induced neurophysiological changes. For the on-task EEG data, a promising approach would be a more specific look into aperiodic data on a trial-by-trial basis (Arnett et al., 2022; Gyurkovics et al., 2022). Lastly, future developments in algorithms used to disentangle spectral components, as well as the development of frameworks to better understand its intricate effects and interactions will likely help in approximating a mechanistic understanding of tDCS effects.

Conclusions

This study offers preliminary insights that contribute to our understanding of cognitive-load dependent effects of HD-tDCS on the EV decrement by considering the aperiodic parameters as a mediating factor. The present study highlights the relevance of using adequate frequency ranges to extract aperiodic parameters, as findings were more evident when using a higher frequency range (30-45 Hz compared to 1-35 Hz). Furthermore, the results highlight the need to consider task-induced neural activity when anticipating the efficacy of tDCS interventions: in a high-load but not overdemanding task, further increasing the E/I balance with tDCS leads to a mitigated EV decrement, potentially by facilitating the firing of near-threshold neurons involved in task-relevant processes. In a low-demand task, further increasing the E/I balance with tDCS leads to a more pronounced EV decrement, potentially due to the facilitation of task-irrelevant processes. In parallel, a push-pull relationship between the aperiodic exponent and offset seems to be taking place, countering the effect observed in each task type, and reducing the overall effect. In summary, the study presents an intriguing look at the potential of aperiodic EEG markers in elucidating the effects of tDCS on vigilance, with the caveat that these findings are an initial step that requires further exploration. Continued investigation in this field is essential for developing more precise and individualized applications of tDCS for cognitive modulation.

Supplementary Material

Appendix A. Selection of frequency ranges for FOOOF

In **Fig. A.1.**, we can see that, whilst when reducing the upper limit of the frequency range from the initially planned and pre-registered value (45 Hz), in 5 Hz intervals, visually there's no apparent difference between the fit of the modelled spectrum (red line) to the original data (black), but the aperiodic exponent fits more appropriately the spectrum as the upper limit of the frequency range is lowered. Furthermore, in **Table A.1**, we can observe that the GoF measures reflect a better fit in the more reduced frequency range (1-35 Hz): with higher R^2 and lower error values.

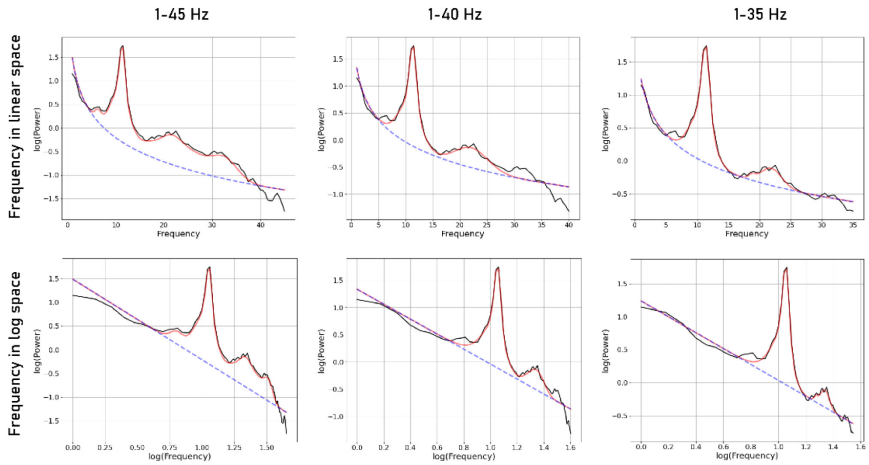


Fig. A.1. Representation of the fit of the modelled data (red line) over the original data (black) of a sample participant (participant 46, pre-stimulation EEG recording from P4) for three different frequency ranges. The same plot is presented with frequency in the x-axis in linear space (upper row) and in log-space (bottom row).

Table A.1. Goodness-of-fit (GoF) measures of the fitted model to the original data, for a sample participant's power density spectrum after running the FOOOF algorithm over different frequency ranges.

	Goodness-of-fit	
Frequency Range	R^2	error
1-45 Hz	.98	.07
1-40 Hz	.97	.08
1-35 Hz	.99	.04

Note. Sample participant: participant 46, pre-stimulation EEG recording from P4.

In **Fig. A.2.**, we can see that, compared to the inadequate model fit in the higher frequency range in the model from 1-45, especially over higher frequencies, an adequate model fit is observed over a frequency range of 30-45 Hz.

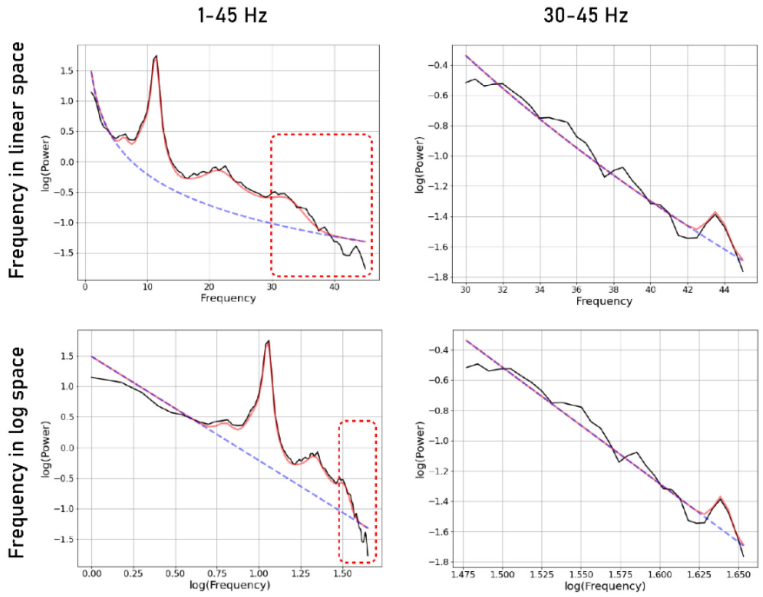


Fig. A.1. Representation of the fit of the modelled data (red line) over the original data (black) of a sample participant (participant 46, pre-stimulation EEG recording from P4), showing how the fit over the 30-45 Hz range (enclosed in the dotted red box) is inadequate in the broader frequency range, whereas when fitting the model only over the 30-45 Hz range it adequately aligns with the slope of the spectrum. The same plot is presented with frequency in the x-axis in linear space (upper row) and in log-space (bottom row).

Table A.2. Goodness-of-fit (GoF) measures of the fitted model to the original data, for a sample participant's power density spectrum after running the FOOOF algorithm over the 30-45 Hz range.

	Goodness-of-fit	
Frequency Range	R^2	error
1-45 Hz	.98	.07
30-45 Hz	.97	.05

Note. Sample participant: participant 46, pre-stimulation EEG recording from P4.

Appendix B. Δ Aperiodic results by electrode

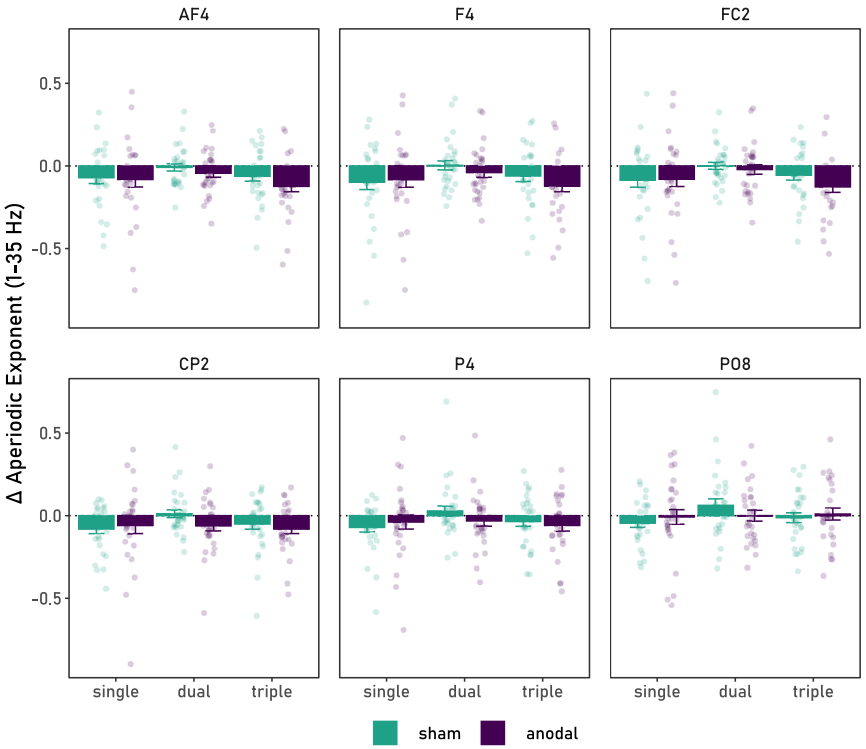


Fig. B.1. Δ Aperiodic Exponent extracted from the 1-35 Hz range as a function of electrode, task type and stimulation condition.

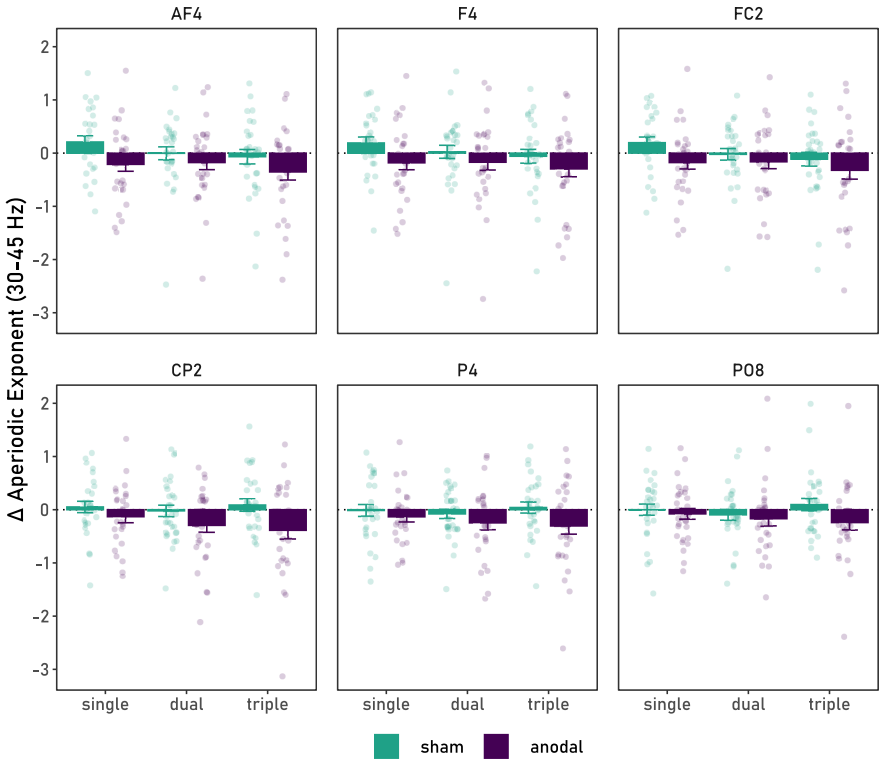


Fig.B.2. Δ Aperiodic Exponent extracted from the 30-45 Hz range as a function of electrode, task type and stimulation condition.

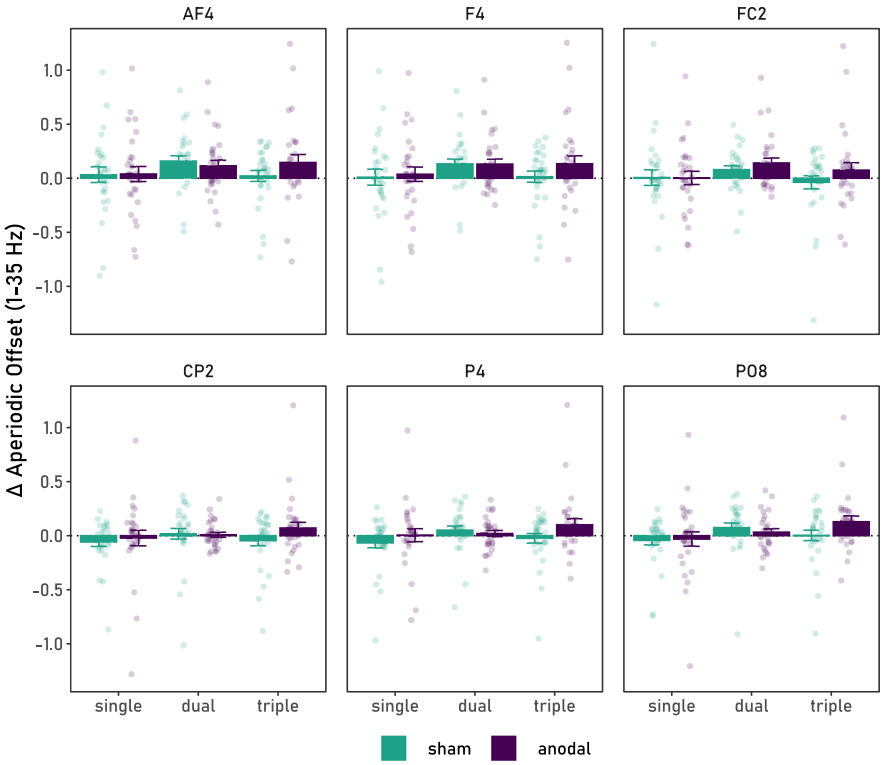


Fig. B.3. Δ Aperiodic Offset extracted from the 1-35 Hz range as a function of electrode, task type and stimulation condition.

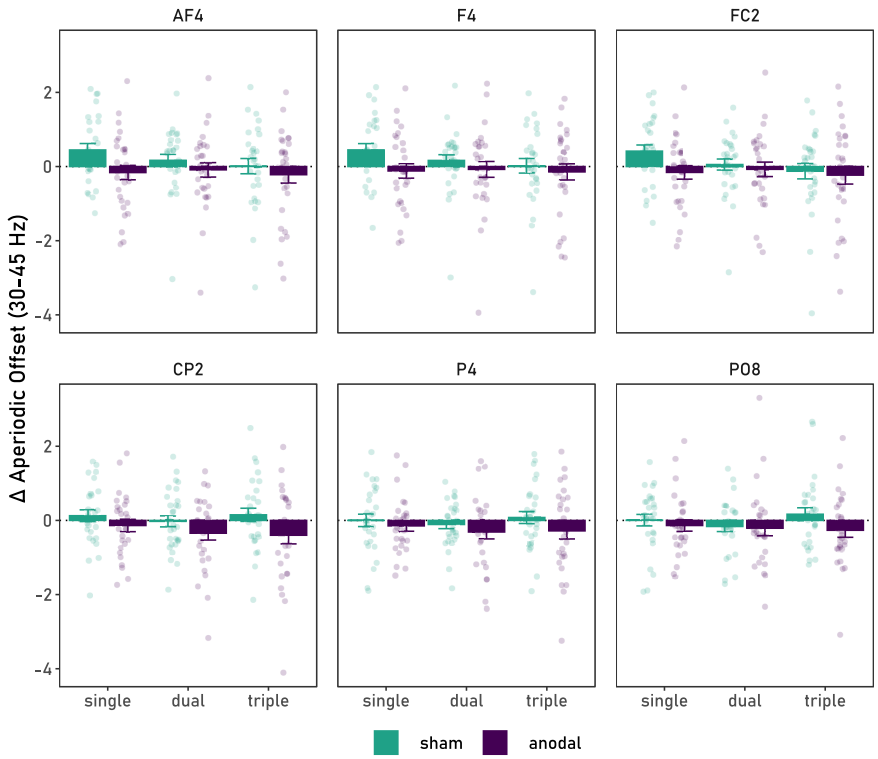


Fig. B.4. Δ Aperiodic Offset extracted from the 1-35 Hz range as a function of electrode, task type and stimulation condition.

Appendix C. Mediation results for aperiodic data in dual task

Table C1. Mediation model for aperiodic data in dual task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
	a-paths: effect of Stimulation Condition on each mediator					
a_1: Δ Exponent (1-35 Hz)	-0.054	0.033	-0.110	0.001	-0.122	0.010
a_2: Δ Exponent (30-45 Hz)	-0.183	0.153	-0.423	0.091	-0.467	0.126
a_3: Δ Offset (1-35 Hz)	-0.008	0.045	-0.083	0.067	-0.097	0.082
a_4: Δ Offset (30-45 Hz)	-0.207	0.212	-0.542	0.156	-0.608	0.219
	b-paths: effect of each mediator on EV Slope					
b1: Δ Exponent (1-35 Hz)	0.066	0.156	-0.169	0.338	-0.231	0.377
b2: Δ Exponent (30-45 Hz)	-0.052	0.144	-0.309	0.172	-0.349	0.211
b3: Δ Offset (1-35 Hz)	-0.059	0.094	-0.224	0.081	-0.254	0.112
b4: Δ Offset (30-45 Hz)	0.033	0.097	-0.116	0.203	-0.147	0.231
	Total and indirect effects (Stimulation Condition > EV Slope)					
c (Total Effect)	0.003	0.008	-0.010	0.016	-0.012	0.019
c' (Direct effect)	0.004	0.008	-0.010	0.017	-0.013	0.020
	Indirect effects (Stimulation Condition > Mediator > EV Slope)					
a_1b_1: tDCS → Δ Exponent (1-35 Hz)	-0.004	0.010	-0.022	0.010	-0.028	0.013
a_2b_2: tDCS → Δ Exponent (30-45 Hz)	0.009	0.034	-0.045	0.068	-0.062	0.091
a_2b_3: tDCS → Δ Offset (1-35 Hz)	0.001	0.005	-0.006	0.010	-0.010	0.012
a_4b_4: tDCS → Δ Offset (30-45 Hz)	-0.007	0.029	-0.056	0.041	-0.075	0.055

Note. N = 59. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Appendix D. Single mediation results for aperiodic data

Triple Task:

Table D1. Single mediation model with Δ Aperiodic Exponent (1-35 Hz) in the triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AE 1-35	-0.038	0.037	-0.097	0.022	-0.110	0.034
b: Δ AE 1-35 > EV Slope	-0.005	0.036	-0.068	0.051	-0.081	0.061
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.001**	**0.035**	-0.002	0.038
ab: Stim. Cond. → Δ AE 1-35 > EV Slope	0.000	0.002	-0.003	0.004	-0.003	0.005

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D2. Single mediation model with Δ Aperiodic Exponent (30-45 Hz) in the triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AE 30-45	**-0.313**	**0.171**	**-0.597**	**-0.033**	-0.639	0.015
b: Δ AE 30-45 > EV Slope	-0.005	0.008	-0.017	0.009	-0.019	0.012
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.017**	**0.010**	**0.000**	**0.034**	-0.004	0.037
ab: Stim. Cond. → Δ AE 30-45 > EV Slope	0.002	0.003	-0.003	0.006	-0.004	0.007

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D3. Single mediation model with Δ Aperiodic Offset (1-35 Hz) in the triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AO 1-35	**0.121**	**0.070**	**0.012**	**0.244**	-0.014	0.267
b: Δ A:O 1-35 > EV Slope	-0.002	0.021	-0.039	0.032	-0.047	0.037
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.001**	**0.035**	-0.002	0.039
ab: Stim. Cond. → Δ AO 1-35 > EV Slope	0.000	0.003	-0.004	0.005	-0.005	0.007

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D4. Single mediation model with Δ Aperiodic Offset (30-45 Hz) in the triple task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AO 30-45	-0.302	0.250	-0.729	0.091	-0.783	0.195
b: Δ AO 30-45 > EV Slope	-0.003	0.005	-0.011	0.007	-0.013	0.008
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.017**	**0.010**	**0.001**	**0.034**	-0.003	0.037
ab: Stim. Cond. → Δ AO 30-45 > EV Slope	0.001	0.002	-0.002	0.004	-0.003	0.005

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Single Task:

Table D5. Single mediation model with Δ Aperiodic Exponent (1-35 Hz) in the single task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AE 1-35	0.019	0.049	-0.063	0.096	-0.080	0.117
b: Δ AE 1-35 > EV Slope	-0.021	0.021	-0.060	0.009	-0.067	0.013
c: Total Effect (Stim. Cond. > EV Slope)	-0.010	0.008	-0.023	0.003	-0.025	0.006
c': Direct effect (Stim. Cond. > EV Slope)	-0.010	0.008	-0.023	0.004	-0.025	0.006
ab: Stim. Cond. → Δ AE 1-35 > EV Slope	0.000	0.002	-0.004	0.001	-0.005	0.002

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D6. Single mediation model with Δ Aperiodic Exponent (30-45 Hz) in the single task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AE 30-45	**-0.244**	**0.135**	**-0.454**	**-0.014**	-0.508	0.010
b: Δ AE 30-45 > EV Slope	0.000	0.007	-0.013	0.011	-0.015	0.014
c: Total Effect (Stim. Cond. > EV Slope)	-0.010	0.008	-0.023	0.003	-0.025	0.006
c': Direct effect (Stim. Cond. > EV Slope)	-0.010	0.008	-0.023	0.004	-0.026	0.006
ab: Stim. Cond. → Δ AE 30-45 > EV Slope	0.000	0.002	-0.004	0.003	-0.005	0.004

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D7. Single mediation model with Δ Aperiodic Offset (1-35 Hz) in the single task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AO 1-35	**0.121**	**0.070**	**0.012**	**0.244**	-0.014	0.267
b: Δ AO 1-35 > EV Slope	-0.002	0.021	-0.039	0.032	-0.047	0.037
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.001**	**0.035**	-0.002	0.039
ab: Stim. Cond. → Δ AO 1-35 > EV Slope	0.000	0.003	-0.004	0.005	-0.005	0.007

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table D8. Single mediation model with Δ Aperiodic Offset (30-45 Hz) in the single task.

	b	SE	90% CI		95% CI	
			LLCI	ULCI	LLCI	ULCI
a: Stim. Cond > Δ AO 30-45	-0.302	0.250	-0.729	0.091	-0.783	0.195
b: Δ AO 30-45 > EV Slope	-0.003	0.005	-0.011	0.007	-0.013	0.008
c: Total Effect (Stim. Cond. > EV Slope)	**0.018**	**0.010**	**0.002**	**0.035**	-0.002	0.038
c': Direct effect (Stim. Cond. > EV Slope)	**0.017**	**0.010**	**0.001**	**0.034**	-0.003	0.037
ab: Stim. Cond. → Δ AO 30-45 > EV Slope	0.001	0.002	-0.002	0.004	-0.003	0.005

Note. N = 58. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Appendix E. Mediation results for periodic data in single and dual tasks

Table E1. Mediation model for periodic data in the single task.

	b	SE	95% CI	
			LLCI	ULCI
a: Stim. Cond > Δ Alpha Power	0.011	0.013	-0.105	0.128
b: Δ Alpha Power > EV Slope	0.025	0.026	-0.013	0.068
c: Total Effect (Stim. Cond. > EV Slope)	-0.011	0.009	-0.029	0.006
c': Direct effect (Stim. Cond. > EV Slope)	-0.012	0.009	-0.029	0.006
ab: Stim. Cond. → Δ Alpha Power > EV Slope	0.000	0.002	-0.004	0.004

Note. N = 49. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Table E2. Mediation model for periodic data in the dual task.

	b	SE	95% CI	
			LLCI	ULCI
a: Stim. Cond > Δ Alpha Power	0.038	0.039	-0.054	0.132
b: Δ Alpha Power > EV Slope	0.022	0.023	-0.018	0.061
c: Total Effect (Stim. Cond. > EV Slope)	0.006	0.009	-0.011	0.023
c': Direct effect (Stim. Cond. > EV Slope)	0.005	0.009	-0.012	0.023
ab: Stim. Cond. → Δ Alpha Power > EV Slope	0.001	0.002	-0.002	0.005

Note. N = 52. LLCI = lower limit of the CI, ULCI = upper limit of the CI.

Chapter 9

Microstructural white matter connectivity as a potential predictor of HD-tDCS outcomes: dataset description and initial inspection

Abstract

This report focuses on the potential influence of microstructural white matter connectivity on the outcomes of transcranial direct current stimulation (tDCS) aimed at mitigating the executive vigilance decrement (EV). We analysed diffusion-weighted imaging (DWI) data from participants (N = 172) involved in two previous studies (i.e., data from Chapter 6 and 7), each completing one of three different versions of the ANTI-Vea Task (triple, dual, or single), while receiving online either sham or anodal HD-tDCS over the right posterior parietal cortex (rPPC). Diffusion-weighted imaging (DWI) was collected from each participant prior to the experimental task and brain stimulation. The integrity of white matter tracts relevant to attentional and vigilance functioning was indexed by means of the Hindrance Modulated Orientational Anisotropy (HMOA) index. The preliminary findings of this report point towards the right SLF III, the left SLF II, the Cingulum, and the Splenium of the Corpus Callosum as potentially relevant for future causal analyses, such as moderation analyses. These results could offer novel insights into the neural substrates underlying vigilance and pave the way to find future neural markers that can predict tDCS outcomes.

Background

Microstructural white matter connectivity offers an interesting, yet underexplored point of insight to further understand behavioural outcomes of transcranial direct current stimulation (tDCS) (Zhao et al., 2021). Using diffusion-weighted imaging (DWI), the structural organization of white matter connections in the brain can be reconstructed (Jones et al., 2013; Leemans et al., 2009). This reconstruction can be further dissected into fibre bundles—a fasciculus or tract—through virtual *in vivo* dissections of the acquired data (Catani & Thiebaut de Schotten, 2008; Jones et al., 2013). An index of the connectivity of a tract can then be related to behavioural performance (Catani & Thiebaut De Schotten, 2012b; Chica et al., 2018; Niogi et al., 2010; Thiebaut De Schotten, Dell'Acqua, et al., 2011; C. Wang et al., 2022), and thus, aid in understanding responsiveness to tDCS (Kurtin et al., 2021; Zhao et al., 2021).

Compared to other neuroimaging measures (such as electroencephalography or functional magnetic resonance imaging), that capture dynamic signatures of cognitive processes, DWI measures more static properties of the brain. However, white matter structures are only relatively static, as they will react to plastic changes that the brain goes through in order to best adapt to the environment (Janelle et al., 2022), as is the case of learning a new skill (Concha, 2014). In this sense, an individual's white matter connections will represent how their specific learning history throughout their life has shaped and prioritized the most functionally relevant pathways for efficient signal transmission in the brain. More importantly, these "static" measures are the substrate of the adequate functioning of more dynamic cognitive processes, as they rely on the transmission of excitatory signals along the myelinated axons of interconnected neurons (Purves & Williams, 2001). This function may be especially relevant for cognitive processes such as vigilance, that require the exertion of cognitive control to maintain task goals active (Thomson, Besner, et al., 2015), discern targets from non-targets, and adequately and periodically re-energize task-relevant processes, whilst inhibiting task-irrelevant processes (Clayton et al., 2015a; Stuss et al., 1995).

From general models of attentional functioning that apply to vigilance, potential candidates can be identified. Long-ranging connections through

frontoparietal networks and fronto-occipital connections, such as the inferior fronto-occipital fasciculus (IFOF) and the superior longitudinal fasciculus (SLF) may be of special interest. The IFOF potentially exerts fast top-down control from frontal regions over the visual cortex, while the SLF is involved in the integration of visual information through dorsal and ventral pathways (Bartolomeo & Seidel Malkinson, 2019; Corbetta & Shulman, 2002). Furthermore, a hub in the right posterior parietal cortex (rPPC) showing high structural connectivity as a core in itself and in connection to other areas (Hagmann et al., 2008), is functionally relevant for vigilance processes (Singh-Curry & Husain, 2009; Stevens et al., 2005), which may be supported by white matter projections of the SLF. Furthermore, this parietal hub may act as a relay switch between on-task processes and off-task or self-referential processes attributed to the default-mode network (DMN, Giacometti Giordani et al., 2023). It has been shown that adequate sustained attention is in fact supported by a push-pull relationship between a frontoparietal network (FPN) and regions of the DMN (Esterman et al., 2013). The relay between the FPN and DMN is supported by the anterior and posterior region of the cingulate cortex (Menon, 2011), which posits the Cingulum as an additional relevant candidate for inspection in DWI data.

Furthermore, recent studies exploring DWI data have provided more direct insight into specific white matter tracts that are associated with attentional functioning, and specifically vigilance or sustained attention, as summarized below. Higher structural integrity in the SLF, for example, predicts improved sustained attention performance in typically developing children (Klarborg et al., 2013), whereas an alteration of this pathway predicts inattentive symptomatology in teenagers with attention-deficit hyperactivity disorder (Chiang et al., 2015). The SLF connects frontal, temporal, parietal, and occipital areas and has further been divided into three branches (I, dorsal, II, medial, and III, ventral, Janelle et al., 2022). The SLF-I, specifically, has been associated with fewer attentional lapses (Clemente et al., 2021) and improved executive vigilance reaction times (Luna, Lupiáñez, et al., 2021). Furthermore, the Cingulum, which runs around the Corpus Callosum (CC; Catani & Thiebaut de Schotten, 2008), has also been associated with improved sensitivity in the detection of infrequent targets (Takahashi et al., 2010). Moreover, the integrity of the posterior limb

of the internal capsule (PLIC) has been associated with Posner & Petersen's (1990) alerting network (Niogi et al., 2010), which might be relevant for the maintenance of an adequate level of arousal to sustain vigilance. Furthermore, spatial orienting has been associated with the integrity of the splenium of the CC (Niogi et al., 2010), which corresponds to the posterior section of the CC, that may subserve adequate inter-hemispheric integration (Catani & Thiebaut De Schotten, 2012a). Additionally, the right DLPF-C, a tract connecting the dorsolateral prefrontal area and the caudate nucleus, has been associated with vigilance performance (Chiang et al., 2015). Lastly, the right IFOF may have a relevant role in response inhibition (Pironti et al., 2014); which might be relevant for the inhibition of task-irrelevant stimuli during a vigilance task.

Improving our understanding of whether and how white matter tracts associated with vigilance can predict outcomes of a tDCS intervention designed to mitigate the vigilance decrement could enhance our knowledge of the technique. It would also assist in creating markers that predict the outcomes of tDCS interventions. Altered integrity of white matter tracts due to aging or lesions have shown to impact the outcome of tDCS interventions (Indahlastari et al., 2021; Kurtin et al., 2021; Zhao et al., 2021). However, it is unclear whether individual differences in healthy populations could also serve as a predictor of tDCS outcomes. For now, structural white matter data has been used as an index of induced plastic changes from tDCS studies (Antonenko et al., 2023; Sherwood et al., 2021), but it remains to be explored whether baseline values can predict tDCS outcomes on cognitive functioning, and specifically in relation to vigilance.

About this report

The present report includes the description of a dataset comprising behavioural data collected during the performance of a task measuring vigilance by means of three different cognitive load conditions, whilst receiving either sham or anodal HD-tDCS over the rPPC (Hemmerich et al., 2023, under review). As a transversal measure through these experiments, at baseline (i.e., before completing the task in conjunction with the brain stimulation protocol), participants underwent an MRI scan to acquire diffusion-weighted images. The above outlined tracts of interest were

dissected *in vivo*, in order to serve as a potential measure that can predict HD-tDCS outcomes in mitigating the vigilance decrement. This report includes a detailed description of the methodology followed for the image acquisition and fibre dissection, as well as an overview of the results through descriptive analyses. Lastly, a first look into potential associations with behavioural outcomes is provided by means of simple correlations. This can inform the selection of specific tracts of interest for future analyses with a causal approach (e.g., moderation analysis), to potentially inform future research into utilizing neuroimaging to predict responsiveness to a brain stimulation intervention. On the other hand, the sample accumulated so far could further serve for future higher-powered analyses if combined with other data through open-science and collaborative practices, to better grasp the potential role of white matter structures as a predictor of tDCS outcomes.

Methods

Participants

DWI-MRI data from a total of 180 participants has been collected as part of two prior studies (Hemmerich et al., *under review*, 2023). The interaction of the intra-participant manipulations—Stimulation Condition (sham/anodal HD-tDCS) and Cognitive Load (single/dual/triple task)—led to a sample of 30 participants per experimental condition. The sample size was calculated based on prior studies of behavioural effects of tDCS (reported in detail in Hemmerich et al. 2023). Furthermore, this sample size per experimental condition is comparable to prior studies (Luna, Lupiáñez, et al., 2021; Thiebaut De Schotten, Dell'Acqua, et al., 2011). However, it is likely that to perform correlation analyses is rather small. A priori sample size calculations performed in G*Power yield a sample size of 29 participants for a large effect (ρ = 0.5, Cohen, 1988), at 1-β = *.80* and α = .05; whereas much larger samples would be needed for medium (ρ = 0.3, N = 84) or small effects (ρ = 0.1, N = 782). Furthermore, it has been suggested that in studies investigating individual differences, the categorization of effect sizes should be altered given that effect sizes of ρ = .5 are unlikely to be observed; and should rather be categorized into ρ = .1, ρ = .2, and ρ = .3, as relatively small, typical and relatively large (Gignac & Szodorai, 2016). This further highlights

that the current sample of $N \leq 30$ may be insufficient to detect relevant correlations.

All participants were right-handed, had normal or corrected-to-normal vision, no neurological or psychiatric conditions, and complied with all safety criteria to safely undergo the MRI procedure as well as the tDCS protocol (Rossi et al., 2009; Rossini et al., 2015). All participants signed an informed consent and received monetary compensation for their participation (10 €/hour). The study was approved by the embedded in larger research projects (PID2020-114790GB-I00 and B-CTS-132-UGR20) approved by the Ethical Committee of the University of Granada (2442/CEIH/2021 and 1188/CEIH/2020), following ethical standards of the 1964 Declaration of Helsinki (last update: Brazil, 2013).

Due to data filtering and missing data (reported in detail in the results section), the final sample was comprised of 172 participants. Demographic data by experimental condition is summarized in **Table 9.1**.

Table 9.1. Demographic characteristics of participants per experimental condition after data filtering.

		N	Mean age (SD)	Sex (female)
Single task	Sham	*n* = 27	24.52 (4.07)	18
	Anodal	*n* = 29	22.10 (2.82)	20
Dual task	Sham	*n* = 27	23.60 (4.03)	13
	Anodal	*n* = 30	22.30 (4.13)	20
Triple task	Sham	*n* = 30	24.13 (4.57)	21
	Anodal	*n* = 29	22.69 (3.53)	21

Apparatus and stimuli

Behavioural measures

Participants performed different versions of the ANTI-Vea Task (Coll-Martín et al., 2023; Luna, Barttfeld, et al., 2021). A triple task condition constituted the standard ANTI-Vea Task, where 60% of trials consisted of a flanker task (ANTI trials), 20% of trials consisted of Executive Vigilance (EV) trials (where

the central arrow between the flankers was vertically displaced and participants need to press an alternate key upon detection), and the remaining 20% of trials are Arousal Vigilance (AV) trials (where a large red countdown appeared in the middle of the screen, which participants had to stop as fast as possible by pressing any key). In the dual task participants had to respond to AV and EV trials, whereas in the single trials, only EV trials had to be responded to (for more details on these task manipulations, see **Chapter 7** or Luna et al., 2022). Note that across all three task types, the same stimuli were presented with the same timing (except response times). Therefore, all tasks were perceptually identical, and only instructions and coding of correct responses were changed. All versions of the task included 7 task blocks (as shown in **Fig. 9.1**), which were used for analyses and adjustment of the stimulation protocol but constituted a continuous task without interruption for the participants.

The behavioural indices correspond to measures relating to the EV component, which has shown to be mitigated by anodal HD-tDCS over the rPPC in prior research (Hemmerich et al., 2023; Luna et al., 2020). As was done in these prior studies, EV indices were extracted from blocks 1-6, to include performance from baseline up to the offset of the stimulation protocol). The Mean EV Hits were obtained by extracting the mean proportion of correct responses to EV trials across blocks 1-6. The EV Slope was obtained by calculating the regression line for hits for each participant across Blocks 1-6, to obtain a summarized index of the linear decrement of performance with time-on-task.

HD-tDCS and EEG procedure

In parallel to performing either of the versions of the ANTI-Vea, participants received either anodal or sham HD-tDCS over the right posterior parietal cortex (rPPC). HD-tDCS was applied from the 2nd to the 6th task block (for ~28 minutes), with an intensity of either 1.5 mA (anodal stimulation group) or 0 mA (sham group) and a ramp-up and ramp-down of 30 seconds. The sham procedure consisted of two ramps at the beginning and end of the stimulation period with a stimulation duration of 30 seconds. Stimulation was applied with a Starstim 8 device (Nueroelectrics®, Barcelona), via five of the total eight hybrid NG Pistim Electrodes (with a 12 mm Ag/AgCl

sintered pellet, with a circular contact area of 3.14 cm2), set up in a 4 × 1 ring-like array with the central anode over P4, and the four surrounding cathodes over CP2, CP6, PO4, and PO8, in order to target the rPPC. Furthermore, during the 1st and 7th task blocks (i.e., pre-post stimulation), EEG data was recorded, which has been analysed as part of a different study.

Procedure

The experimental session began with the MRI scan to acquire T1, T2, diffusion-weighted, and resting-state imaging (beyond the scope of this report), for a total duration of ~28 minutes. During image acquisition, participants watched a documentary or animated film (except for the final resting-state sequence which was acquired with closed eyes and lights and screens turned off). After the MRI sequence, participants sat in another dimly lit room to complete the ANTI-Vea task and stimulation. Participants read task instructions and familiarized themselves with the corresponding version of the ANTI-Vea according to their assigned cognitive load condition through a practice block. After that, electrodes for HD-tDCS and EEG were set up. During the performance of the task, EEG data was acquired during the 1st and 7th block (5:47 minutes each), and the sham or anodal HD-tDCS stimulation protocol was applied from the 2nd to the 6th task block (28:48 minutes). Subjective assessments of mental and physical fatigue were completed by participants at three points: before the practice block (baseline), before (pre-task), and after the task (post-stimulation). Right after, participants completed a tES Survey, recording their subjective experience during stimulation to test the study's blinding efficacy (Fertonani et al., 2015). The experimental procedure is depicted in **Fig. 9.1**.

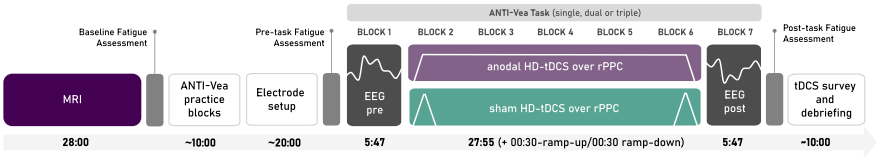


Fig. 9.1. Experimental procedure.

MRI data acquisition

Structural images were collected on a 3-T Siemens Trio MRI Scanner located at the Mind, Brain, and Behavioral Research Center (CIMCYC, University of Granada). A 32-channel whole-head coil was used. T1-wheighted anatomical images (acquisition time = 6:03 min) were collected, in order to check for any gross anatomical abnormalities, with the following parameters: repetition time (RT) = 2530 ms, echo time (ET) = 3.5 ms, flip angle = 7º, slice thickness = 1 mm, field of view (FoV) = 256 mm. Then, a sequence optimized for tractography of DWI was used (acquisition time = 9:55 min), collecting a total of 70-near axial slices, isotropic 2 mm resolution (i.e., voxel size of 2 mm^3), providing coverage of the whole head through a posterior-anterior acquisition phase, and the following additional parameters: RT = 8400 ms, ET = 88 ms, slice thickness = 2 mm, FoV = 220 mm. At each slice location, 6 images were acquired with no diffusion gradient applied 60 diffusion-weighted images, in which gradient directions were uniformly distributed in space. The diffusion weighting was equal to a b-value of 1500 s/mm^2. Additionally, a resting-state sequence was administered (acquisition time = 8:02 min), but this data is not included in the present report.

Data analysis

DWI pre-processing

Preprocessing for virtual *in* vivo dissections was performed following procedures from prior research (Luna, Lupiáñez, et al., 2021; Martín-Arévalo et al., 2019; Martín-Signes et al., 2019). In a first step, diffusion-weighted data were simultaneously registered and corrected for subject motion and geometrical distortion in each slice, adjusting the gradient accordingly using the Explore DTI toolbox (Leemans et al., 2009), run in Matlab on MATLAB R2017a (The MathWorks, Inc.). After this step, TrackVis (R. Wang et al., 2007) was used in order to perform individual dissections of the tracts of interest using a single or multiple region of interest (ROI) approach.

The following white matter tracts were dissected *in vivo* for each participant (depicted in **Fig. 9.2**).

The **SLF I, SLF II**, and **SLF III** were isolated in each hemisphere by means of a multiple-ROI approach (Luna, Lupiáñez, et al., 2021; Thiebaut De Schotten, Dell'Acqua, et al., 2011). Bilateral parietal ROIs, as well as three bilateral frontal ROIs corresponding to the superior frontal gyrus (for SLF I), the middle frontal gyrus (for SLF II), and the precentral gyrus (SLF III) were delineated as 'AND' ROIs (i.e., to select fibres crossing both ROIs). Additionally, the following 'NOT' ROIs (i.e., to exclude fibres selected from the prior approach that cross these regions) were delineated in the Corpus Callosum as well as in the temporal lobe excluded potential fibres crossing between hemispheres or belonging to the arcuate fasciculus.

The **Cingulum** was isolated in each hemisphere by means of a one-ROI approach, where it crosses next to the Corpus Callosum in the frontal region of the axial plane (Catani & Thiebaut de Schotten, 2008; Luna, Lupiáñez, et al., 2021), and a 'NOT'-ROI in the CC to avoid fibres that cross between the hemispheres.

The **Splenium of the CC** was isolated by a one ROI approach in the axial plane (Catani & Thiebaut de Schotten, 2008; Catani & Thiebaut De Schotten, 2012a; Luna, Lupiáñez, et al., 2021). In some cases, to exclude fibres projecting towards frontal brain regions, a 'NOT'-ROI was used in a more anterior coronal plane.

The **PLIC** was isolated in each hemisphere by means of a multiple-ROI approach: four 'AND'-ROIs delineated the ascending fibres in the axial plane (Luna, Lupiáñez, et al., 2021; Niogi et al., 2010), and an additional 'NOT'-ROI over the CC and brain stem excluded fibres crossing between hemispheres (Luna, Lupiáñez, et al., 2021).

The **DLPF-C** was isolated in each hemisphere through a multiple-ROI approach with two 'AND' ROIS in the dorsolateral prefrontal cortex and in the caudate nucleus, and an additional 'NOT'-ROI in the CC (Chiang et al., 2015; Luna, Lupiáñez, et al., 2021).

Lastly, the **IFOF** was isolated in each hemisphere by a multiple-ROI approach, with two 'AND'-ROIs in the external/extreme capsule and the occipital lobe (Catani & Thiebaut de Schotten, 2008).

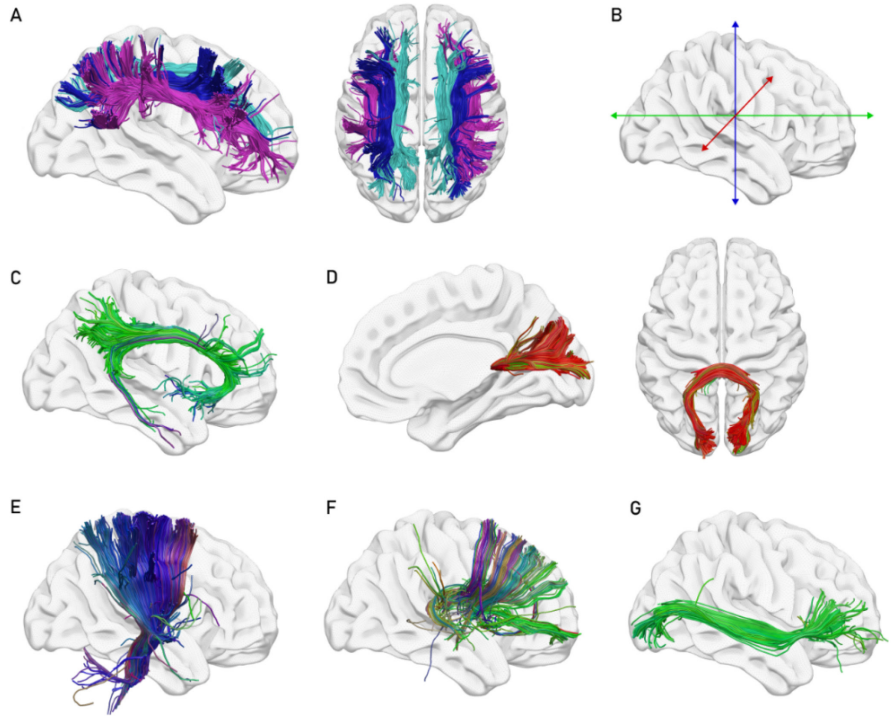


Fig. 9.2. Reconstructed virtual in vivo dissection of the tracts, extracted from TrackVis software and plotted over a standard brain using, as an example for each tract from one representative participant in the right (or both) hemisphere(s). **(A)** The three branches of the SLF: SLF I (light blue), SLF II (dark blue), and SLF III (pink). These tracts have been coloured to distinguish each branch. **(B)** Note that the remaining tract's colour reflects the direction of the fibres: antero-posterior orientations are represented in green, latero-lateral in red, and dorsal-ventral in blue, following standard convention (Catani & Thiebaut de Schotten, 2008). **(C)** Cingulum. **(D)** Splenium of CC. **(E)** PLIC. **(F)** DLPF-C. **(G)** IFOF.

Mean Hindrance Modulated Orientational Anisotropy (HMOA) was used as a proxy for each these tracts' microstructural organization (Dell'Acqua et al., 2013). The HMOA index reflects the absolute amplitude of each lobe of the fibres orientation distribution within a specific white matter orientation (Dell'Acqua et al., 2013). It has proven to be a valuable measure to characterize diffusion properties along each fibre orientation in white matter regions with a complex organization, as it is highly sensitive to axonal myelinization, fibre diameter, and fibre dispersion, which renders it especially useful in areas where different fibres are crossing (Dell'Acqua et al., 2013). The HMOA uses the highest fibre orientation distribution amplitude that can be realistically measured in a biological sample as a

reference, providing values that range from zero (absent signal) to one (signal as strong as the reference).

Descriptive and exploratory analyses

To obtain a summary of behavioural outcomes, an ANOVA was run on both Mean EV Hits and EV Hits Slope, with Task Type (triple, dual, or single) and Stimulation Condition (sham or anodal) as a between-participant factor.

In order to control the reliability of the performed dissections, lateralization indices for each bilateral tract (all tracts except the Splenium of the corpus callosum) were extracted as follows:

$$\frac{(HMOA\ right - HMOA\ left)}{(HMOA\ right + HMOA\ left)}$$

It was tested whether the lateralization index deviated significantly from zero. The lateralization was then contrasted with lateralization indices reported in the literature.

Lastly, in order to obtain a first look at relevant tracts in the relationship between the manipulation of cognitive load and brain stimulation, correlation analyses were performed between the behavioral measures and extracted HMOA indices for each experimental condition.

Results

Outliers and missing data

DWI data is missing from 7 participants: Tracts were not extracted from one dataset due to a motion artifact that could not be cleaned during pre-processing, and the remaining six, due to the field of view (FoV) being misaligned during acquisition. The head appears tilted forwards within the FoV, which has led to voxels that should appear in different slices to appear in the same slice. ROI's cannot be drawn in adequately onto these slices. Furthermore, regarding behavioural data, one participant was flagged and excluded from further analyses (described in Hemmerich et al., *under review*).

Descriptive results

As a summary of behavioural outcomes, the analysis of Mean EV Hits showed a significant Task Type × Stimulation interaction, $F(2, 166) = 4.43$, $p = .013$, $\eta_p^2 = .05$. Tuckey-corrected follow-up contrasts revealed a significant difference between Stimulation Conditions in the triple task, $t(166) = 2.37$, $p = .019$, a trend towards the opposite effect in the single task, $t(166) = -1.76$, $p = .080$, and no difference in the dual task ($p = .680$), as depicted in **Fig. 9.4.A**. The analysis of the EV Hits Slope also showed a significant interaction, $F(2, 166) = 3.15$, $p = .045$, $\eta_p^2 = .04$, with a significant difference between Stimulation Conditions in the triple task, $t(166) = 2.17$, $p = .032$, but no significant differences in the single ($p = .168$) or dual ($p = .819$) tasks, as depicted in **Fig. 9.4.B**.

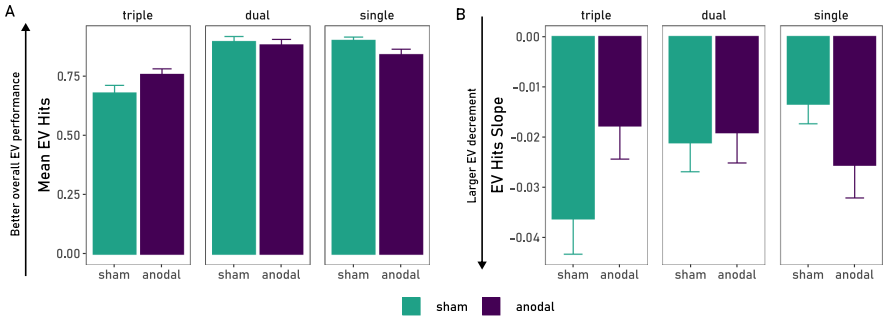


Fig. 9.4. **(A)** Mean EV Hits as a function of Task Type and Stimulation Condition. **(B)** EV Hits Slope as a function of Task Type and Stimulation Condition.

Descriptives of mean HMOA indices for each of the in vivo dissected tracts are depicted in **Figure 9.3.A**. A summary of the results is depicted in **Figure. 9.3.B**. While prior research has found no significant lateralization in the SLF I, it showed a trend towards a left lateralization (Luna, Lupiáñez, et al., 2021; Thiebaut De Schotten, Dell'Acqua, et al., 2011), that was observed as a significant lateralization towards the left hemisphere in this study, $t(170) = -4.56$, $p < .001$. In line with prior studies (Luna, Lupiáñez, et al., 2021; Thiebaut De Schotten, Dell'Acqua, et al., 2011), we observed a significant right-lateralization of the SLF II, $t(170) = 13.09$, $p < .001$, and SLF III, $t(170) = 14.63$, $p < .001$. Akin to prior results (Gong et al., 2005; Luna, Lupiáñez, et al., 2021; Takao et al., 2011), a lateralization towards the left hemisphere was observed for the Cingulum, $t(170) = -13.20$, $p < .001$, and PLIC, $t(170) = -3.24$, $p = .001$.

While prior studies observed no lateralization of the DLPF-C (Chiang et al., 2015; Luna, Lupiáñez, et al., 2021), a significant lateralization towards the left hemisphere was observed in the present dataset. Lastly, the IFOF also showed a significant left-lateralization in the present study, $t(170) = -4.43$, $p < .001$. This result contrasts with previous studies observing a right-lateralization of the IFOF (Chechlacz et al., 2015; Thiebaut De Schotten, Ffytche, et al., 2011), which, however, relied on different white matter integrity measures (Thiebaut De Schotten, Ffytche, et al., 2011), or on a non-exclusively right-handed sample of participants (Chechlacz et al., 2015). Additionally, the lateralization pattern was relatively weak compared to that of the SLF (Chechlacz et al., 2015). Additionally, Vassal et al. (2018) found that IFOF terminations exhibit varying lateralization patterns, with parietal projections often right-lateralized and inferior frontal gyrus projections predominantly left-lateralized. The use of a multiple-ROI approach in our study, potentially emphasizing frontal over parietal projections, may help explain these discrepancies.

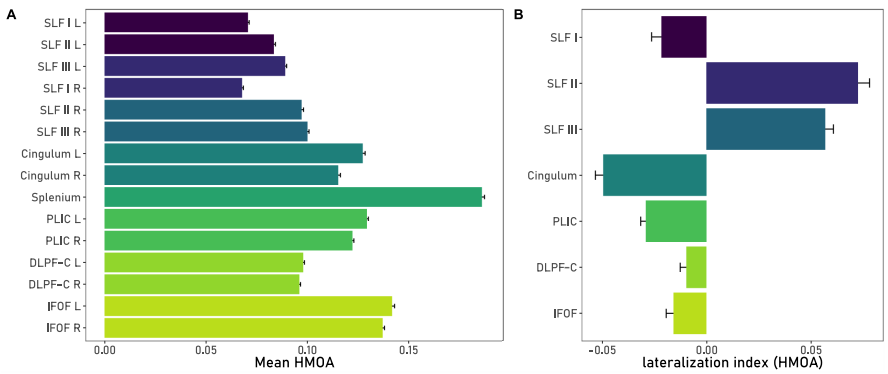


Fig. 9.3. **(A)** Descriptives of HMOA indices for the different *in vivo* dissections. **(B)** Lateralization indices for bilateral tracts, showing a significant lateralization to the left hemisphere of the SLF I, Cingulum, PLIC, DLPF-C, and IFOF; and a significant right-lateralization of the SLF II and SLF III. *Note*. Error bars represent standard errors.

Exploratory results

As depicted in **Table 9.2**, for the triple task condition, a significant negative correlation was observed between the HMOA index of the right SLF III and the Slope of EV Hits, i.e., a higher integrity of the tract associated with a more pronounced EV decrement. Notably, this association was only

observed in the sham condition (i.e., when performing the high-load task under normal conditions), but was abolished in the anodal group, as depicted in **Fig. 9.5.A**.

Furthermore, in the dual task, an opposite relationship between EV indices and the HMOA index of the left SLF II was observed. As depicted in **Fig. 9.5.B**, in the sham condition a negative trend was observed for Mean EV Hits, and a significant negative relationship was observed for EV Hits Slope, whereas significant positive relationships were observed in the anodal group for both behavioral variables. An additional negative correlation between the HMOA index of the left Cingulum and Mean EV Hits in the anodal condition was observed (in the absence of a relationship in the sham condition), as depicted in **Fig. 9.5.C**.

Lastly, in the single task, a significant negative correlation between the integrity of the Splenium of the CC and Mean EV Hits was observed. As shown in **Fig. 9.5.D**, this was significant in the anodal condition, and followed a similar trend in the sham condition, without reaching significance.

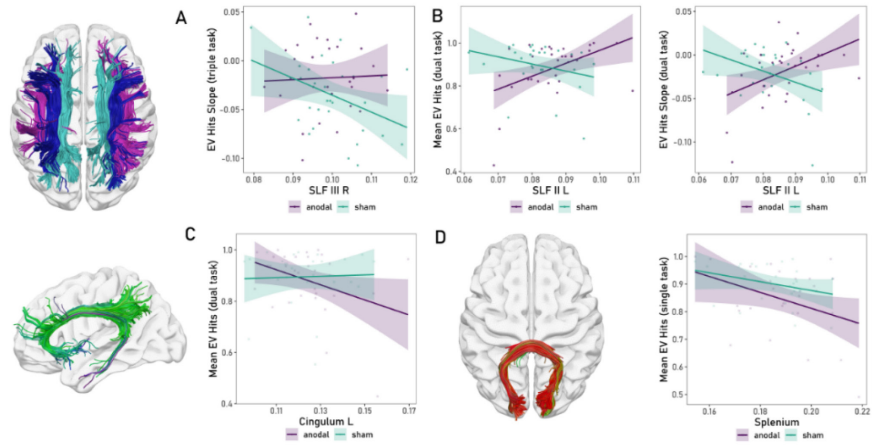


Fig. 9.5. **(A)** Linear relationship between the HMOA index of the right SLF III and the Slope of Hits in the triple task condition by stimulation condition. **(B)** Linear relationship between the HMOA index of the left SLF II and the mean Hits (across blocks 1-6) in EV trials and the Slope of Hits, by stimulation condition. **(C)** Linear relationship between the left Cingulum and mean EV Hits in the dual task, by stimulation condition. **(D)** Linear relationship between the Splenium of the CC and mean EV Hits in the single task, by stimulation condition.

Table 9.2. Pearson correlation coefficients between the Mean or Slope of Hits in EV trials and HMOA indices of each tract, by experimental

	Triple task				**Dual task**				**Single task**			
	Sham (n = 30)		Anodal (N = 29)		Sham (n = 27)		Anodal (n = 30)		Sham (n = 27)		Anodal (n = 29)	
	Mean	Slope	Mean	Slope	Mean	Slope	Mean	Slope	Mean	Slope	Mean	Slope
SLF I L	-.25	.05	-.06	-.27	-.08	.07	.13	.02	-.01	-.13	.18	.04
SLF II L	-.23	-.02	-0.01	-.28	-.27	-.38	**.47****	**.46****	-.09	-.13	.07	.30
SLF III L	-.17	-.05	0.21	.03	.00	-.03	.24	.15	-.08	.04	-.03	-.09
SLF I R	.08	.03	.00	-.19	-.06	-.09	-.08	.11	.02	-.15	.06	.05
SLF II R	-.19	-.10	0.03	-.02	.17	.21	-.10	-.05	.36	.15	-.14	-0.1
SLF III R	-.02	**-.39***	0.08	.04	-.18	.08	.03	.12	-.04	-.28	-.01	-.13
Cingulum L	-.17	-.20	0.27	.06	.04	.10	**-.37***	-.29	.02	-.11	.06	.04
Cingulum R	-.10	-.14	0.13	-.17	.24	.13	-.10	-.18	.11	-06	.06	-.01
Splenium	-.04	.01	0.17	-.03	.09	.11	.08	-.02	-.31	-.24	**-.38***	-.01
PLIC L	-.10	-.08	0.13	.10	.24	-.07	.14	.09	.36	.19	-.01	.06
PLIC R	-.19	-.08	-	-.12	.16	.14	.01	.02	.30	.02	.15	.29
DLPF-C L	-.10	.03	0.16	-.07	.11	-.02	.04	.14	.09	-.06	-.15	-.14
DLPF-C R	-.17	-.09	0.05	-.24	.25	.17	.29	.26	.13	.05	.25	.11
IFOF L	.31	-.11	0.01	-.16	.09	.07	.32	.25	-.09	.16	.08	-.04
IFOF R	.09	-.36	0.04	-.16	.26	.09	.06	.16	-.05	-.03	.00	.12

Note. * $p < .05$, ** $p < .01$

Discussion: an overview of potential future research

The present report set out to explore potential candidate white matter tracts that could serve to be explored in preregistered future analyses with the goal of identifying potential predictors of the outcomes of an HD-tDCS intervention targeting the rPPC in mitigating the vigilance decrement across different levels of cognitive demand. The lateralization of the dissected tracts follows the pattern observed in prior literature, which attests to the reliability of the extracted HMOA indices. However, the differences observed in the EV decrement across experimental conditions, leading to sample sizes of $N \leq 30$, was likely to not yield sufficient power for analyses. Therefore, the present report serves more primarily to provide the methodological background of the data acquisition and pre-processing, as well as the obtained data with the aim to pool it with future data for a more adequate sample size, due to its current limited its potential to establish any firm conclusions.

By correlating —as a first exploratory step— the HMOA indices with behavioural performance in EV trials (both Mean EV Hits and the EV Hits Slope throughout the tasks), several tracts of potential interest for further analysis have been identified. The findings reveal that the integrity of specific white matter tracts, such as the right SLF III and the left SLF II, significantly correlates with EV performance, in the triple and dual task, respectively, with these associations varying by stimulation condition. Notably, higher integrity in these tracts was linked to a greater decrement in vigilance performance under sham conditions, but this effect was either reversed or abolished under anodal tDCS, suggesting that the integrity of these tracts could potentially be a predictor of positive outcome of tDCS in mitigating the EV decrement. These results highlight the relevance of the SLF, specifically the right SLF III, as it shows a relevant opposite pattern in the task condition where a behavioural effect of tDCS is observed. This aligns with the theoretical relevance of the structure in attention (Bartolomeo & Seidel Malkinson, 2019), and would indicate a potential network or distribution effect in response to tDCS, facilitated by higher integrity within the SLF III. However, it must be noted that the significant result observed for the sham condition, does not align with the results observed by Luna, Lupiáñez, et al. (2021); and should therefore be

interpreted cautiously. Nevertheless, Luna, Lupiáñez, et al. (2021) used a previous version of the ANTI-Vea (the ANTI-V), which is more difficult to perform (as the overall hit rate was much lower, 46%, as compared to the data from the triple task in the sham group in the present study, 70%), which could explain the observed differences.

Additionally, two other structures show a negative association with tDCS outcomes. Specifically, a negative correlation was observed between the integrity of the left cingulum and vigilance performance in the anodal condition of the dual task, suggesting that higher structural integrity might be associated with decreased performance in this scenario. This result is more difficult to interpret in light of the absent behavioural effects of tDCS.

Conversely, the integrity of the splenium of the corpus callosum showed a significant negative correlation with vigilance performance in the anodal condition of the single task, indicating that higher integrity of this tract might lead to poorer performance. This could be a potential explanation of the non-significant trend of detrimental effects of tDCS observed in the single task condition. Other neuroimaging data has suggested that simpler vigilance tasks show a greater lateralization toward the right hemisphere (Helton et al., 2010). In this sense, if a higher integrity of the Splenium leads to a greater tDCS-induced inter-hemispheric communication, this could induce network effects that disturb ongoing processes to adequately perform the task.

These interpretations must be taken with caution, given the exploratory nature of the analyses. Furthermore, whilst the overall sample is substantial, as stated above, and given that the analyses were performed within each experimental condition, the sample size is relatively small to make adequate predictions from correlation analyses. Future analyses should explore the role of the tracts identified by these preliminary analyses in a more causal way, to better understand the intricate and cognitive-load dependent effects of HD-tDCS on the vigilance decrement. This could be achieved by means of moderation analyses (Harty et al., 2017), where the HMOA index of the identified tracts can be introduced as a moderator on the effect of HD-tDCS over the rPPC on the vigilance decrement. As a means to operate with a larger sample size, the analyses could be performed by including task type as a moderating variable of the moderated effect (i.e., Hayes's Model 3,

Hayes, 2022). Nevertheless, more data, which we hope will be accumulated across subsequent studies in our group, seems to be necessary for performing those analyses.

Conclusion

This report offers a first look at the potential predictive power of the integrity of white matter tracts supporting vigilance functioning on the outcomes of applying anodal HD-tDCS over the rPPC of mitigating the vigilance decrement. Preliminary exploratory analyses have unveiled several potential tracts of interest, to be considered for future analyses, namely the right SLF III, the right SLF II, the left Cingulum, and the Splenium of the corpus callosum. The right SLF III may be of special interest given that it shows an opposite association with performance in the triple task depending on the stimulation condition, where prior research has observed a mitigatory effect of tDCS on the executive vigilance decrement. Given the exploratory nature of this study and the limitations posed by the small sample sizes within each experimental condition, these findings require further investigation. While future replication of these results and an exploration of this complex relationship with larger sample sizes is needed, some further analyses can be conducted on this dataset to gain further insight. For instance, the potential causal relationships between white matter tract integrity and the cognitive-load dependent effects of HD-tDCS on the executive vigilance decrement could be explored by means of moderation analyses. Nonetheless, this should ideally be explored through future research with larger sample sizes or by aggregating data from multiple studies with the current findings.

PART IV
General discussion

Chapter 10

General discussion and concluding remarks

Attention is vital yet limited. It implies a constant choice—voluntary or not—to select and enhance a certain portion of the surrounding illimited reality, which entails turning our back to other realities. Given its value, attention can indeed be considered a form of currency. This is reflected quite literally in the English language, where we *pay* attention. Meanwhile, other languages attribute different values; for instance, in Spanish, we *lend* our attention, and in German, we *gift* it.

In all instances, however, it is implied that attention is highly valued, a fact modern forms of entertainment seem to be vying to capitalize on for as long as possible. Within this fast-paced, attention-demanding environment, one might wonder if vigilance still holds value. I argue that it does. In hand with technological developments competing for our attention, we are also automatizing many processes, transitioning the individual to a more passive, supervisory role (Hancock, 2017). On an assembly line, for example, rather than manufacturing the product itself, one might only need to detect a machine malfunction occasionally, or in the case of a self-driving car, intervention might only be necessary in exceptional circumstances.

These examples illustrate that our future will demand this ***ability to monitor and detect infrequent and unpredictable events***. More pressingly, in our present, we must consider instances in which an individual's attentional capacity may be impaired, due to delays in brain development or acquired brain lesions. As the ability to sustain a vigilant state often serves as a pre-requisite for other more complex attentional or cognitive processes to function adequately (Raz & Buhle, 2006), its alteration will inevitably string along an impairment of many other cognitive processes (Fish et al., 2017).

Therefore, building a better empirical basis of potential applications of neuromodulation could greatly benefit this crucial aspect in designing interventions to rehabilitate or compensate attentional functions. These potential applications across everyday and clinical settings, highlight that the phenomenon of vigilance and potential avenues that could mitigate its decrement deserve our attention as researchers in the present. This thesis aims to contribute to advancing the foundational research required to achieve this broader and more distant goal in the future.

Summary of findings

The main aim of this thesis was to further explore and understand the potential of tDCS to mitigate the executive vigilance decrement using a stimulation protocol of anodal high-definition tDCS (HD-tDCS) over the right posterior parietal cortex (rPPC). This was addressed more specifically through 3 specific aims: (i) to explore and extend the viability of the rPPC HD-tDCS protocol, (ii) to investigate potential cognitive load-dependent effects, and (iii) to further understand its potential effects through neuroimaging data. To offer an overview in line with the objectives established in **Chapter 5**, explicit reference to each aim and their specific objectives will be made in the following sections (e.g.: aim 1 – objective 1, as A1-O1).

Viability of the rPPC HD-tDCS protocol to mitigate the EV decrement

Regarding the first aim (**A1-O1**), in **Study I** we successfully replicated prior findings of a mitigated EV decrement with anodal HD-tDCS applied over the rPPC (Luna et al., 2020). This outcome validates the efficacy of this protocol in the standard ANTI-Vea task (corresponding to a triple task), which in the context of this thesis is considered as imposing high cognitive demands as it required solving three different types of tasks (sequentially but with a random order of trials, therefore involving a high proportion of task switching situations).

Cognitive load-dependent effects of the HD-tDCS protocol

The second aim was to explore how manipulations of cognitive load would affect the effect of the established HD-tDCS protocol on the EV decrement. This was explored in **Study II** by combining a manipulation of cognitive load (in addition to the data from the triple task from Study I, low and medium load conditions were created through a single and dual task) with the HD-tDCS intervention. Here, two main objectives had been established. Firstly, we expected (**A2-O1**) to replicate the effect of manipulating cognitive load in the sham conditions as observed in a prior study (Luna, Barttfeld, et al.,

2022). Namely, Luna et al. (2022) observed a pronounced EV decrement in the single and triple task conditions, whereas performance in the dual task remained stable with time-on-task (TOT). However, in the sham condition of the single and dual tasks of Study II, similar significant EV decrements with TOT were observed. Thus, the decrement in the single group was not as pronounced as expected, and in the dual task group, a decrement was observed whilst stable performance was expected.

The second objective (**A2-O2**) was based on the expected effect of tDCS on the behavioural effects that were not replicated. We expected a mitigated EV decrement in the single task group receiving anodal HD-tDCS over the rPPC, and no effect of tDCS in the dual group (as no EV decrement was expected). However, we observed no effect of anodal HD-tDCS over the rPPC on the EV decrement neither in the single nor the dual task load conditions. In this study, thus, based on the similar EV decrement, the single and dual task conditions were grouped together into a condition of low demands. Nonetheless, it is worth pointing out that a slight detrimental effect of tDCS seemed to be apparent in the condition of lowest demand (i.e., the single task). A non-significant tendency for this effect was observed when comparing the linear decrement or the overall hit rate between groups. Moreover, a significantly lower overall sensitivity (i.e., the ability to distinguish signal from noise) was observed in the group performing the single task and receiving anodal HD-tDCS, compared to participants in the sham condition. We highlight this here as it will gain further relevance with the subsequent results that account for neuroimaging data.

Understand the efficacy of the rPPC HD-tDCS protocol through neuroimaging data

To better understand the prior effects (and lack of effects) of HD-tDCS on the EV decrement under the different cognitive load conditions, we inspected neuroimaging data at different levels through the third aim. Firstly, in **Study I**, we replicated prior findings of the effects of the HD-tDCS protocol on the power of oscillations in the alpha band (**A3-O1**). As was observed by Luna et al. (2020), the increment of alpha power from the first to the last task block observed in the triple task condition was significantly reduced in the parietal region by the HD-tDCS protocol. Secondly, when

further exploring different frequency bands (**A3-O2**), it was observed that gamma power also increased with TOT, which was further increased by HD-tDCS, especially in the frontal region. As this was not explored by Luna et al. (2020), **Study I** aggregated EEG data from Luna et al. (2020) and observed that the same effect with gamma power was observed.

To further link these results with the behavioural outcomes of the HD-tDCS protocol in the triple task condition (**A3-O3**), the effect of the stimulation protocol on EEG measures was summarized in one index: the $Alpha_{parietal}/Gamma_{frontal}$ index. When participants were split-half divided into showing a decrement or increment of the $Alpha_{parietal}/Gamma_{frontal}$ index index from the first to the last task block an interesting dissociation was observed. Participants with a decrement of the $Alpha_{parietal}/Gamma_{frontal}$ index showed a moderate vigilance decrement, which was not affected by HD-tDCS. However, participants with an increment in the $Alpha_{parietal}/Gamma_{frontal}$ index showed a pronounced EV decrement in the sham condition, which was not only mitigated but abolished in the HD-tDCS group. While not presenting a causal explanation, this result offers a first look at a potential indicator of relevance along the tDCS-EEG-behaviour axis, which with further research could aid in understanding tDCS efficacy in a more nuanced way.

Recent advances that permit exploring EEG data in further detail, namely the parametrization of power spectra into their periodic (oscillatory) and aperiodic (non-oscillatory) contribution (Donoghue, Haller, et al., 2020), highlighted some shortcomings of the analyses of EEG data performed in Study I. The aperiodic exponent (the slope of the power spectrum irrespective of the presence of peaks at certain frequencies) can reflect the neural balance of excitation and inhibition (E/I, Ahmad et al., 2022), whereas, the aperiodic offset (the intercept of the spectral slope) can reflect the spiking of larger populations of neurons (Manning et al., 2009). Therefore, by not accounting for the potential contribution or confounding of aperiodic variables (Manning et al., 2009), the results observed in alpha and gamma power in Study I could be reflecting a more nuanced effect. Furthermore, recent evidence of the relevance of aperiodic markers being predictors of outcomes in studies using other forms of transcranial electrical stimulation, mainly transcranial random noise stimulation (tRNS,

Dakwar-Kawar et al., 2023; Sheffield et al., 2020; van Bueren et al., 2023), further motivated this exploration.

Therefore, in **Study III**, the contributions of periodic and aperiodic data in explaining the outcomes of the HD-tDCS protocol were explored separately. Firstly, the potential contribution of parametrized periodic and aperiodic markers as mediators in the effect of tDCS on the EV decrement was explored (**A3-O4**), as a means of establishing a potential mechanistic explanation (Harty et al., 2017). The results revealed opposite mediated effects for the single and triple task conditions via the change of the aperiodic exponent extracted from a higher frequency range (30-45 Hz). In both tasks, a decrement of the exponent was observed (reflecting an increment of E/I). However, in the triple task, this increment of E/I was associated with a mitigated EV decrement, whereas in the single task, a detrimental effect on the EV decrement was observed. Nonetheless, these results should be interpreted with caution and still require further research, as the results were only obtained as part of a parallel mediation model across all the extracted aperiodic variables but were not observed in simple mediation models. Furthermore, mediation effects were only significant when considering a directional hypothesis.

Notably, in the single and triple conditions, an opposite indirect (i.e., mediated) effect was observed for the offset (in the 1-35 Hz range for the triple task, and the 30-45 Hz range for the single task). An increment of the aperiodic offset may reflect the spiking of larger populations of neurons (Manning et al., 2009). However, its association with cognitive effects is sparser (Robertson et al., 2019), and its association with the effects of tDCS has not been reported in the literature up to this date, as of our knowledge. Therefore, this antagonistic effect could have potentially concealed the effect observed through the aperiodic exponent and highlights that more research is needed to further understand this effect. Lastly, with the new parametrized data, alpha power in the triple task increased with TOT, and, as was observed in Study I, HD-tDCS significantly reduced the increment. Whilst offering a relevant replication of the effect across different analysis approaches, this was not associated with behavioural effects.

Study III also explored another objective, which was the potential effect of periodic or aperiodic variables at baseline (i.e., during the first task block

prior to the onset of the tDCS protocol) on tDCS outcomes (**A3-O5**). However, against prior findings using other tES techniques (namely, transcranial random noise stimulation, tRNS, Sheffield et al., 2020; van Bueren et al., 2023), baseline periodic (alpha power) or aperiodic (exponent and offset) data did not moderate the effect of the stimulation protocol on the EV decrement.

Lastly, within the broader aim of obtaining a more nuanced understanding of the effects of tDCS on the EV decrement through neuroimaging, and in line with the prior objective, of exploring baseline values, the potential contribution of the integrity of white matter tracts measured prior to the experiment was inspected (**A3-O6**). A preliminary and exploratory inspection of the data pointed towards the right SLF III, the left SLF II, the Cingulum, and the Splenium of the Corpus Callosum as potentially relevant tracks to be further explored in future analyses, especially along with more data collected by prospective studies.

Findings in context

An integrative view of cognitive load-dependent effects of tDCS

This section aims to integrate the findings of this thesis within the framework of existing models of the vigilance decrement and models that explain the non-linear way tDCS can affect behavioural outcomes. This integration inspects the results under the frameworks of: (i) the resource-control account (Thomson, Besner, et al., 2015) to explain the emergence of the vigilance decrement, (ii) the "two-state" model from Esterman et al. (2013) to account for the neural basis of different processing strategies (and thus also different causes for the vigilance decrement) depending on the level of task demands, and (iii) the stochastic resonance model (Abrahamyan et al., 2011; Miniussi et al., 2013), to account for how the cognitive load-dependent effects interact with the application of the HD-tDCS protocol over the rPPC.

Thomson et al. (2015) stipulate that overall available cognitive resources, as well as the specific level of resources required by a certain task, are constant. While this assumption opens up its own debate, for the sake of simplicity in the following argument, we will follow this assumption. As

illustrated in **Fig. 10.1**, this would lead to different scenarios depending on the cognitive load imposed by the task. In a task with low demands (such as the single task in the present thesis where only EV trials were responded to) the resources required by the task would run far below the overall level of available resources (**A.1**). In contrast, the proportion of required resources from the overall total available would increase across conditions of medium demand[1] (such as the dual load used in the present thesis, **B.1**), and a high demand condition (such as the triple task, **C.1**). Whilst not directly tested in the present thesis, based on prior results in conditions of overtaxing demands (Roe et al., 2016), a fourth hypothetical scenario may emerge, where the required resources exceed the resources that are available (**D.1**).

As hypothesized by Thomson et al. (2015) and empirically tested by Luna, Tortajada, et al. (2022), with TOT, executive control diminishes which causes a gradual redistribution of resources away from task-relevant processes, and more onto task-irrelevant processes, such as mind-wandering; giving rise to the vigilance decrement as performance degrades (see the first column of **Fig. 10.1**). Notably, this re-distribution of resources could also occur due to cost-benefit analyses that render the alternatives of other tasks more attractive as time goes on (Boksem & Tops, 2008; Kurzban, 2016; Kurzban et al., 2013). While the specific reason for the reallocation of resources, or the actual allocation of resources was not directly tested in the present thesis, we observed its effect indirectly through the EV decrement across the different task conditions. Therefore, this posits further avenues of research to more directly assess this relationship, as was accomplished by Luna, Tortajada, et al. (2022).

As proposed by Esterman et al. (2013) different levels of demand may elicit different modes of processing at the neural level. According to these authors, lower demand tasks require an overall less effortful processing mode, but run at the risk of excessive default mode network (DMN) activity inducing more errors; which would represent the redistribution of resources towards off-task or mind-wandering processes (Smallwood & Schooler, 2006), as proposed by Thomson et al. (2015), and also in line with

[1] Note that in **Chapter 7**, based on the behavioural results the single and dual tasks are grouped as low demand conditions in the Discussion section. However, the additional evidence from aperiodic EEG parameters in **Chapter 8**, suggests that they should be differentiated. Hence, here the single task is referenced as low demand, and the dual task as medium demand.

underload theories (Danckert & Merrifield, 2018; Manly, 1999; Robertson et al., 1997; Yakobi et al., 2021). The potential re-distribution of this activity has been depicted in the second column of **Fig. 10.1**. Whilst not informed directly by these theoretical models, we could assume that the lack of differences in the EV decrement observed between the single (low demand) and the dual tasks (medium demand), could be attributed to a different allocation of resources "behind the scenes". The dual task requires monitoring for two different infrequent targets, posing a slightly higher demand on resources, which could mean that there is a lower risk of "slipping out of the task" and into DMN-governed mind-wandering as compared to the single task (**A2 vs. B2**). The more effortful processing combined with a slight loss of resources would explain the similar behavioural outcomes when comparing the single and dual tasks at the behavioural level, without the observed EV decrement necessarily being caused by the same underlying neural processes.

This is further emphasised by the neurophysiological effect we observe from the applied stimulation protocol. In the single task we observe an increment of the E/I balance from pre- to post-stimulation. In line with models of functional targeting or stochastic resonance (Bikson et al., 2013; Miniussi et al., 2013), this increased E/I balance would reflect the tDCS-facilitated depolarization of the resting membrane potential of task-activated near-threshold populations of neurons (Krause et al., 2013; Reato et al., 2019). Given that in this low demand task many free resources are devoted to mind-wandering or to other non-task related processes, and as time progresses, resources required for the task also are devoted to these self-generated thoughts, the application of tDCS may be, in fact, further accelerating this re-allocation of resources to mind-wandering. As in the single task excessive DMN activity posits a risk for worse performance, potentiating this pattern of activity by increasing the E/I balance via tDCS will likely exacerbate the vigilance decrement. This could explain the detrimental effects of tDCS that were observed in **Chapter 8** when accounting for the effect that the HD-tDCS protocol had on the aperiodic exponent in the higher frequency domain. Furthermore, this is supported by the lack of effects of tDCS on EV performance in the dual task, and the lack of effect of tDCS on the aperiodic exponent in this task condition.

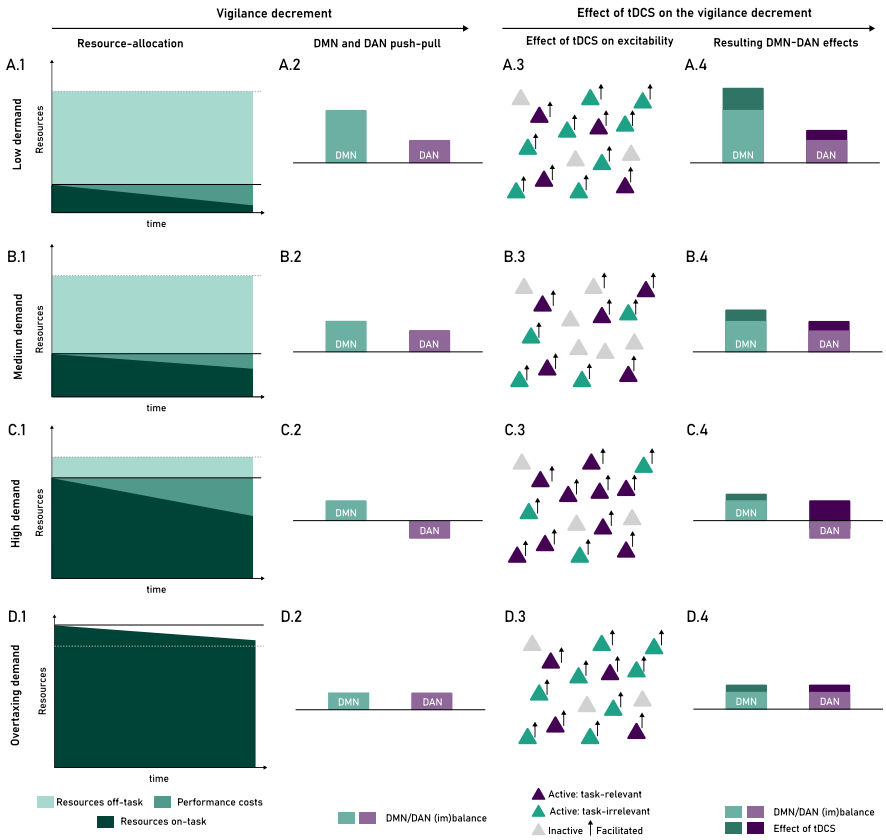


Fig. 10.1 The **first column** represents the allocation of resources towards task or other non-related processes with time-on-task, assuming as proposed by Thomson et al. (2015) that overall available resources and resources required by a certain task are constant, for: **(A.1)** a low demand task, **(B.1)** a task of medium demand, **(C.1)** a high demand task, and **(D.1)** and a task with overtaxing demands. The **second column (A.2-D.2)** represents the proposed push-pull relationship between task-related processing controlled by the dorsal attentional network (DAN) and task-unrelated processes controlled by the default mode network (DMN), that give rise to the vigilance decrement in the different conditions. While for the medium and overtaxing conditions it is less clear, in the low demand condition, the vigilance decrement emerges with excessive DMN activity, whereas in the high load condition, the decrement emerges with insufficient DAN activity (Esterman et al., 2013). The **third column** illustrates how the effects of anodal tDCS will impact near-threshold neurons, and therefore, potentiate the underlying proportion of task-relevant/task-irrelevant activity, indirectly measured through the aperiodic exponent. As depicted in the **fourth column**, applying tDCS **(A.4)** in the low demand task could lead to even higher DMN activity, which could explain the detrimental effects of tDCS, **(C.4)** whereas in the triple task, the increased activity leads to heightened activity of the DAN, acting as a protective factor. Notably, in the conditions of low (**A.3-4**) and overtaxing (**C.3-4**) demand, the pattern of underlying activity may be relatively similar, but in the first case, resources are more clearly devoted to mind-wandering, whereas in the second case, they are devoted to unsuccessful strategies to solve the task.

In contrast to what is observed in the single task or low demand condition under the "in the zone" more effortless processing style, Esterman et al. (2013) observed that tasks that pose a higher demand, operate under a more effortful processing strategy ("out of the zone"), where the vigilance decrement would be explained by insufficient activity in the dorsal attention network (DAN). This, again, ties in with our results observed at the behavioural and neurophysiological level, as the mitigated EV decrement observed with HD-tDCS in the triple task condition was mediated through an increment of the aperiodic exponent in higher frequencies. Thus, in this task condition, we believe that the increased E/I ratio shields the DAN from being underactive, or at least, lessens its reduction in activity with TOT, mitigating the vigilance decrement observed in the triple task condition (**A2-4**).

Lastly, while not directly tested in the present thesis, we hypothesize that if demands are further increased up to a level where they are overtaxing, the underlying neural activity may be operating in a chaotic state, where no balance between E/I (i.e., supercritical state, characterized by runaway excitation, Ahmad et al., 2022) nor between DAN and DMN activity is possible, as resources are overpowered. This demand condition, as depicted in **Fig. 10.1.D.3**, would induce a high proportion of task-irrelevant activity, but instead of being devoted to mind-wandering as in the low demand task, it would be devoted to unsuccessful attempts of solving the task. If this pattern is further reinforced by facilitating the firing of near-threshold neurons, no beneficial effects will be achieved. On the contrary, as observed by Roe et al. (2016), a detrimental effect of tDCS may be observed.

This potential explanation highlights a further shortcoming in predicting tDCS outcomes. The use of an HD-tDCS protocol and its online application in combination with a task, allow for higher focality (Edwards et al., 2013) and functional specificity (Bikson et al., 2013; Miniussi et al., 2013), with the tDCS protocol targeting near-threshold neurons activated by the task. However, the consequences of the vigilance decrement, depending on the demand of the task, will produce different parallel processes. Thus, if the activity induced by the task is not in a higher proportion related to the task, but rather unfavourable signal-to-noise ratio is present due to mind-

wandering (low demand) or failed iterations to solve the task at hand (overtaxing demands), the task goals will likely not be met, and a detrimental effect of tDCS can be observed. This latter scenario can be further tied in with the "off-task" state described by Mittner et al. (2016), during which increased overall network activity is observed, reflecting the consideration or exploration of alternative behavioural responses. Mittner et al. (2016) further link this state to high tonic release of norepinephrine from the locus coeruleus (LC-NE), coupled with a low phasic response (i.e., high activation that is not directed or coupled to any specific stimulus). This ties back to the role of LC-NE commanded effect of arousal, acting as a filter for the input of task-relevant and irrelevant information described by Esterman & Rothlein (2019). In the case of overtaxing demands, the arousal-based filter would permeate to much information, whereas in a low demand task, the opposite occurs.

These results highlight the importance of considering and better studying the pattern of brain activity induced by the task performed online to the application of tDCS. This offers a potential integrative view of the obtained results, and a speculative explanation of their mechanisms (extended into untested terrains), highlighting potential avenues for further research.

Lastly, this potential interpretation of the results emphasises that the increased specificity achieved by functional targeting (Bikson et al., 2013) has its limitations: as anodal tDCS will affect the near-threshold neurons activated by the task, but indistinctively affect both, task-relevant processes, and other processes, activated indirectly by the task, that actually do not serve the task goals, as would be the case of mind-wandering (Smallwood & Schooler, 2006). However, while prior studies exploring the association of the aperiodic exponent as a measure of the E/I balance suggest that a higher E/I balance emerges when comparing sleep or rest state to active engagement in a task (He et al., 2010; Lendner et al., 2020; Podvalny et al., 2015), the findings associated with cognitive demands or difficulty seem to be more mixed (Ouyang et al., 2020; Pathania et al., 2021; Waschke et al., 2021), and have currently not been explored in regards to the vigilance decrement.

Contribution of the parametrization of EEG data

As highlighted in the previous section, the integration of parametrized EEG data aids in further understanding the mechanisms behind the cognitive load-dependent effects of tDCS on the EV decrement. Whilst in Study I, a relevant dissociated effect had been observed by factoring in the change in the $Alpha_{parietal}/Gamma_{frontal}$ index, from what was observed in Study III, the contribution of the "coarser" approach to obtaining the power within each frequency may have actually confounded periodic and aperiodic contributions. The results on alpha power observed in Study I, hold up when inspecting purely periodic contributions (only peaks above the aperiodic exponent) within this frequency range. Namely, we observed an increment of alpha power from the first to the last task block, in line with prior findings (Boksem et al., 2005a; Craig et al., 2012; Hemmerich et al., 2023; Luna et al., 2020), which was reduced with anodal tDCS, in line with the findings from Luna et al. (2020).

However, regarding gamma power, we observed in Study III that there were few observations of "true" gamma (peaks above the aperiodic exponent in the 30-45 Hz range), whereas tDCS had a significant effect on the change of the aperiodic exponent in that range. Thus, these results suggest that what was reported as changes in gamma power in Study I, likely corresponds to a change in aperiodic parameters (mainly the aperiodic exponent in the higher frequency range) instead. The lack of "true" gamma observed in the data, hindered the exploration of its role as a mechanism in the effects of tDCS on the EV decrement. Furthermore, the null findings when this approach was completed with oscillations in the alpha band, clashed with theories on the oscillations supporting the vigilance decrement. As reviewed in more detail in **Chapter 1**, orchestrated by oscillations in theta power (Clayton et al., 2015a; Fiebelkorn & Kastner, 2019; Helfrich et al., 2018), oscillations in the alpha band have been attributed to the inhibition of task-irrelevant processes, whereas gamma has been attributed to the re-activation of task relevant-processes (Clayton et al., 2015a). A potential explanation for not observing a link to the behavioural effect in the present data may be due to the oscillatory contributions playing a more complex role that could not be grasped in the present study (e.g., event-related instead of global effects or more complex interactions of

different aperiodic and periodic contributions). While the second approach to inspect the EEG data (i.e., parametrization of the power spectrum vs. more coarse extraction of power in different bands) is evidently truer to the actual data, both approaches may offer relevant complementary information with future refinements.

Individualized adaptation of cognitive load

Another point of interest raised by the results from the present thesis, as highlighted in the previous section is the high sensitivity of tDCS efficacy to specific levels of cognitive load. This could help inform future research to adequately adjust cognitive load levels if a mitigation of the EV decrement is pursued.

What could help further refine these results is to step beyond pre-defined categories of low, medium, high, or overtaxing demands, and instead, employ a performance-based categorization of task demands. While not directly focused on vigilance or sustained attention, Vergallito et al. (2018) observed interesting findings on working memory and motor performance. An initial session in the experiment was used to assess participants' specific levels of demand; observing that by increasing cognitive demands tailored individually, performance declined (Vergallito et al., 2018). The application of anodal tDCS over the rIFG further impaired performance in the highest demand condition (Vergallito et al., 2018). Furthermore, Dockery et al. (2009) reported detrimental effects of anodal tDCS during the initial learning stages of a task, where again, an overload or chaotic processing is likely to occur due to the lack of familiarity and practice with the task. These results align with the proposed idea that enhancing excitability via tDCS in a system that is in a chaotic state due to not being able to cope with task demands will yield detrimental results, as tDCS cannot specifically target task-relevant processes.

Overall, these results suggest that, whenever possible, task demands should be taken into account, and specifically assessed and adjusted on an individual level. This might be especially fruitful in clinical interventions where multiple sessions are used and tDCS is normally combined with cognitive training as reviewed in **Chapter 3** (Breitling et al., 2016, 2020; Y.

Liu et al., 2021; Park et al., 2013; Sotnikova et al., 2017; Westwood, Criaud, et al., 2021). The training effects facilitated by tDCS will likely be maximised, if during the training, demand levels are gradually and individually adjusted, to avoid creating situations of cognitive underload, where tDCS may be more likely to enhance mind-wandering or other task-irrelevant processes, or situations of cognitive overload, on the other hand, where tDCS will likely enhance the underlying error-prone and chaotic processing.

A potential role for cathodal tDCS?

In line with the previous idea, it must be considered that there will be cases where the cognitive demand of a task is fixed and does not permit a gradual adjustment during an intervention. In those cases, a different strategy may be more useful. The above-mentioned study by Dockery et al. (2009), reported that, during the initial stages of more error-prone and trial-and-error processing when learning a new task, where anodal tDCS had a detrimental effect on performance, cathodal tDCS seemed to offer a benefit. It might reflect a way of reducing general neural noise to help the signal (i.e., task-relevant processes) to emerge (Antal et al., 2004; Miniussi et al., 2013). Thus, when the cognitive demands of a task cannot be adjusted to an adequate level, then cathodal tDCS could serve to reduce the excessive noise of underload-induced mind-wandering, or overload-induced criticality or chaos.

This is, however, only a speculative proposal, which would require further research. Current evidence is not clear, as Roe et al. (2016), for instance, observed the same detrimental effect of tDCS with over-demand with both active protocols (i.e., anode over rPPC and cathode over lPPC, and vice versa). However, here again, the potential antagonistic effect of the "return" electrode in the other hemisphere may be concealing potential effects (Antal et al., 2015).

Furthermore, whether cathodal tDCS could also help in reducing task-irrelevant thought seems to be less supported by current evidence. Whilst designed with a different purpose, studies aiming at inducing mind-wandering, have observed that cathodal tDCS over the right inferior parietal lobe (IPL) had either no effect on mind-wandering propensity (Coulborn et

al., 2020), or led to an increase of task-unrelated thoughts (Filmer et al., 2021). Moreover, a recent meta-analysis suggests that, whilst the current evidence is not highly reliable, anodal tDCS over the rIPL may potentially reduce mind-wandering propensity.

The rPPC and beyond: charting new territories for tDCS protocols to mitigate the EV decrement

The results collected in the present study lend support to the viability of the rPPC as a target of tDCS to mitigate the EV decrement. This finding aligns with the potential role of the highly interconnected rPPC (Hagmann et al., 2008) as a *relay switch* (Giacometti Giordani et al., 2023) between task-relevant processes subserved by the DAN (Corbetta & Shulman, 2002; Esterman et al., 2013), or the frontoparietal network (FPN, Unsworth & Robison, 2017), and self-referential and task un-related processes, supported by the DMN (Menon & Uddin, 2010; Unsworth & Robison, 2017), overall orchestrated by the central executive network (CEN, Menon & Uddin, 2010).

However, while the viability of the rPPC as a potential target to mitigate the EV decrement can be supported by the present results, given the lack of an active control group (i.e., targeting another brain region with anodal HD-tDCS), or the exploration of different potential targets for tDCS in the present thesis, it cannot be claimed that it is the only area to hold this potential. In fact, Luna et al. (2020) observed similar behavioural effects to those obtained by the rPPC protocol, by stimulating the right dorsolateral prefrontal cortex (rDLPFC); namely a mitigated EV decrement in the standard ANTI-Vea task. Moreover, as reviewed in the introductory chapters by the large heterogeneity, not only among specific stimulation parameters but also the regions targeted with stimulation, we currently do not have a consensus on a tDCS protocol that is unequivocally the most appropriate to mitigate the vigilance decrement. Mitigatory effects with tDCS over the rDLPFC have also been reported in prior studies (Brosnan et al., 2018; Leffa et al., 2022; Sacco et al., 2016; Shaker et al., 2018). These promising findings in the rPPC and rDLPFC are likely due to the targeting of right-lateralized attentional networks (Bartolomeo & Seidel Malkinson, 2019; Langner & Eickhoff, 2013). However, other studies across healthy and clinical

populations, as reviewed in **Chapters 3** and **4**, have observed beneficial effects of tDCS on vigilance performance across healthy and clinical populations by targeting the left frontal eye fields (lFEF, Gan et al., 2022; Nelson et al., 2015), right inferior frontal cortex (rIFC, Breitling et al., 2016, 2020), but even more prominently the left DLPFC (Alfonsi et al., 2023; Liu et al., 2021; McIntire et al., 2014, 2017; Nelson et al., 2014; Sakai et al., 2014; Ulam et al., 2015).

Furthermore, while the present beneficial results of tDCS over the rPPC align with findings observed in a prior study in our laboratory (Luna et al., 2020), they stand in contrast with other findings of null (Coulborn et al., 2020) and detrimental effects (L. M. Li, Leech, et al., 2015; Roe et al., 2016) of anodal tDCS over the rPPC. These discrepancies could be explained by the diverging use of montage between studies, especially the use of conventional tDCS, where together with the effect of the anode over the rPPC, the potential confounding effects of the cathode over the contralateral PPC (L. M. Li, Leech, et al., 2015; Roe et al., 2016), or the more diffuse induced e-field by using a return electrode that was not located over the brain (e.g., cheek, Coulborn et al., 2020) must be considered as well. However, in addition to the differences among protocols that could explain the diverging effects, the online task and thus also the outcome measure used to assess the efficacy of the tDCS protocol seems to contribute to this variability (Li, Uehara, et al., 2015).

Given the seeming specificity to the triple task condition of the efficacy of the rPPC protocol in the present thesis, the different cognitive load conditions might not only benefit from stimulation protocols with different polarities, as suggested above but also from charting new territories as potential targets. The single task condition employed in the present thesis may be more akin to the sustained attention to response task (SART, Manly & Robertson, 2005) or Mackworth clock test (MCT, Lichstein et al., 2000), used among many of the cited studies (Adelhöfer et al., 2019; Brosnan et al., 2018; Coulborn et al., 2020; Dai et al., 2022; Filmer, Griffin, et al., 2019; McIntire et al., 2014, 2017). This could open up future avenues of research to find specific tDCS targets that maximize results at different cognitive load levels, considering its interaction with the pattern of underlying neural activity.

Open questions, limitations, and future lines of research

In this final section, we will outline potential future research directions stemming from the results and limitations of this thesis, as well as broader open questions that warrant future investigation.

Improving experimental designs for better predictions

One first critical aspect concerns the sample size employed in the different studies in the present thesis. While the overall sample is substantial, the division into experimental conditions greatly limits the analyses to be performed. As illustrated in Chapters 3 and 4, sample sizes vary greatly between studies, and may contribute to the heterogeneity of effects observed and the difficulty in replicating findings (Filmer et al., 2020; Guerra et al., 2020). Further research should employ larger sample sizes, or within-participant designs, where more fine-grained responsiveness to tDCS can be assessed, and the high variability induced from modulating factors of the vigilance decrement and the effects of tDCS can be better controlled.

Furthermore, the use of a within-participant experimental design instead of the between-participant design used in the studies from the present thesis could aid in more clearly identifying tDCS-related changes from other factors of variability (Steingrimsdottir & Arntzen, 2015). If we assume a relatively low intra-participant variability in within-session vigilance performance (Luna, Roca, et al., 2021), and EEG response to the task (Ip et al., 2018), within-participant designs could aid in detecting factors that determine responsiveness to tDCS and potentially aid in predicting responsiveness to tDCS at an individual level.

A closer look at EEG data

A further aspect that posits a limitation to the results observed in the present thesis is that the EEG data is limited to the information gathered from 6 EEG channels, distributed along frontal and parietal regions of the right hemisphere. Despite this limitation, we have been able to monitor tDCS-induced effects as well as regions relevant to vigilance itself (Langner & Eickhoff, 2013). However, as prior evidence has established, the effects of

tDCS can range beyond the targeted area (Cosmo, Ferreira, et al., 2015; Luft et al., 2014; Morya et al., 2019) in what are considered network activity-models of tDCS (Fertonani & Miniussi, 2017). While a certain right-lateralization of vigilance has been established (Koski & Petrides, 2001; Langner & Eickhoff, 2013; Malhotra et al., 2009; Singh-Curry & Husain, 2009), the structural DWI data collected in this thesis showed interesting links in left hemisphere structures. Moreover, the potential role of left hemispheric structures have been highlighted more recently for attentional processes (Mengotti et al., 2020) and mind-wandering (Giacometti Giordani et al., 2023). Therefore, future research with greater coverage of different brain regions will be more informative about whole-brain effects, and potential specific effects in the left hemisphere.

Apart from increased spatial resolution, future research using EEG data in combination with tDCS protocols could benefit from a higher temporal resolution as well. As has been done recently with periodic EEG data in the ANTI-Vea task (Luna et al., 2023), event-related data in relation to aperiodic components could further our understanding of its interpretation. In fact, by exploring stimulus-induced changes in aperiodic EEG activity, Gyurkovics et al. (2022) observed that infrequent stimuli induced a steeper spectral slope (lower E/I balance) than frequent stimuli. While due to the coding of data, this could not be observed in the present thesis, future research could explore whether pre- and post-stimulus aperiodic EEG data could enhance our understanding of the vigilance decrement.

Another aspect to consider in regard to the EEG data collected in the present thesis is that, given that it was collected during the performance of the behavioural task, it has the advantage of being highly informative of the brain state induced by the task, whilst potentially entailing the risk of containing too many "layers" to actually be informative. Different overlapping and interacting effects may be registered simultaneously: (i) the processing of the stimuli and the required processes to adequately solve the task (Smit et al., 2004a), (ii) parallel unrelated task-irrelevant activity in the target area as well as other and remote areas (Bergmann & Hartwigsen, 2021), (iii) time-on-task or fatigue induced EEG signatures (Smit et al., 2004a), and (iv) more purely electrophysiological effects of tDCS. Furthermore, practice effects and strategy changes could also conflate EEG

measures (Smit et al., 2004a). Whilst the former was relatively controlled in the present thesis, due to the extended practice block that participants performed prior to starting the experimental task, the former is not accounted for and could be adding heterogeneity to the observed effect.

The interaction of these different effects may become impossible to disentangle. While this inherent problem cannot be solved in itself, two avenues to better understand different contributions could be considered in future research. One first aspect would be the above-mentioned increased spatial (larger electrode array) and temporal resolution (inspect event-related data) of the recorded EEG data. A second aspect to provide more clarity in future research could be the additional collection of resting-state EEG (rs-EEG) data before and after the completion of the task and administration of tDCS. The rs-EEG data could serve to differentiate tDCS-induced effects that outlast the stimulation protocol and could potentially be better visible in absence of ongoing task-processing. More importantly, a parallel contrast between the on-task and rs-EEG data might bring us closer to understanding and disentangling neural signatures that serve as potential mechanistic explanations from those that co-occur but lead to no causal explanations. Potentially with rs-EEG data, better predictions from the baseline brain-state on tDCS efficacy data could be made (Sheffield et al., 2020; van Bueren et al., 2023). Furthermore, the pre-task rs-EEG data, specifically, could potentially be integrated with pre-stimulation DWI data, as a means to better characterize basal predictors of neuromodulation through a multimodal approach (Garcés et al., 2016).

The "behind the scenes" of the vigilance decrement

In addition to the use of neuroimaging as described in the present thesis, the use of direct assessments of resource consumption as well as self-reported mind-wandering, could help further elucidate the effects of what occurs "behind the scenes" of the vigilance tasks at different levels of cognitive load, as well as expand and validate some of the more speculative interpretations of the present data.

Resource consumption could be recorded by assessing the brain's metabolic rate in response to the vigilance task and the application of tDCS

through the use of near infrared spectroscopy (fNIRS, Borragán et al., 2018), simultaneous tDCS and functional magnetic resonance imaging (fMRI-tDCS, Antal et al., 2011), functional transcranial doppler ultrasound (fTCD McIntire et al., 2014), or positron emission tomography (Pardo et al., 1991; Rudroff et al., 2020).

On the other hand, while mind-wandering has been the focus of tDCS studies (Chaieb et al., 2019; Coulborn et al., 2020; Filmer et al., 2021; Filmer, Griffin, et al., 2019; Nawani et al., 2023), it has not been explored in detail as a further measure to better understand how resources re-distribute towards this more self-referential process throughout the task to explain the vigilance decrement. A recent study has proposed a dissociation between mind-wandering and the vigilance decrement, as the application of anodal tDCS over the lDLPFC increased the propensity to mind-wander, but did not have effects on behaviour (Martínez-Pérez et al., 2023). This highlights the need for further research to better understand the interaction or independence of mind-wandering and the vigilance decrement. Given the reliance of vigilance and mind-wandering processes on wide-spread regions of the brain, stimulation protocols with multiple different foci of active HD-tDCS could potentially bridge this gap in the future (Fischer et al., 2017). A future better grasp of mind-wandering might encompass its combined measure through direct but subjective self-reports (Weinstein, 2018) and other complementary objective but indirect measures of task engagement, such as eye movements (Krasich et al., 2018).

Subjective beliefs about tDCS: placebo and nocebo effects

After completing the experiment and filling out the post-tDCS questionnaire on sensations associated with stimulation (Fertonani et al., 2015) to ensure that blinding was effective, debriefing participants about the experiment often sparked interesting conversations and questions. Their personal experience and background can often help identify potential confounding variables that could be better controlled in future studies. Among these factors are the subjective beliefs one has about stimulation. These are generally addressed in the post-stimulation questionnaire by inquiring if the participant believes to have received *real* or *placebo*

stimulation, to which either option, as well as "I don't know" can be answered.

In addition to comparing the sensations associated with the sham and real protocol, to ensure that they do not diverge between groups, this final question can provide further evidence of whether blinding of the stimulation condition was effective. The standard approach to reporting results from this last question was to provide the "correct guess rate", i.e., indicate the percentage within each stimulation group that correctly guessed the stimulation condition that they really belonged to in the experiment. However, Fassi & Cohen Kadosh (2021) have raised a relevant issue with this manner of reporting and assessing blinding. While it is adequate in cases where the correct guess rate is around 50% in each group, if it is above that, it would actually indicate that participants may have been aware of the group they belonged to, compromising the study's blinding. As a countermeasure, Fassi & Cohen Kadosh (2021) propose to use the "active stimulation guess" rate instead, i.e., the percentage of participants within each group who believed to have received active stimulation. To conclude effective blinding, this guess rate should be similar across both groups (Fassi & Cohen Kadosh, 2021).

This debate has sparked further inspection of the potential influence of these subjective beliefs on the outcomes of a tDCS protocol. In a reanalysis of publicly available data from prior studies, it was observed that both subjective and objective active stimulation conditions predicted lower inattention scores following a tDCS intervention in adults with attention deficit hyperactivity disorder (ADHD, Fassi et al., 2023). In a re-analysis of data studying the effect of tDCS on mind-wandering propensity, subjective stimulation better predicted outcomes (Fassi et al., 2023; although see for a rebuttal: Gordon et al., 2022). While the specific role of subjective beliefs about stimulation is not yet clear, and it is likely subject to large inter-participant variability, it points towards an additional aspect to consider in controlling and understanding the effects of tDCS on behaviour. Tentatively, we have plotted the EV decrement as a function of the cognitive load manipulation and either objective (i.e., actual allocation of stimulation condition in the experiments, **Fig. 10.2.A**) or subjective stimulation (i.e., participants response to the final question of the post-tDCS questionnaire,

Fig. 10.2.B). While it suggests a potential reversal of the effects (e.g., participants in the triple task who believed to be receiving active stimulation show a more pronounced EV decrement than those who believed to be receiving placebo stimulation) between the objective and subjective conditions, further inspection of this outcome lies beyond the scope of this thesis but serves to highlight a potential avenue for further research[2].

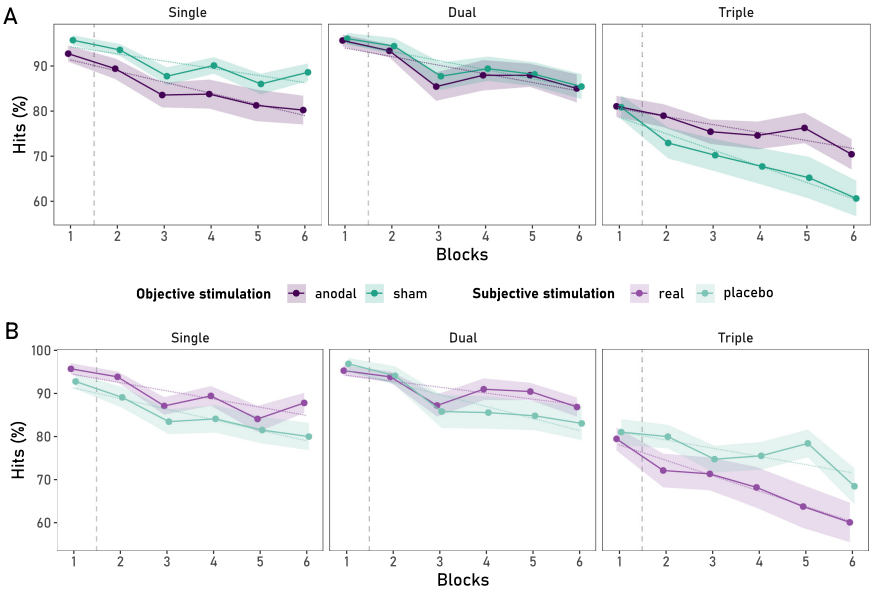


Fig. 10.2. **(A)** EV decrement as a function of task type and *objective* stimulation condition. **(B)** EV decrement as a function of task type and *subjective* stimulation condition. *Note.* The shaded ribbons represent the standard error of the mean (SEM).

A last point in regard to subjective beliefs pertains to a personal observation from the post-debriefing conversations with participants mentioned above. While most participants seem to believe that the application of stimulation will aid them in their performance of the task, a fraction of participants reported to have believed that the stimulation would in fact negatively affect their ability to perform the task, i.e., the nocebo effect (Benedetti, 2014).

[2] Note that the differences between the percentage of participants believing to belong to the active condition in the two different stimulation conditions were not significantly different in Study I and Study II (see the **Blinding Efficacy** sections in **Chapters 7** and **8** respectively). Thus, the blinding efficacy of the studies was ensured. However, the plotted results should be interpreted cautiously as they might be skewed by potentially uneven distributions of the sample in the re-grouped data (as a slightly higher number of participants who reported believing to have received real stimulation when in the objective anodal condition, compared to the sham group).

While this is based on qualitative accounts, which were by no means collected systematically nor in all cases; they spark an interesting and neglected point of view in the above-mentioned debate on subjective beliefs. The nocebo effect is largely overlooked in medical fields (Greville-Harris & Dieppe, 2015), and almost no reports of its assessment have been established in the tDCS literature (Braga et al., 2021).

While this debate is ongoing and far from establishing any firm conclusions, I would argue that it is an important aspect to incorporate in further research. For example, in the standard post-tDCS questionnaire (Fertonani et al., 2015), an additional question about the expected direction of effects could be included. This could, by accumulating data across different studies over time, potentially provide a more systematic insight into the impact of beliefs on tDCS outcomes.

A critical re-examination of vigilance

In Chapter 1 of this thesis, we disentangled a working definition of vigilance, attempting to separate it from other terms with which it is often used interchangeably. In observing the results from the present thesis and, specifically, the high sensitivity to changing task demands and the application of tDCS on the same measure of executive vigilance, the integrity of the studied phenomenon could be questioned. Are we really measuring executive vigilance per se in the three different task versions? If we refer back to the distinction provided in Chapter 1, based on the *intensity* continuum, vigilance is attributed to the detection of one specific target that appears infrequently, whereas sustained attention would require more active and ongoing processing towards a broader set of stimuli (van Zomeren & Brouwer, 1994; Zimmermann & Leclercq, 2002). While the outcome measure for executive vigilance has been held constant in the different cognitive load conditions in this thesis (i.e., the hit rate in detecting vertically displaced arrows), could the triple task condition be considered more akin to a sustained attention task? Given the different patterns of responsiveness to tDCS, an alternative explanation to the effects is that the efficacy of mitigating the EV decrement in the triple task condition could be in fact that it is targeting a different cognitive process. While this cannot be tested in the present data, it opens up a relevant debate to be considered

for the design of future experiments and real-life applications of tDCS interventions.

Moreover, more critical accounts of the vigilance decrement have suggested that it may, in fact, be an iatrogenic phenomenon (Hancock, 2013, 2017). Hancock (2013) argues that the vigilance decrement emerges due to the artificial imposition of the vigil itself, stating that it is more an in-lab than a real-life phenomenon. While this critical and recurrent re-inspection of the phenomena we are studying is crucial, and it is true that vigilance is a hard-to-grasp concept, as described at the beginning of this chapter, whether one calls it vigilance or something else, our interaction with the environment requires this process. Nonetheless, this debate raises a relevant point regarding engagement and motivational aspects where in-lab settings may differ greatly from reality, e.g., performing well due to the feeling of being assessed or observed in an experiment may differ greatly from the conscious perception that one's inattention could cause an accident. The complex intersection of motivational (Reteig et al., 2019a) or emotional aspects potentially affecting task performance should be explored in more detail in future research and could aid in developing more ecological assessments of the vigilance decrement (Chuang et al., 2018; Ma et al., 2020), which in turn could help the transference of in-lab validated protocols to real-life scenarios and clinical settings in a more straightforward manner.

Real-life and clinical applications: ethical considerations

It is interesting to note that the historical beginnings of vigilance research—with Mackworth's first studies—and research of tDCS applied to vigilance—with studies from Nelson et al. (2014)—stem from the military or human factors environment. However, this also highlights an inherent problem: the ethical use and application of tDCS and its research outcomes. On the one hand, military research has a clear tie to applying tDCS research on vigilance with a human factors perspective; which can be potentially problematic in its application (Davis & Smith, 2019). This would be the case of applying countermeasures to vigilance and fatigue to justify exploitative labour practices, as well as the ethical/moral ambiguity of applying it more directly in warfighting. If in the wrong hands, the principled human nature to strive

for improvement and re-invention, could be perverted into exploitation and destruction, e.g., under the pretence of avoiding human errors in air-trafficking, one could reduce much-needed breaks or adopt inhumane working hours.

Likewise, more "honourable" applications, such as those in clinical settings, are also not free from issues. The overselling of findings, that, as reviewed in **Chapter 3** are, as of now, still largely unclear as far as identifying a specific protocol that can target attentional deficits, can lead to malpractice and the exploitation of desperate patients and families on the lookout for a solution. Especially critical here is the commercial availability of devices for unregulated self-application, ranging from home use kits to even do-it-yourself approaches where the stimulator is built from scratch (Wexler, 2016). By searching tDCS on the Amazon store website, for example, one could purchase a kit available for $140 that promises stimulation intensities up to 4 mA. Whilst 4 mA falls within the researched safety parameters (Bikson et al., 2016), it is much more sparsely researched and deviates substantially from the current intensities generally used in research (1-2 mA), and incurs the additional risk that no control over safety parameters can be ensured. Furthermore, some of these home kits are sold accompanied by booklets about stimulation parameters to follow, based on single studies (at best) or no evidence at all. Given the variability among outcomes and the many unanswered questions we still have today, the bridge towards widespread clinical and personal use should be crossed when we have sufficient evidence to do so safely and backed up by sufficient evidence (Cabrera et al., 2014; Cohen Kadosh et al., 2012).

Concluding remarks

The thesis aimed to explore the potential of anodal high-definition tDCS (HD-tDCS) over the right posterior parietal cortex (rPPC) to mitigate the executive vigilance decrement. This thesis corroborated the viability of targeting the rPPC with anodal HD-tDCS to mitigate the EV decrement by replicating prior findings (Luna et al., 2020). However, this effect was dependent on the cognitive load imposed by the task performed along with the brain stimulation. The EV decrement under varying conditions of cognitive load was not observed as anticipated: the mitigatory effect was

only observed in a high-demand condition. Neuroimaging data offered additional insights into the effects of HD-tDCS, by observing that: (i) the change in a combined index of the parietal alpha to frontal gamma ratio could stratify responders from non-responders to the tDCS interventions under high cognitive demand, (ii) provide a tentative mechanistic explanation of tDCS effects on the EV decrement via the effect of the technique on aperiodic EEG parameters that can indirectly measure neural excitability changes, and iii) provide a preliminary overview of potential white matter structures that could predict tDCS outcomes.

This thesis contributes to the understanding of the vigilance decrement and the potential of tDCS to mitigate it, highlighting the importance of considering cognitive load and individual differences in neurophysiological responses. Despite mixed results regarding the efficacy of tDCS under different conditions, the research underscores the complexity of brain stimulation effects on cognitive performance and the need for further investigation. The results from this thesis align with the current notion that tDCS applications are not a *"one size fits all"* solution and underscore the need to consider individual performance and neuroimaging data to better predict stimulation outcomes in the future. It highlights that the effects of tDCS are highly sensitive to the underlying pattern of brain activity (Bikson et al., 2013; Miniussi et al., 2013), emphasizing the need to look beyond simple hypotheses of using anodal tDCS to improve performance and cathodal tDCS to impair it (Jacobson et al., 2012), and instead assess and further investigate the intricate relationship between ongoing brain activity and changes induced by tDCS to improve future causal interpretations from tDCS interventions (Bergmann & Hartwigsen, 2021).

Despite the more critical view on stimulation and the expressed opposition to prematurely inflated results being disseminated to the general public for widespread application, we do not echo the more general critiques against the potential effectiveness of the technique (Horvath et al., 2015, for a rebuttal see Antal et al., 2015). We believe the countermeasure to the potential shortcomings is not a halt of its investigation, but rather a change in its pace (Frith, 2020), by employing all means to produce more reliable outcomes, such as larger sample sizes, pre-registrations, replications, adequate control conditions, among many others (Bergmann &

Hartwigsen, 2021; Filmer et al., 2020). With these considerations in mind, we certainly believe that this technique can make a major advance in our understanding and management of the vigilance decrement in the future, one small step at a time.

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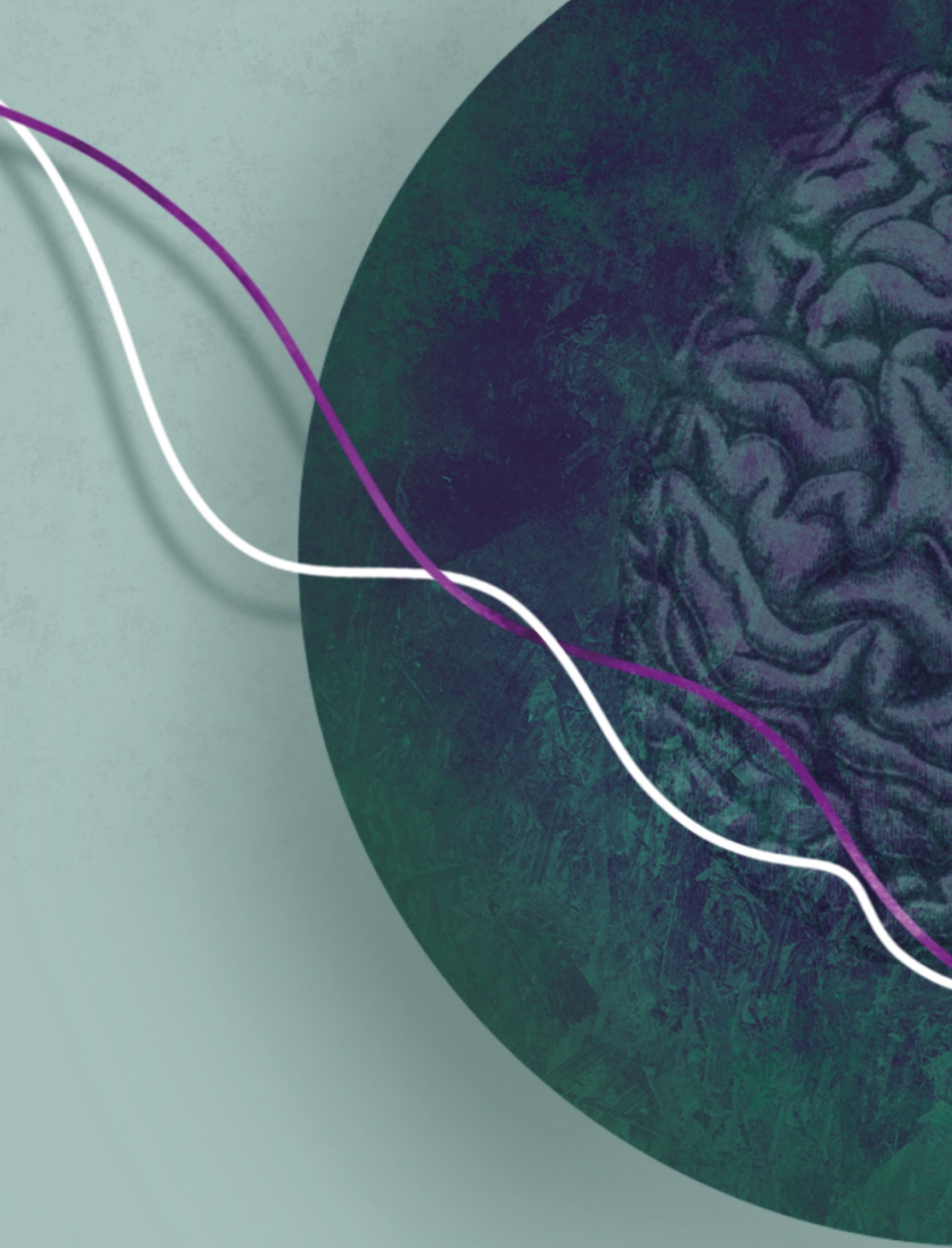

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