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ATTENTIONAL ASYMMETRIES THROUGH THE LENSES OF EYE MOVEMENTS: FROM BEHAVIORAL EVIDENCE TO BRAIN STIMULATION

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Declaration

I declare that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this has been reported in the thesis.

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Abstract

Visuospatial attention and its asymmetries have always attracted great interest: plenty of research has focused on lateralized attentional mechanisms in the healthy brain, the asymmetrical spatial biases following brain lesions (e.g., the neglect syndrome), and the possibility of modulating such asymmetries with non-invasive brain stimulation techniques, such as transcranial Direct Current Stimulation (tDCS). In this direction, the study of eye movements can provide direct evidence regarding the way we shift our attention in the surrounding space, i.e., overt attentional processes. The Free Visual Exploration (FVE) task is a simple, ecological, eye-tracking task, shown to reliably detect visuospatial asymmetries both in healthy individuals and patients with neglect. However, compared to other experimental paradigms, the FVE has received little attention as to the factors influencing attentional asymmetries in this task, its relationship with other behavioral paradigms, and, importantly, whether spatial asymmetries during visual field exploration can be modulated by tDCS. The experiments of this doctoral thesis aimed at addressing these issues. Specifically, in Study 1, I investigated the temporal dynamics of FVE in a sample of 60 younger and older adults, showing that pseudoneglect, the typical leftward attentional asymmetry of healthy individuals, in the FVE task is significantly reduced with increasing age and correlates with the performance in a line bisection task, a task most commonly used to assess visuospatial biases. In the experiments of Study 2, I explored the effects of anodal tDCS on the temporal dynamics and exploration asymmetries of FVE, addressing some crucial aspects related to: the stimulation focality (by employing both conventional and High Definition tDCS), differential effects of parietal and frontal stimulations, as well as the state-dependency of the tDCS by considering the impact of baseline performance on tDCS after-effects. Taken together, the results provide a novel behavioral and neuromodulatory characterization of overt attentional orienting in the healthy brain, encouraging future applications of FVE paradigms in clinical and experimental neuropsychological settings, as well as further research into the complexity of tDCS modulation of visuospatial processes.

L'attenzione visuospaziale e le sue asimmetrie hanno sempre suscitato un grande interesse scientifico. Molte ricerche si sono concentrate sull'indagine della lateralizzazione dell'attenzione spaziale nel cervello sano, sulle asimmetrie spaziali conseguenti a lesioni cerebrali (es. negligenza spaziale unilaterale o neglect) e sulla possibilità di modulare tali asimmetrie con tecniche di stimolazione cerebrale non invasive, come la stimolazione transcranica a corrente diretta (*transcranial Direct Current Stimulation*, tDCS). In tal senso, lo studio dei movimenti oculari può fornire prove dirette sul modo in cui orientiamo la nostra attenzione nello spazio circostante (i.e., attenzione esplicita). Il compito di esplorazione visiva libera (*Free Visual Exploration*, FVE) è un semplice compito che si avvale della registrazione dei movimenti oculari per rilevare, in condizioni ecologiche, asimmetrie visuospaziali sia negli individui sani che nei pazienti con neglect. Tuttavia, rispetto ad altri paradigmi sperimentali, è carente l'indagine dei fattori che modulano la prestazione al FVE, tra cui: l'influenza di variabili individuali (es. l'età) sulle asimmetrie esplorative, l'associazione con altri compiti comportamentali e, soprattutto, se tali asimmetrie possano essere modulate da stimolazioni transcraniche dei circuiti frontoparietali. Gli esperimenti di questa tesi di dottorato affrontano queste lacune attraverso l'analisi dei movimenti oculari e la modulazione delle relative asimmetrie visuospaziali mediante tDCS. Nello specifico, nello Studio 1, ho studiato le dinamiche temporali della FVE in un campione di 60 giovani adulti e

anziani, dimostrando che lo pseudoneglect, la tipica asimmetria attentiva verso sinistra che presentano gli individui sani, è significativamente ridotto con l'aumentare dell'età e correla con la performance in un compito di bisezione di linee, un compito standard per misurare le asimmetrie spaziali. Gli esperimenti dello Studio 2 indagano gli effetti della tDCS anodica sulle dinamiche temporali e le asimmetrie esplorative in un compito di FVE, affrontando alcuni aspetti cruciali relativi alla focalità di stimolazione (utilizzando sia la tDCS sia convenzionale che ad alta definizione), gli effetti differenziali della stimolazione parietale e frontale dell'emisfero destro, nonché la "dipendenza" degli effetti tDCS dallo stato individuale, ovvero l'impatto delle prestazione di baseline sugli effetti della stimolazione. Nel complesso, i risultati degli studi forniscono una nuova caratterizzazione comportamentale e neuromodulatoria dell'orientamento attentivo esplicito nel cervello sano, incoraggiando sia applicazioni future dei compiti di FVE in ambito neuropsicologico sperimentale e clinico, sia ulteriori indagini della complessità della tDCS per la modulazione dei processi visuospaziali.

CHAPTER 1

1. Covert and overt attentional orienting: theoretical background

1.1. Introduction

In everyday life, we constantly explore and interact with the surrounding world: attentional processes allow to respond to the external and internal environment by bringing relevant stimuli into the focus of attention (i.e., by orienting our attention), to further analyze, and, ultimately, interact with them. In general, attentional orienting can be experienced and along two dimensions, i.e., overt vs. covert orienting and endogenous vs. exogenous orienting. In fact, we can move the attentional spotlight overtly, by means of eye movements, or covertly, namely without eye movements but still attending peripheral stimuli. Moreover, attention can be shifted voluntarily - endogenously - across the visual field according to plans and intentions. However, behaviorally salient, unexpected, stimuli can automatically – exogenously – attract our attention, possibly interrupting ongoing top-down processes. In the present chapter, I will elucidate the main neuro-cognitive mechanisms behind attention and attentional orienting, paying special attention to the shared neural underpinnings of overt attention and eye movements.

"Attention" is a broad term that encompasses several neurophysiological and cognitive processes. According to a famous model (Posner & Petersen, 1990; Petersen & Posner, 2012), three main networks can be identified, namely, the *alerting* network, the *orienting* network, and the *executive* network.

The alerting network allows to maintain an optimal state of arousal and regulate fluctuations of alertness over the course of the day (i.e., tonic alertness), as well as transient activations in response to salient stimuli that interrupt a state of resting (i.e., phasic alertness). Norepinephrine-mediated activity in cortico-thalamic circuits underpins these processes, with some hemispheric asymmetries between tonic alertness (more right-lateralized) and phasic alertness, more left lateralized (Petersen & Posner, 2012).

The executive attentional network subserves higher cognitive functions whereby attention is needed to exert a control over them, as for instance to filter relevant target stimuli from distracters, to maintain (or to switch between) goal-related mental sets, to monitor our behavior according to these goals and detect potential errors. At least two functionally-related networks for executive control have been identified (Dosenbach et al., 2008): a cingulo-opercular system to maintain a task set, and a frontoparietal system to initiate and switch between tasks and for on-line adjustments of behaviour according to task requirements. Naturally, alerting and executive processes act in concert in everyday life, and more recent evidences point toward a higher degree of overlap than previously thought (see, e.g., Sadaghiani & D'Esposito, 2015 for a perspective on tonic alertness and the cingulo-opercular network).

Finally, the third network conceptualized by Posner and Petersen (1990) is the orienting network. This network, as the name suggests, supports the ability to deploy attentional resources in the surrounding space, i.e., to "guide" our attention both according to internal states or goals and to salient sensory stimuli that may attract our attention automatically. Because of their centrality to the present thesis, orienting processes will be discussed in more detail.

1.2. Neurophysiological bases of covert and overt attentional orienting

In their original work, Posner and Petersen (1990) described the orienting system as a network of cortico-subcortical areas based on human (and animal) lesional studies and early functional imaging works. Specifically, these authors focused on the lateral pulvinar of the thalamus, the superior colliculus and the parietal cortex. They reported that lesions of these three areas would affect three components of attentional orienting with specific impairments of the attentional disengagement - namely the end of preferential processing - following parietal lesions, a deficit in shifting (i.e., moving the attention) after collicular lesions and deficits of selective engagement of attention, that is the beginning of preferential processing, after pulvinar lesions.

The advancements of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), allowed to extend the original "posterior attentional system" by incorporating areas of the frontal cortex, such as the frontal eye field (FEF), an area mainly studied for its role in eye movements (Schall, 2009). In this respect, among the most influential models is the one by Corbetta and Shulman (2002). This model describes two, partially segregated, frontoparietal systems for attentional orienting: a ventral network for bottom-up, stimulus driven orienting and a dorsal network for goal-driven, top-down orienting. Specifically, the dorsal attentional network (DAN) includes the FEF, the Intra

Parietal Sulcus (IPS), and the superior parietal lobe (SPL); it sustains top-down control of attentional processes being responsible for the generation and maintenance of attentional sets to voluntarily drive our attention to goal-relevant locations or features of a stimulus (see also Corbetta et al., 2002 for dorsal network and working memory). Activation of the DAN has been observed with classic cueing paradigms: when the observer is instructed by a central cue (e.g. an arrow) about the location of a forthcoming stimulus, the abovementioned areas show a sustained response to the presentation of such cue, reflecting a top-down orienting of attention even in absence of a subsequent motor response (e.g., an eye movement towards the target). The DAN shows bilateral activations for either the leftward or rightward spatial orienting (e.g., Hopfinger et al. 2000).

In contrast, when attention is exogenously – automatically – captured by highly salient or unexpected stimuli, a more ventral attentional network (VAN) is activated. The VAN includes the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC). The VAN is predominantly mediated by the right hemisphere. Unlike the DAN, this network is not engaged by the activation and maintenance of attentional sets, rather, its activity is specifically enhanced when a target appears at an unexpected location and even when low-frequency stimuli are detected in expected locations. The VAN may serve as an alerting mechanism or “circuit breaker” of the DAN when the ongoing attentional set needs to be changed to evaluate a novel, relevant stimulus. More recently, alternative interpretations on the role of the VAN (especially of the TPJ) have been proposed, showing its involvement in contextual updating and adjustments of top-down expectations (Geng & Vossel, 2013).

After Corbetta and Shulman’s proposal (2002), plenty of research has further characterized the intra- and inter-hemispheric mechanisms of the DAN and VAN, especially in terms of structural and functional connectivity (see Mengotti et al., 2020 for a review). Regarding structural connectivity, tractography works (e.g., Thiebaut de Schotten et al., 2005, 2011), highlighted the centrality of the three branches of superior longitudinal fasciculus (SLF). In particular, the dorsal branch of the SLF, i.e., the SLF I, connects areas of the DAN; the ventral component, the SLF III, mostly connects temporo-parietal and inferior frontal areas of the VAN, whereas the intermediate fibers of SLF II would connect the posterior part of the VAN with the frontal areas of the DAN (see also Bartolomeo et al., 2012). Notably, Thiebaut de Schotten et al. (2011) demonstrated that the degree of lateralization of the SLF II correlated to the spatial asymmetry observed in behavioral tasks.

Moreover, whereas the SLF I showed a symmetrical distribution between the right and the left hemisphere, the SLF III showed a significant rightward lateralization.

fMRI-based functional connectivity was investigated, for example, by Vossel and colleagues (2012). The authors, employing a cueing paradigm, showed top-down functional connections from the IPS to the visual cortex contralateral to valid targets and bidirectional connections between FEFs of both hemispheres. Instead, in the ventral network, invalid cues enhanced bottom-up connections from visual areas to right TPJ, which exerted direct influence on right IFG (part of the VAN) and right IPS (part of the DAN). Functional connectivity of these networks has also been studied from the perspective of magnetoencephalography (MEG) and electroencephalography (EEG), investigating the dynamic synchronizations of brain oscillations within specific frequency bands (e.g., Doesburg et al., 2016; Proskovec et al., 2018).

Corbetta and Shulman's model has been used to explain attentional asymmetries arising from brain damage of the attentional networks, such as in hemispatial neglect. Neglect is a neuropsychological syndrome - commonly associated to right hemispheric lesions - characterized by lateralized and non-lateralized attentional problems, whose hallmark trait is an attentional bias towards the ipsilesional side of space and a reduced ability to process and interact with stimuli on the contralesional side (Heilman et al., 1980). Corbetta and Shulmann (2011) suggested that such a complex pattern of lateralized (biased locus of spatial attention) and non-lateralized deficits (arousal, target detection, and saliency coding) arises from an altered intra- and interhemispheric interaction of ventral and dorsal mechanisms, including the visual cortex. Specifically, lesions of the right-lateralized VAN (most commonly associated to neglect severity) may physiologically hypoactivate the intra-hemispheric functionality of the right DAN, thus increasing the inter-hemispheric inhibitory activity of the left DAN and giving rise to the typical right-sided bias (He et al., 2007). Accordingly, Thiebaut de Schotten and colleagues (2014) showed that degree of damage of the of the SLF II was the best predictor of left spatial neglect. Additionally, neglect deficits are associated to significant large-scale alterations of functional connectivity within the right hemisphere and between the two hemispheres (Baldassarre et al., 2014), which tend to normalize alongside neglect recovery (Ramsey et al., 2016). Taken together, these findings extend and complement the original model of "interhemispheric rivalry" by Kinsbourne (1987, 1994), postulating the existence of two, mutually-inhibiting, interhemispheric vectors for orienting attention to the contralateral visual field. According to Kinsbourne's model, lesions of the right hemisphere would cause an inter-hemispheric imbalance, with the left-hemispheric vector (less inhibited by the right one) leading to the spatial bias towards the right side of space, typical of neglect. Importantly, such inter-hemispheric balance (or imbalance) is the target of non-invasive brain stimulation (NIBS) studies aiming to modulate spatial asymmetries in neglect patients and healthy individuals. These studies will be discussed in the section 1.4.2. of this Chapter.

Asymmetries of visuospatial attention have been consistently observed also in healthy individuals. This is the case of the well-known "pseudoneglect", which consists in a small leftward attentional bias that emerges in visuospatial tasks (Bowers & Heilman, 1980; Friedrich et al., 2018; see Jewell and McCourt, 2000 for a review and section 1.3.1 of this Chapter). Pseudoneglect is thought to emerge from the previously described functional and structural lateralization of frontoparietal networks (Thiebaut de Schotten et al., 2005; 2011), with a prominent engagement of right hemispheric circuits in the majority of right-handed healthy individuals (Fink et al., 2001; Foxe et al, 2003; Cai et al., 2013). For example, an EEG study by Benwell and colleagues (2014) demonstrated the involvement of early stimulus-driven processes mediated by the VAN, more specifically by the right temporo-parietal junction. Moreover, in line with the competition model by Kinsbourne (1987), Bultitude and Davies (2006) highlighted the centrality of inter-hemispheric connections for the emergence of pseudoneglect, with the most activated hemisphere biasing the attentional weight contralaterally. Nonetheless, besides neurophysiological factors, attentional asymmetries in the healthy brain seem to be influenced by environmental (i.e., cultural) factors, such as the reading habits (Chokron & Imbert, 1993; Chokron et al., 1998; Rinaldi et al., 2014). These studies highlight an interplay between hemispheric specialization, handedness, and reading direction (left-to-right vs. right-to-left) in the establishment of asymmetrical biases. For example, Rinaldi and colleagues (2014), testing monolingual Italians (i.e., reading left-to-right) and Hebrew-speaking individuals (i.e., reading right-to-left), showed characteristic (often opposite) asymmetries during the execution of visuospatial tasks.

1.2.1. Shared neural substrates of attention and eye movements

So far, I have discussed the neural mechanisms of attentional orienting and visuospatial asymmetries in the healthy human brain and after a brain damage causing the neglect syndrome. As this PhD thesis investigates visuospatial attention from the perspective of eye movements, in the next paragraphs, I am going to show the shared neural bases of eye movements and orienting processes.

Although orienting has been largely investigated with cueing paradigms of covert attention, such as the classic Posner's cueing detection task (Posner et al., 1980; for details, see section 1.3. of this thesis), spatial orienting in everyday life is nearly always associated to eye movements, in particular saccades and fixations. Saccades, the actual eye movements, are made to bring a given target object into the fovea. Subsequently, the gaze can be hold in order to acquire further information about that target: this stop of the visual field scanning represents a fixation. Evidence from animal, neuropsychological, neurostimulation, and neuroimaging studies converge towards a strong (although not complete) coupling of frontoparietal networks of attentional orienting and eye movements.

Starting from the animal studies, the frontal cortex has received a lot of attention with regards to eye movements (Ferrier, 1874). Early electrophysiological studies in the monkey (Bruce & Goldberg, 1985; Bruce et al., 1985) identified an area containing visuo-motor cells (in the proximity of the anterior arcuate fissure, corresponding to Brodmann's area - BA - 8) whose activation is associated to the preparation and execution of saccades (Moore et al., 2003). This area was accordingly named Frontal Eye Field. The FEF was shown to be a key node, projecting and receiving inputs from other areas of the frontal cortex (e.g., supplementary eye-field and cingulate eye field), temporo-parietal areas and the visual cortex, as well as subcortical nuclei (see also Vernet et al., 2014). With respect to the parietal circuits, different areas of primate parietal cortex have been associated to visual, visuo-motor, and fixation activity. These areas include the BA 7a (putatively corresponding to the human angular gyrus) and the lateral intraparietal area, whose human homologue has been called the parietal eye field (PEF), localized in the posterior IPS (Pierrot-Deseilligny et al., 2004). Importantly, both the PEF and FEF have direct and independent connections to the superior colliculus, a mesencephalic structure playing a main role in saccade initiation and the maintenance of fixation (Munoz and Wurtz, 1992; Pierrot-Deseilligny et al., 2004).

The involvement of frontoparietal circuits in eye movements has also been corroborated by neuropsychological studies in brain-damaged patients. For example, Pierrot-Deseilligny and colleagues (1991a; 1991b) recorded the latency of reflexive saccades towards (pro-saccades) or away (anti-saccades, requiring inhibition of response) from a target in 45 patients with unilateral brain lesions affecting PPC, FEF, or the prefrontal cortex (PFC). The authors found a significant increase of bilateral saccadic latency (i.e., the time needed to initiate a saccade) following lesions of the right PPC, whereas damage to the left PPC induced less severe deficits, mostly affecting saccades to contralesional stimuli. Lesion to the PFC was, instead, associated to a higher percentage of errors related to anti-saccades. Other studies focusing on anti-saccades (e.g., Machado & Rafal, 2004; Gaymard et al., 1999) found increased latencies for bilateral targets and increased percentage of errors towards contralesional targets following FEF lesions. Overall, lesional studies seems to indicate that the triggering of reflexive saccades is mostly under PPC control, with FEF and PFC exerting a top-down control over voluntary saccades (Müri & Nyffeler, 2008; for a review on oculomotor deficits following FEF and PPC damages see, respectively, Vernet et al., 2014 and Pierrot-Deseilligny et al., 2004). However, despite their undeniable values, lesional studies have some obvious limitations. In fact, lesion in a given area is rarely isolated and may, as well, alter the functioning of a broader network of structurally and functionally connected areas. Avoiding these limitations, fMRI studies have provided further evidence showing a functional overlap of networks for attention ad eye movements.

In a seminal study, Corbetta and colleagues (1998) tested their participants in two experimental tasks: in the “shifting attention” task, participants were instructed to endogenously shift their attention to predetermined locations without moving their eyes (i.e., covertly), whereas in the “eye movement” task, they were instructed to attend the same locations, by shifting their gaze overtly. Overall, results showed a strong overlapping activation of temporo-parietal regions (e.g., superior temporal sulcus, anterior and posterior IPS) and a large activation of frontal areas along the precentral gyrus, including the FEF. Similar results were obtained by Nobre et al. (2000), who additionally showed that common frontoparietal circuits were more activated during the covert attentional task, as compared to the eye movement task. Along the same line are the fMRI findings from Beauchamp et al., (2001) and de Haan et al. (2008), who, however, found stronger activation of frontoparietal circuits for overt attentional orienting. Finally, a meta-analysis of 59 studies by Grosbras et al. (2005) confirmed a very high similarity between the activation maps of covert shifts of attention and saccadic eye movements.

It has to be acknowledged that the link between attention and oculomotor processes is still a matter of debate, in particular regarding the differences between endogenous and exogenous shifts of attention. The Premotor Theory of Attention (Klein, 1980; Rizzolatti et al., 1987) proposes a complete functional equivalence of spatial attention and eye movements, with the programming of a saccade being necessary and sufficient for covert orienting of attention. More recent theorizations (Belopolsky & Theeuwes, 2012; Smith and Shenck, 2012; Casteau and Smith, 2019) have confirmed the importance of the oculomotor system for bottom-up exogenous orienting, but argue against such coupling for the endogenous, volitional orienting. Accordingly, a recent study with cueing paradigms by Casteau and Smith (2020) showed that exogenous attention, but not endogenous attention, was impaired when the target appeared beyond the range of saccadic eye movements (i.e., when a saccadic motor plan was not implemented), thus proving the dependency of oculomotor and attentional systems for the exogenous processes.

1.3. Assessment of visuospatial attention and its asymmetries

As introduced, attentional orienting has been mainly investigated along two dimensions, i.e., overt vs. covert attention and endogenous vs. exogenous attention. Several experimental works (e.g., Corbetta et al., 1998; Kincade et al., 2005; Casteau and Smith, 2020) employed covert behavioral paradigms, in order to isolate the sub-components of orienting from oculomotor processes. Covert orienting paradigms have a long-standing tradition, starting from the early works of Posner and colleagues (1978; Posner, 1980). Basically, the participants are instructed to detect peripheral targets by pressing a button, while keeping their fixation at the center of a screen. To test endogenous orienting, the target can be preceded by a central spatial cue (e.g., an arrow) which indicates the side where the target can appear, thus inducing a covert attentional shift. Notably, targets preceded by “valid” - correct - cues (i.e., pointing to the direction of the incoming target location) are associated to faster reaction times (RTs), as compared to neutral cues and “invalid” cues (i.e., pointing to the opposite direction), whereby target detection is delayed and RTs are slower. The same paradigm can be employed to test exogenous orienting by means of peripheral cues, such as flashing the target location briefly before its appearance (Posner & Cohen, 1984). By means of this manipulation, attention is automatically captured at the cued location and, depending on cue validity, benefits (valid cues) or costs (invalid cues) in RTs can be observed. In general, exogenous cues lead to faster shifts as compared to endogenous cues (Jonides, 1981; Mueller and Rabbit, 1989), however the time between the onset of the cue and the onset of the target (stimulus onset asynchrony, SOA) can affect the abovementioned effects of cue validity. For example, the facilitatory effect of peripheral exogenous cues can disappear, or even reverse, so that with longer SOAs responses are slower at the cued location than at the opposite location, the so-called “inhibition of return” (see Lupianez et al., 2006 for a review). Cueing paradigms have also been adapted with more naturalistic, social cues, such as eye gazes looking towards or away from a forthcoming lateralized target (e.g., Friesen & Kingstone, 1998), inducing robust exogenous orienting of attention and associated validity effects (see Frischen et al., 2007, for a review). Lastly, covert cueing paradigms have been adapted to study the efficiency of the three attentional networks by Posner and Petersen (1990), i.e., the Attention Network Task (ANT; Fan et al., 2002) and the Lateralized Attention Network Task (LANT; Greene et al., 2008).

1.3.1. Tasks for pseudoneglect

In section 1.2, I introduced the concept of pseudoneglect, a leftward attentional bias observed of neurologically healthy individuals performing spatial tasks (Bowers & Heilman, 1980). Pseudoneglect has been described in numerous experimental paradigms; among the most employed ones are the bisection tasks, where participants tend to indicate the half of visual (i.e., line bisections) and visuo-tactile stimuli (i.e., rod bisection task), or even mental representations (i.e., mental number line bisection) to the left of the actual midpoint (Bowers & Heilman, 1980; Brooks et al., 2016). Moreover, pseudoneglect has been reported when participants are asked to make a forced choice about the lengths of the two halves of pre-bisected lines (i.e., the landmark task; Milner et al., 1992) or greyscales gradients (Nicholls et al., 1999). In these paradigms, pseudoneglect is indexed by the perception of the right end of the stimulus as longer than the left one. Pseudoneglect asymmetries were also described in lateralized detection tasks (i.e., greater detection accuracy for left- compared to right-presented stimuli; e.g., Learmonth et al., 2015) and even in visual search tasks (Nicholls et al., 2017), as indicated by faster RTs for left-sided targets of visual arrays. Interestingly, pseudoneglect has been observed in an eye tracking task where participants are asked to explore pictures of everyday life, such as the Free Visual Exploration (FVE) task (Dickinson & Intraub, 2009; Nuthmann & Matthias, 2014; Ossandon et al., 2014; Hartmann et al., 2019). In this task, pseudoneglect is reflected by the tendency to start the exploration of the picture from the left side.

Pseudoneglect is characterized by a certain degree of variability, modulated by different and interacting factors, such as: the task employed (Learmonth et al., 2015; Brooks et al., 2016), the hand used to perform the task (e.g., Luh, 1995), sex (Roig & Cicero, 1994), individual level of arousal (Benwell et al., 2013), and the age of participants (see Jewell & McCourt, 2000, for a review). With respect to age, some studies report a reduction or reversal of pseudoneglect with increasing age (e.g., Schmitz & Peigneux, 2011; Benwell et al., 2014), in line with a reduction of lateralized cognitive processes postulated by the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Cabeza et al., 2002). However, other studies reported opposite results, indicating the persistence (Learmonth & Papadatou-Pastou, 2021), or even an increase of pseudoneglect over age (Brooks et al., 2016; Friederich et al., 2016; see also Friedrich et al., 2018 for a review). As previously introduced, cultural factors such as reading habit (Rinaldi et al., 2014; Chokron et al., 1998), was shown to play role in the asymmetrical deployment of visual attention, interacting with the well-known right-hemispheric specialization.

Notably, most research has been conducted on line bisection or landmark tasks; only few studies examined pseudoneglect in more ecological tasks, such as the FVE task (e.g., Nuthmann & Matthias, 2014; Hartmann et al., 2019) and no studies characterized the effect age on FVE pseudoneglect.

1.3.2. Eye tracking-based tasks to study visuospatial attention and orienting

The analysis of eye movements provides important information on a multitude of levels: form basic neurophysiology (i.e., the correct functioning of oculomotor pathways, including the cranial nerves, the vestibular system and the cerebellum) to “higher” cognitive processes, such as attention, memory, and language. Regarding the attentional orienting, eye movements recording can be exploited to explore the overt deployment of attention, by providing both quantitative (e.g., ocular reaction times to peripheral targets) and qualitative indexes, such as the strategy employed during a visual search.

As previously said, eye movements are generally analyzed in terms of saccades and fixations. With respect to saccades, several paradigms with different degrees of cognitive demands have been devised (Gooding & Basso, 2008). For example, participants can be instructed to simply make a saccade towards a forthcoming lateralized target (i.e., visually-guided, reflexive pro-saccade), or to refrain from this automatic process and make a volitional saccade towards the opposite location of the target appearance (i.e., anti-saccade). Moreover, endogenous, delayed saccades can be made towards a previously signaled location (i.e., memory-guided saccades in the so-called oculomotor delayed response tasks, ODR). Irrespective of the task employed, saccades can be measured in terms of latency (or saccadic reaction time, SRT, i.e., the time needed to initiate a saccade from the target onset), amplitude and duration, velocity, or gain (i.e., the spatial accuracy of a saccade with respect to the target). Moreover, important information can be gathered by counting saccades, e.g., the number of saccades in the wrong direction in anti-saccade task or the number of saccades towards the left and the right hemifield in patients with visuospatial disorders.

Pro-saccadic tasks can be employed to study overt, endogenous (e.g., memory-guided or following central cues) and exogenous (e.g., visually guided), orienting processes towards lateralized targets (e.g., Corbetta et al. 1998; Nobre et al., 2000). On the other hand, anti-saccades paradigms (Hallet & Adams, 1980) involve a higher number of cognitive process, namely, a first covert shift of exogenous attention, inhibition of reflexive saccade, and the transformation of the cue position to the spatial position of the saccade goal. As such, they are largely employed to study inhibitory processes, especially in neuropsychiatric conditions such Parkinson's disease (Gallea et al., 2021), traumatic brain injury (Stuart et al., 2020), and schizophrenia (Radant et al., 2007).

Notably, saccadic tasks have been employed to characterize attentional orienting in patients with parietal and frontal lesions (e.g., Pierrot-Desilligny et al., 1991; Machado & Rafal, 2004), including patients with hemispatial neglect. For instance, an early study by Girotti et al. (1983) reported increased latency and reduced amplitude of contralesional saccades in neglect patients, whereas Niemeier and Karnath (2000), in a free exploration of space found, reduced saccadic amplitude for all directions. Furthermore, Ptak and colleagues 2007, employed a saccadic paradigm to investigate lateralized and non-lateralized attentional deficits in neglect patients, finding that a distracter in the ipsilesional hemifield attracted the gaze reflexively, causing an increased number of saccades erroneously directed to the distracter.

Another paradigm that has been largely studied is the *gap* saccadic task, in which the central fixation disappears (i.e., the gap) briefly prior to the target onset (Saslow, 1967). Gap saccades are associated to fast latencies compared to the condition when the fixation does not disappear and the target onset "overlaps" with the fixation (i.e., the overlap condition). This particular benefit of the fixation offset is referred to as the *gap effect* (Saslow, 1967; Reuter-Lorenz et al., 1991), and is mediated by a facilitation of attentional disengagement from central fixation. Therefore, gap-overlap paradigms can be employed to study attentional orienting under different degrees of attentional disengagement. For example, Paladini et al. (2016), used a gap-overlap paradigm to study the interaction of tonic alertness and attentional asymmetries. The authors observed that an increased level of fatigue (induced by prolonged task execution) induced a rightward attentional bias, indexed by a facilitated attentional disengagement for right targets in the overlap condition. In the Study 2 of this thesis, I employed a gap-overlap paradigm to study the effects of non-invasive brain stimulation on attentional orienting and disengagement.

Beyond saccadic metrics, the study of fixation position provides a direct proof of where attention is being deployed. Indeed, the analysis of fixations distribution (e.g., cumulative fixation duration in a given region of interest or the average gaze position on the screen) can be declined in several ways. For example, it is the foundation of the preferential looking technique widely used to study language development in infants (Golinkoff et al., 2013); nonetheless, it has also been employed to assess memory impairments in patients with Alzheimer's disease (e.g., Bueno et al., 2019) and, as previously mentioned, to characterize attentional asymmetries in healthy individuals and patients with hemispatial neglect while exploring pictures (Hartmann et al., 2019; Kaufmann et al., 2020).

1.3.3. Scene viewing and free visual exploration

Within the field of visuospatial attention, an experimental paradigm that has been receiving more and more attention is the visual exploration of scenes of everyday life. In its simplest form, participants are first presented with a central fixation and are then required to freely explore a series of pictures of everyday scenes, while their gaze position is recorded by an eye tracker. In fact, the study of what features of a visual stimulus attract the attention (e.g., color contrasts, and edges) is not novel as such and it has been the focus of computational studies aiming to predict human gaze behavior through saliency algorithms (see e.g., Itti, Niebur and Koch, 1998). More recently, some researchers realized that scene viewing could represent a window into visuospatial processes and related asymmetries (Dickinson & Intraub 2009; Foulsham et al., 2013; Nuthmann & Matthias 2014; Ossandon et al. 2014; Hartmann et al., 2019).

Among the first, Dickinson and Intraub (2009) conducted a series of experiments in which they presented healthy participants with sets pictures of indoor and outdoor scenes, briefly displayed for 500 ms. The authors discovered an early leftward bias that manifested itself as a better recognition for left-sided objects in a subsequent memory test. In a different experiment, participants were let free to explore pictures presented for either 500 ms or 10 seconds (i.e, free visual exploration - FVE - task): in both conditions a high percentage of first left-oriented saccades were observed, providing further evidence of an early leftward asymmetrical bias in healthy individuals. A similar percentage of initial leftward saccades in an FVE task was also reported by Foulsham and colleagues (2013).

Ossandon et al. (2014), through the analysis of fixations distribution under different experimental conditions of scene viewing, further showed an initial leftward bias followed by the exploration of the right side of the pictures. Specifically, they showed a persistency of pseudoneglect in the majority of right-handers across different picture categories (i.e., natural and urban landscapes, as well as noise and fractal images), irrespective of the spectral content, and even when pictures were displayed continuously, i.e., without a central fixation.

Nuthmann & Matthias (2014) investigated more specifically the time-course of scene viewing attentional asymmetries in a large sample of participants (n = 72), each exploring 135 pictures. The study included three experimental conditions, namely, an FVE, a memorization task, and a visual search. A pseudoneglect was observed in all conditions and its maximum extent (about 1° lasting for 1500 ms) was reached in the memory task and the visual search condition, both conditions guided primarily by top-down mechanisms. Notably, an initial leftward bias was present even when the object to search was in the right part of the picture. The time-course of visuospatial asymmetries in FVE was further studied by Hartmann and colleagues (2019), who tested the effects of viewing distance on pseudoneglect. The authors expected to observe a reduced pseudoneglect at increased distances between the stimulus and the observer (140 cm vs 70 cm), an effect previously observed in other spatial tasks (e.g., McCourt and Garlinghouse, 2000). The results showed that the viewing distance modulated spatial asymmetries in the FVE task, but this effect occurred later, around 4000 ms of visual exploration. Importantly, this pattern was identified thanks to a fine-grained spatio-temporal analysis, i.e., by testing spatial asymmetries (i.e., the average gaze position on the horizontal axis) at a very high temporal resolution, namely, for small temporal bins of 10 ms of the viewing time (a total of 700 timebins for 7 s of picture exploration). This approach showed that a temporal investigation of spatial phenomena can provide valuable information about overt mechanisms of attentional orienting.

Interestingly, the FVE task was also employed in TMS studies investigating the mechanisms of frontoparietal networks for attentional orienting (e.g., Nyffeler et al., 2008;

Cazzoli et al., 2015; Paladini et al., 2017). Whereas Nyffeler and colleagues (2008) induced neglect-like asymmetries (fewer fixations in the left part and more fixations in the right part of pictures) after the inhibition of right PPC by means of high frequency TMS (i.e., continuous theta burst stimulation, cTBS), Cazzoli et al. (2015) found a bilateral decrease of exploration in the peripheral part of the pictures after cTBS applied to right FEF.

Finally, eye tracking-based tasks such as the FVE have proved particularly helpful in assessing visuospatial asymmetries in neglect patients (e.g., Pflugshaupt et al., 2008; Kortman et al., 2016; Delazer et al., 2018; Ohmatsu et al., 2019; Paladini et al., 2019; Kaufmann et al., 2020). In the study by Delazer and colleagues (2018), 22 patients with acute stroke in the territory of right middle cerebral artery were administered an FVE of photographs and a visual search test, in addition to a standard neuropsychological battery; a fixation-based index of spatial asymmetry was able to detect a rightward exploration bias even in those patients who performed at ceiling at standard paper-and-pencil examination. Furthermore, the study by Pflugshaupt and colleagues (2008) demonstrated that value of this approach also in chronic neglect patients: employing an FVE task, the authors observed an increased number of first saccades towards the ipsilesional part of pictures, thus showing residual chronic deficits, otherwise not detectable.

More recently, Ohmatsu et al. (2019) administered couples of flipped images to a group of neglect patients and a control group with right hemispheric damage without neglect, further confirming that neglect patients exhibited a significantly larger rightward asymmetry in the distribution of fixations. Interestingly, this asymmetrical bias was shown to correlate with the score of the Behavioral Inattention test (BIT), a neuropsychological battery for neglect, and the Catherine Bergego Scale (CBS), a scale of neglect symptoms in everyday life. Similar findings were reported by Kaufmann and collaborators (2020). Notably, they considered 78 patients with neglect (diagnosed with the CBS) who underwent both the FVE task and a neuropsychological battery. Results showed that the mean gaze position on the horizontal axis in the FVE task identified neglect more accurately than the paper-and-pencil tests and correlated significantly with the CBS.

To conclude, eye tracking-based tasks such as the FVE are helpful to characterize spatial asymmetries in neurologically healthy individuals (e.g., pseudoneglect) and brain-lesioned patients with hemispatial neglect. In the Study 1 of this thesis, I have tried to answer some open questions about the FVE task in healthy volunteers, specifically the influence of age on FVE-based pseudoneglect and its relationship with a line bisection task.

1.4. Neuromodulation of visuospatial attention and eye movements

1.4.1. Introduction to transcranial Direct Current Stimulation

In the last decades, we have witnessed a rise in the application of non-invasive brain stimulation (NIBS) techniques to modulate cognitive functions both in healthy individuals and clinical populations (Lefaucheur et al., 2017). Among these techniques, transcranial Direct Current Stimulation (tDCS) has received a great attention thanks to its ease of use, low costs, and tolerability. tDCS is based on the application of a weak electrical current on the participant's scalp, conventionally delivered by means of two electrodes, i.e., anode and cathode. Several neurophysiological studies showed that tDCS can exert polarity-dependent, long-lasting changes of membrane resting excitability (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001), by modulating neural plasticity mechanisms (e.g., Monte-silva et al., 2013) and altering long-range connectivity of functionally connected areas (Romero Lauro et al., 2014).

Despite its acknowledged potential, tDCS is often associated with large inter-individual variability of responses and scarce reproducibility of results (Horvath et al., 2015). In fact, multiple interacting factors concerning both the stimulation protocol (e.g., polarity, intensity, duration, focality of stimulation) and the characteristics of the individual receiving tDCS (e.g., healthy vs lesioned brain, brain at rest vs brain already active, baseline performance, morphological variability of brain structures) may deeply impact the effects of tDCS.

Many studies have been conducted on the motor cortex, because it is relatively easy to obtain measures of brain excitability (i.e., motor evoked potentials, MEPs) by means of single pulses of transcranial magnetic stimulation (TMS). In general, anodal tDCS results in the depolarization of the underlying cortex (i.e., increased excitability), whereas cathodal stimulation in cortical hyperpolarization (i.e., decreased excitability; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). It is important to note that his association does not always parallel an enhancement (or reduction) of behavioral performance brought about by anodal (or cathodal) stimulation (see. e.g., Weiss & Lavidor, 2012). In fact, the polarity of stimulation interacts non-linearly with the duration of tDCS protocol: whereas to some extents, at least on the motor cortex, longer durations yield longer after effects (e.g. 90 minutes after 13 minutes of tDCS, Nitsche & Paulus, 2001), it was shown by Monte-Silva et al. (2013) that 26 minutes of anodal stimulation may result in a reduced excitability, thus mimicking the effects of cathodal tDCS. The same applies to current intensity (usually between 1mA and 2 mA): in fact, although some works reported stronger behavioral effects at higher intensities (e.g., Fiori et al., 2019), others observed more consistent effects after 1mA compared to 2mA (Papazova et al., 2018; Ehrhardt et al., 2021). Interestingly, Batsikadze et al., 2013 found that 20 minutes of cathodal tDCS (as compared to 1mA) applied to the motor cortex could increase the cortical excitation like anodal tDCS.

With respect to the electrodes, tDCS has been conventionally delivered by means of large rubber electrodes, normally sized 25-35 cm^2, with an electrode placed over the target region and a return electrode placed either on a cephalic or extracephalic area. Studies of current-modelling have highlighted the low spatial specificity of this approach and indicated that the electric field may widely spread and peak over unintended areas (Datta et al., 2009). In order to reduce current spread and control for the large variability reported in tDCS experiments, more focal electrodes and montages were introduced, the so-called High Definition tDCS (HD-tDCS). HD-tDCS exploits a smaller target electrode usually surrounded by 4 return electrodes (i.e., 4x1 montage; Datta et al., 2009; Alam et al., 2016) or a ring-shaped return electrode (Bortoletto et al., 2016; Martin et al., 2017). Compared to conventional tDCS, HD-tDCS applied to the motor cortex was shown to induce longer lasting after-effects that peaked 30 minutes after the stimulation (Kuo et al., 2013). However, the efficacy and the timing of HD-tDCS on associative cortices (and in the context of higher cognitive processes) require further investigation.

Beside the complexity related to the stimulation parameters, behavioral and neurophysiological effects of tDCS have been shown to be state-dependent, hence to depend on the state of brain activation during the stimulation (Fertonani & Miniussi, 2017). For example, Hill et al. (2019) compared an “offline” tDCS protocol (i.e., at rest) with an “online” protocol (i.e., during the execution of a concurrent task), demonstrating that target networks are more effectively modulated when they are engaged in a given task, whereas offline protocols may mostly affect the Default Mode Network. Finally, the effects of tDCS are influenced by the individual neurophysiological and behavioral characteristics at baseline, namely the behavioral performance and the brain activation before receiving the stimulation. For instance, participants showing higher performance at a given task may not benefit from tDCS as much as “lower” performers (e.g., Learmonth et al., 2015). Moreover, Masina and colleagues (2021) demonstrated that baseline EEG power at given frequency bands (e.g., alpha and beta) affects tDCS modulatory changes, so that, for example, HD-tDCS over C4 reduced alpha power, but only in those participants with low alpha power at baseline. Moreover, HD-tDCS induced a trend towards baseline-dependent behavioral changes (i.e., faster RTs in a tapping task) in those participants with lower beta power at baseline. In conclusion, tDCS is not a one-fits-all technique, rather its outcomes are state-dependent and results from a complex interaction of numerous variables.

tDCS has been employed to modulate a plethora of neurobehavioral processes, from motor and visual functions, to executive functions and social cognition (Jacobson et al., 2012). Not surprisingly, several works have applied tDCS to modulate visuospatial attention. The next section will review some major contributions in this regard.

1.4.2. tDCS effects on visuospatial attention and eye movements

By far, most of the research conducted on healthy participants focused on the effects of PPC tDCS in wide range of computerized tasks and stimulation paradigms. In their seminal experiment, Sparing et al. (2009) found that 10 minutes of 1mA anodal or cathodal offline tDCS of the right PPC improved (anodal) or impaired (cathodal) detection of contralateral visual targets. Giglia and co-workers (2011) applied 15 minutes of 1mA online cathodal tDCS over right PPC or biparietal tDCS (cathode right PPC – anode left PPC) and reported a "neglect-like" rightward bias in a landmark task. Benwell and colleagues (2015) replicated these findings with a biparietal online protocol, also showing complex non-linear state-dependent effects depending on the stimulation intensity and baseline discrimination sensitivity. However, Loftus and Nicholls (2012), examining pseudoneglect with grayscale gradients, found no effect of either anodal or cathodal offline tDCS on right PPC (1mA, 20 min); rather, the authors observed a reduction of pseudoneglect after the application of anodal tDCS over the left PPC. Finally, in a multisensory audio-visual detection task, Bolognini and colleagues (2010) found that 15 minutes of 2mA anodal stimulation speeded up the detection of contralateral visual targets.

Another target site for modulating spatial orienting has been the frontal cortex, although with negative findings in some studies (Ball et al., 2013; Roy et al., 2015). For instance, Roy and colleagues (2015) found no effects of anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) in a modified Attention Network Task, while confirming the improvements brought about by anodal tDCS over the right PPC on the processing of contralateral targets, especially when attention had to be re-oriented rightwards. By using a conjunction search task, Ball et al. (2013) found no effects of anodal tDCS applied online over either the right PPC and FEF, but a significant effect of online cathodal tDCS over PPC which prevented learning effects (i.e., increasingly faster search times associated to the repetition of the task).

PPC was also chosen as neurostimulation target to treat hemispatial neglect (Salazar et al., 2018; Veldema et al., 2020). In general, according to Kinsbourne (1987), the aim of NIBS in neglect rehabilitation is to restore the altered interhemispheric balance either by increasing the excitability of the lesioned hemisphere (anodal tDCS), decreasing the supposed hyperexcitability of the left hemisphere (cathodal tDCS), or achieving both at the same time with a bihemispheric stimulation (Sunwoo et al., 2013). Among the first studies, Sparing and colleagues (2009) observed an immediate improvement of neglect symptoms after one session of anodal stimulation (1mA, 10 min., offline) over the right PPC or cathodal stimulation over the left PPC. Similarly, Sunwoo and colleagues (2014) investigated the effects of a single session (20 min, 1mA) of either anodal tDCS of right PPC or dual tDCS (i.e., anodal over the right PPC combined with cathodal over the left PPC). Compared to the placebo (i.e., sham) stimulation, the authors observed an immediate improvement in the line bisection task (but not in the star cancellation task) after both anodal tDCS and dual tDCS, with the latter inducing the strongest effects. tDCS was also studied in combination with behavioral treatments, such as prism adaptation (Ladavas et al., 2015; Chieffo et al., 2019), with the aim of potentiate their efficacy. For instance, Ladavas and colleagues (2015) showed in 30 neglect patients that 10 daily sessions of prism adaptation combined with anodal tDCS on the right PPC (20 min at 2mA) induced significant improvements at the BIT.

With regard to eye movements, few studies applied tDCS over the FEF in pro- and anti-saccades tasks (Kanai et al. 2012; Tseng et al. 2018; Reteig et al. 2018). Whereas Kanai et al. (2012) found stimulation- and task-specific effects on saccades directed to the contralateral visual hemifield, Tseng and collaborators (2018) observed that effects of anodal tDCS over the right FEF depended on the probability of target location and the individual level of performance. On the other hand, Reteig et al. (2018) found no effects of either anodal or cathodal stimulation.

Overall, it appears that tDCS has a good potential to modulate frontoparietal networks of orienting, although the inconsistency of protocols (especially for clinical purposes; Elsner et al., 2020), together with small sample sizes and the variability of results, require further investigations to draw definitive conclusion about its usefulness. In particular, only few studies applied tDCS over FEF to modulate attentional orienting and no studies attempted to modulate orienting in more naturalistic setting, for instance by assessing tDCS effect with FVE tasks. Finally, state-dependency of tDCS over associative cortices deserve a deeper investigation.

1.5. Aim of this PhD work

The scientific literature reviewed in this Chapter indicates that the analysis of eye movements in ecological conditions, using tasks such as the FVE, are being increasingly employed in healthy individuals and patients with hemispatial neglect to assess spatial orienting and its asymmetries.

However, as compared to other computerized tasks (e.g., the line bisection or the landmark task), FVE has received relatively less attention. Indeed, the identification and characterization of the individual factors (e.g., age, sex, alertness) modulating attentional asymmetries during the exploration of the surrounding environment is still largely underinvestigated, although the knowledge of such determinants could provide important hints for the establishment of FVE as a gold-standard measure of spatial biases in ecological settings. This is of high relevance especially for clinical purposes: in order for FVE to be extensively used in the neuropsychological assessment, normative data are quintessential and individual variables need to be taken into account. Along the same line, it is crucial to investigate the relationship between FVE-based asymmetries and attentional biases in other tasks used to assess pseudoneglect and neglect (e.g., the line bisection). However, to date, no studies on healthy individuals directly compared FVE with other tasks.

Another related unsolved issue pertains the actual tDCS efficacy in modulating spatial orienting in healthy conditions. Here, some important questions are still open. In general, to what extent overt attentional asymmetries can be modulated by means of NIBS techniques, such as tDCS? Previous studies showed promising results associated to PPC stimulation, however state-dependent effects (e.g., the effect of baseline asymmetry) were only rarely investigated (e.g., Benwell et al., 2015) although they are crucial to determine under which circumstances tDCS is most effective or ineffective. On the other side, so far, the investigation of the efficacy of tDCS when applied over the FEF, another central area for orienting and eye movements, led to inconclusive results at least with respect to visual search (Ball et al., 2015) and saccadic latency (Kanai et al. 2012; Tseng et al. 2018). But what happens if stimulation is applied in ecological contexts that simulate the exploration of space in everyday life? To what extent do individual abilities interact with tDCS effects? Could the baseline performance shape tDCS effects? Moreover, could a more fine-grained spatio-temporal approach for the analysis of overt deployment of spatial orient inform about how tDCS affect spatial asymmetries? Finally, does increasing the focality of the stimulation by means of HD-tDCS reduce the variability of behavioral changes?

The aim of my PhD work was to address these issues for deepening our knowledge of mechanisms of overt visuospatial orienting, through the lenses of eye movements analysis and from the perspective of NIBS. The obtained findings uncover those factors shaping the human ability of overtly explore and pay attention to the environment in everyday life, and to which extent we can influence such ability through the neuromodulation of frontoparietal circuits.

To this aim, in Chapter 2, I will present a first study investigating FVE visuospatial asymmetries in large sample of healthy participants. This study highlights the impact of individual factors, such as age, on FVE-based pseudoneglect and, for the first time, its relationship with the same phenomenon detected with a standard paper-pencil task (i.e., the line bisection).

In Chapter 3, I will present a series of studies in healthy participants assessing the effect of tDCS on attentional orienting assessed with FVE and gap-overlap tasks. The focus is on the exploration of efficacy of two tDCS techniques differing in their spatial resolution, namely the conventional tDCS and the HD-tDCS, both applied over PPC and FEF of the right hemisphere. The assessment of their efficacy in modulating spatial orienting considers the effect of individual baseline performance, by adopting a spatio-temporal perspective. This multi-level approach enriches our understanding of the complex interaction between target area, focality of stimulation and state-dependency, shaping the neuromodulation effects on attentional asymmetries.

CHAPTER 2

2. Spatial asymmetries (“Pseudoneglect”) in free visual exploration – modulation of age and relationship to line bisection: Study 1[1]

2.1. Aim of the study

As shown in the introduction, spatial attentional asymmetries have been studied in different modalities, such as visual and tactile. Within the visual modality, the free exploration of pictures, such as in the FVE task, can be employed to assess visuospatial asymmetries in healthy individuals as well as neglect patients. Some studies showed that the pattern of exploration is often characterized by an early orienting of the left side of the pictures (i.e., pseudoneglect), followed by the exploration of the right side, with a final tendency toward the center of the picture (Nuthmann & Matthias, 2014; Hartmann et al., 2019). However, less is known about how spatial asymmetries in an FVE task are influenced by individual factors such as age and handedness, as well as how they correlate with other task of visuospatial attention.

Thus, this study aims at investigating the time-course of visuospatial asymmetries (more specifically, the pseudoneglect) in an FVE task. The goals of the present study were threefold: (a) to assess the temporal dynamics of pseudoneglect during visual exploration of naturalistic everyday scenes; (b) to investigate the influence of age on pseudoneglect; and (c) to determine whether pseudoneglect, as assessed by a classical paper–pencil task, would correlate with pseudoneglect observed in a free visual exploration task. To this end, 60 healthy participants were recruited, ranging from young adults to elderly (i.e., 22–86 years of age). Furthermore, I also tested the influence of other factors such as sex, handedness, and subjective alertness in modulating visual exploration patterns.

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[1] The present research has been published in Chiffi et al. (2021) under the terms of the Creative Commons CC BY license.

2.2. Materials and methods

2.2.1. Participants

Sixty neurologically healthy adults participated in this study (age range 22–86 years, 31 women, see Table 1). Participants gave their written informed consent prior to participation. The study was given ethical approval by the cantonal ethics committee of the Canton of Bern and was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). All participants had normal or corrected-to-normal visual acuity, and participants with a history of eye diseases were excluded from the study. None of the participants reported any difficulties to clearly perceive the visual stimuli while performing the experimental tasks.

Table 1. Demographic data

	Mean±SD	Range
Age (years)	43.05±19.60	22–86
Education (years)	17.19±2.99	8–22
Subjective alertness	7.36±1.84	2–10
Handedness	88.3% (N=53) right-handed	
Gender	51.7% (N=31) females	

2.2.2. Stimuli and materials

Free visual exploration task

In the free visual exploration task, participants viewed a series of naturalistic, colored photographs of everyday scenes (N=120) in a dimly lit room, while their gaze was recorded by means of a contact-free eye-tracking system (see section Eye tracking below for further details). The images were selected from a free image database (pixabay.com), from the sub-categories “nature” and “architecture”. The selection of the images was based on their saliency maps, as assessed by a dedicated algorithm (Itti et al., 1998; Paladini et al., 2017). This algorithm takes into account different characteristics of the features within an image, such as orientation, color, and intensity, which allow the computation of a map of salient regions within the image. This procedure allowed to balance the overall saliency between the left (M=31.6, SD=7.37) and the right (M=32.3, SD=8.49) halves of the images ($t(119)=-.945$, $p=.347$). Moreover, images containing humans or letterings were not included, in order to reduce automatic orienting and have a higher experimental control over saliency (End & Gamer, 2017). Two examples of presented photographs are shown in Figure 1 and the exhaustive choice of the experimental stimuli as well as the ratings produced by the saliency algorithm (Itti et al., 1998) are available at the URL: https://osf.io/zd3qm/. To avoid fatigue and to allow for periodical calibration of the eye-tracking system, the photographs were distributed into six sets of 20 photographs each. Following a nine-point calibration, the free visual exploration task proceeded by displaying the series of images, one at a time, in a random order. After each set (20 images), participants were allowed to take a short break and the calibration was repeated. Each trial began with a central fixation marker (1.5 s), followed by an image displayed for 7 s. Participants were instructed to freely explore the images, as if they were looking at photographs in a photo album.

Figure 1. Example of stimuli used in the free visual exploration task

Line bisection task

In a classical line bisection task, participants were presented with twenty horizontal lines of different lengths, printed on a landscape A4 paper sheet; the actual center of each line varying along the horizontal dimension (Schenkenberg et al., 1980). The center of the paper sheet was aligned with the participant's midsagittal plane, and participants were instructed to bisect all lines as quickly as possible using their dominant hand. The uppermost and the lowermost lines were used as practice trials. For the remaining 18 lines, the deviation of the bisection mark from the actual center of the line was measured in cm. This value was further divided by the actual midline (in cm) of the respective lines, and then multiplied by 100, thus yielding a percent deviation; thereby, negative values indicated a left-sided deviation, and positive values a right-sided deviation.

Subjective alertness assessment

The subjective level of alertness was assessed by means of a visual analogue scale (VAS). On a 10 cm long vertical line, ranging from “very alert” to “not at all alert”, participants were instructed to draw a horizontal mark to indicate how alert they felt. The distance between the lower extreme of the vertical line and the participants’ mark was measured in mm, with lower values indicating a subjective lower level of alertness.

Handedness

Handedness was assessed by the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), measuring hand preference by asking participants to choose which hand(s) is used for a range of 10 everyday tasks. The EHI scores range from − 100 to 100, with negative scores indicating a tendency to left-handedness, and a positive score indicating a tendency to right-handedness.

Eye tracking

In the visual exploration task, participants viewed a series of images that were presented full-screen on a 22″ computer display (Dell, Dell Inc.), with a refresh rate of 60 Hz, a color-depth of 32 bit, a resolution of 1680×1050 pixels, and subtending a visual angle of approximately 37.48°×23.80°. The screen was placed at the eye level, in line with the participants’ midsagittal plane and participants were seated approx. 65 cm from the screen. A contact-free eye-tracking system, equipped with automatic head-movement compensation, was used to record eye movement data (RED 250, SensoMotoric Instruments GmbH). The eye position was sampled at 250 Hz, with a spatial resolution of .03° and an average gaze accuracy of .4°. Stimulus presentation was controlled by the Experiment Center software (SensoMotoric Instruments GmbH), and the iViewX software (SensoMotoric Instruments GmbH) was used for eye movement data acquisition. Raw data were parsed into fixations and saccades using the default parameters of the manufacturer’s analysis software (BeGaze™, SensoMotoric Instruments GmbH). The results were exported in an open format (.txt) and were analyzed using R (Version 3.5.0; R Core Team; 2021) and Matlab 2019b (The MathWorks Inc.).

2.2.3. Data analysis

To ensure that all scan paths would indeed start from the middle of the images, as enforced by the central fixation cross presented before each image, an offline drift correction was performed. For this purpose, a pixel band of 184 pixels, corresponding to 2° visual angle, around the vertical midline of the image was defined. Images in which the initial fixations started outside of this pixel band were excluded from further analysis (i.e., 472 out of 7200 images). For the remaining fixations, an offline drift correction was applied. To this end, the horizontal deviation from the midline on the x axis was calculated for the last fixation taking place on the fixation cross. Afterwards, all the x values of the fixations of the following trial were shifted by this offset. The mean number of fixations as well as the mean fixation duration were calculated.

To analyze the time course of attentional asymmetries (Nuthmann & Matthias, 2014), the average gaze position deviation was computed over 10 ms bins, i.e., N = 700 for 7 s (Hartmann et al., 2019). In brief, the horizontal deviation from the center of the image, i.e., the difference between × coordinates of the corresponding fixations and the midline, was calculated for every fixation falling within a given 10 ms bin; the values were then averaged within the corresponding bin. This served as a measurement of attentional asymmetries (Hartmann et al., 2019). Thus, negative values indicate a leftward bias, and positive values a rightward bias. Deviation values were computed for each participant and every time bin. The nonparametric random permutation procedure proposed by Maris and Oostenveld (2007) was implemented to account for the problem of multiple comparisons. With this approach, time bins during which the gaze position could be predicted by the age or the performance in the line bisection task, were defined and tested for significance. Specifically, it was tested for each 10 ms bin whether age or the performance in line bisection was a significant predictor for the horizontal gaze position. Adjacent 10 ms bins for which a significant predictor ($p < .05$) was found formed a cluster, and Fisher's F values of all bins within a cluster were summed up, resulting in "cluster mass values". These values were then compared to a "random distribution" of mass values that was obtained by computing the highest "by chance significant" cluster mass value from randomly permutated bins for 5000 times. The *p* value of each initial cluster was then obtained from the position of the cluster mass value within this “random distribution” (see Hartmann et al. 2019). In a next step, the horizontal gaze position was averaged for the time period of significant clusters and correlated with other variables of interest (Spearman’s correlations are reported). The permutations, as well as the corresponding p values, were obtained using the R-package “permuco” (Frossard & Renaud, 2018).

Moreover, to test whether additional factors such as gender or subjective alertness would influence the visual exploration behavior, a linear mixed model with factors age, performance in the line bisection, handedness, gender and subjective alertness was calculated. For this analysis, the average gaze position over the whole presentation time was considered, irrespective of its time-course.

2.3. Results

Free visual exploration pattern

Participants produced on average 21.41 fixations per image (M=21.41, SD=4.37), with an average gaze fixation duration of 250 ms (M=250.41 SD=43.65). Overall, during the initial stages of the exploration, there was a tendency to deviate towards the left side of the image. This initial leftward bias lasted for about 1.5 s, after which the exploration pattern shifted towards the right side of the image. It is worth to note that the maximal deviation from the midline was more pronounced for the left than for the right part of the images, even though overall, participants spent more time on the right than on the left side of the images (see Figure 2).

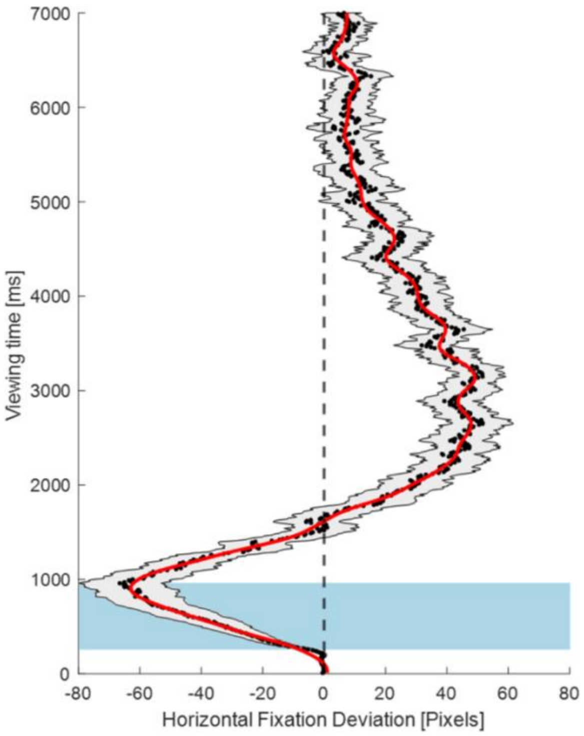

Figure 2. Time-course of the exploration pattern averaged across all images and all participants. The grey area around the smoothed red line represents the standard error of the mean of the averaged gaze position. The blue box represents the time-window during which age was a significant predictor for the average gaze position.

The effect of age on spatio-temporal asymmetries in the free visual exploration task

The nonparametric random permutations indicated a significant time cluster at 260–960 ms (cluster mass=632.6, *p*=.027, see Figure 2). During this early phase of visual exploration, age modulated the exploration behavior in a way that, with increasing age, the initial leftward bias was attenuated (*rs*(60)=.38, *p*=.003, see also Figure 3).

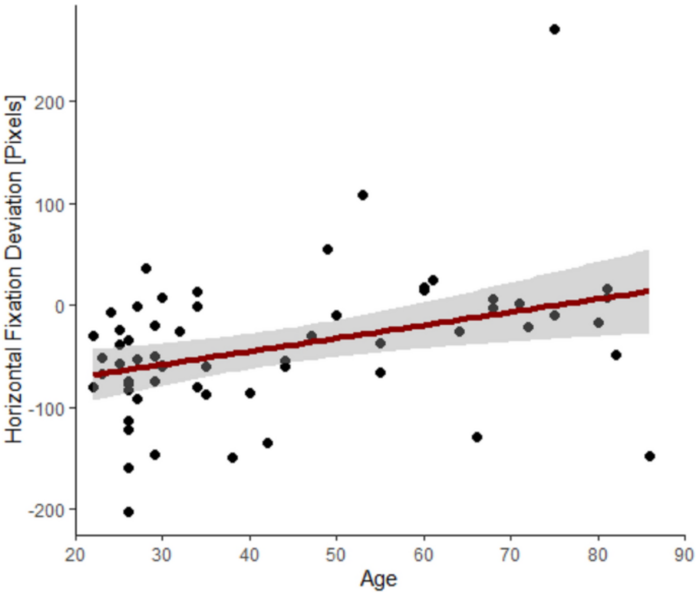

Figure 3. Correlation between age and the average horizontal gaze deviation in pixels between 260 and 960 ms, indicating attenuation of the leftward bias with increasing age.

Visuospatial asymmetries in the line bisection task

I further investigated whether spatial asymmetries in a more naturalistic free visual exploration task would correlate with the performance in a classical test of visuospatial attentional bias, namely, the line bisection task.

Overall, the performance in the line bisection task indicated a small leftward bias (relative deviation from the middle: M=− 0.27%; 95% CI [− 0.97, 0.43]; SD=2.69%, range −6.33–5.71%). The nonparametric random permutations indicated a significant time interval between 300 and 1490 ms (cluster mass=795.87, *p*=.022), in which the performance in the line bisection task was positively correlated with the average gaze position (*rs*(60)=.27, *p*=.34, see Figure 4). As such, performance in the line bisection task was predictive of the mean gaze position in the visual exploration task during the initial phase of exploration.

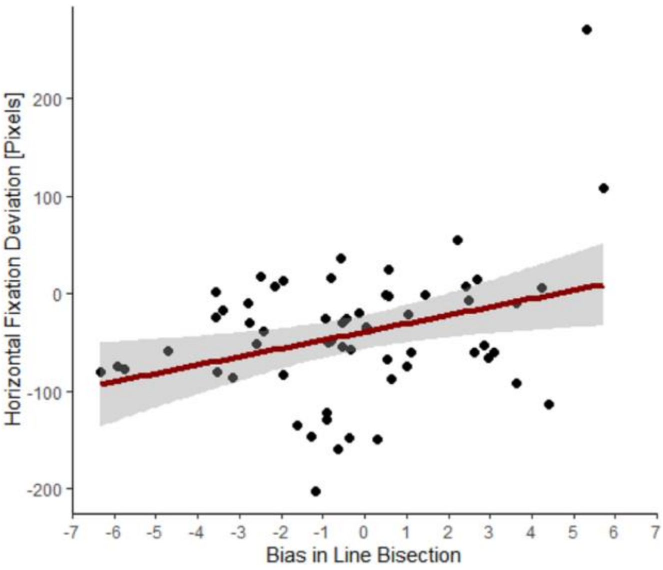

Figure 4. Correlation between the bias in the line bisection task (percentage deviation from the actual midline) and the average horizontal fixation deviation in the free visual exploration task during the time interval between 300 and 1490 ms; this significant correlation indicates that a stronger leftward bias in the line bisection task correlated with a stronger leftward deviation in the free visual exploration

Furthermore, there was no significant correlation between age and the performance in the line bisection task (*r*(60) = .19, *p* =.136).

Influence of other individual factors on the performance in the free visual exploration task

A linear mixed model was calculated to test whether, in addition to age and performance in the line bisection task, other factors such as gender, handedness, and subjective alertness would influence the exploration behavior, as measured by the average gaze position. In line with previous analyses, line bisection performance (*p*=.028) and age (*p*=.035) modulated the average gaze position in the visual exploration task. Yet, none of the additional factors had a significant influence (*p*=.92 for gender, *p*=.38 for handedness, and *p*=.62 for subjective alertness).

2.4. Discussion

The aim of the present study was to investigate the spatial and temporal dynamics of free visual exploration of complex naturalistic images. Furthermore, I assessed whether different individual factors such as age, gender, handedness, and subjective alertness would modulate these spatio-temporal dynamics. In agreement with previous studies (Nuthmann & Matthias, 2014; Hartmann et al., 2019), a pseudoneglect emerged, indexed by a leftward bias during the initial phase of the free visual exploration of an image. Second, and more importantly, I found a significant influence of age during a critical time window in the early phase of exploration (between 260 and 960 ms), i.e., this leftward bias was attenuated with increasing age. Thirdly, I found a significant correlation between the line bisection bias and the spatial bias in free visual exploration, indicating that a stronger leftward bias in the line bisection task correlated with a stronger leftward deviation in the visual exploration task. Finally, I found no significant effect of subjective alertness, handedness, or sex on spatio-temporal fixation dynamics during free visual exploration.

To the best of my knowledge, a critical time window during which age-dependent differences in spatial biases are evident in free visual exploration has never been described before in the literature. A leftward bias in the visual exploration behavior is reminiscent of the phenomenon of pseudoneglect. Several studies yielded evidence for an age-related reduction of pseudoneglect, i.e., from a strong attentional leftward bias in young adults to a suppressed or even reversed bias in the elderly, as in the present study (see Schmitz and Peigneux 2011, for a review). However, the literature is not conclusive, i.e., several other studies failed to show such age-related changes in spatial biases (Beste et al., 2006; Hatin et al., 2012; Brooks et al., 2016). The results of our study suggest that time is a critical factor, i.e., an age-dependent modulation of spatial biases is only evident in a critical time window; this might explain, at least in part, the discrepancies in the earlier literature.

The null results between age and the line bisection underlie the fact that assessing leftward biases within specific time windows, in line with a characterization of dynamic behavior with a high temporal resolution, is necessary. Only few studies examined the influence of age on visual exploration behavior. Urwyler and colleagues (2015) analyzed the influence of age on visual exploration during driving. They found an effect of age, showing that older participants had a narrowed visual exploration field. Furthermore, detection of targets in a visual search task decreased with age, especially for more peripheral targets (Gruber, 2014). However, to the best of my knowledge, this study is the first to use a free visual exploration paradigm in participants of different ages.

The origin of the age-related modulation of spatial biases is still debated. It has been suggested that healthy aging might be associated with a functional decline of the right hemisphere, coupled with a left-hemispheric compensation (Dolcos et al., 2002; Schmitz & Peigneux, 2011). Indeed, an age-related reduction of the right-hemispheric lateralization has been shown in an EEG study applying a landmark task (Learmonth et al., 2017). Such a relative hyperactivity of the left hemisphere would explain the rightward bias shift in older individuals. This phenomenon can be considered as a less pronounced form of the biased spatial dynamics that have been described in classical neglect models (e.g., Kortman & Nicholls, 2016; Delazer et al., 2018). An alternative explanation may be a decline in corpus callosum function, which could impair interhemispheric connectivity. This could then reduce the inhibitory influence that the right hemisphere exhibits in elderly, which would then result in a stronger involvement of the left hemisphere (Schmitz & Peigneux, 2011). It has also been proposed that, in elderly individuals yielding comparable behavioral performances as younger adults, the age-related neuronal decline is counteracted by means of plastic reorganization mechanisms (Cabeza et al., 2002). These plastic reorganization mechanisms seem not to take place in all (or at least not to the same extent) elderly individuals. This could, in turn, explain the age-related increase in variability of the free visual exploration pattern our study.

A possible explanation for the critical time window identified by this study, in which age-dependent differences in the visual exploration task were evident, stems from electrophysiological studies. Störmer et al. (2013) investigated neural correlates of age-related differences in spatial attention using event-related potentials (ERPs). They found that healthy aging affects attentional selection (supporting the resolution of competition between visual information) at early stages of attentional modulation. To this end, they showed that older adults showed less pronounced selective attentional modulation in the early phase of the visual P1 component (100–125 ms) than younger adults. However, with a 25 ms delay relative to younger adults, older adults showed distinct processing of targets (125–150 ms), i.e., a delayed yet intact attentional modulation. Moreover, the magnitude of the delayed attentional modulation was related to the behavioral performance in older adults. Further ERP studies on attention in young (Foxe et al., 2003; Longo, 2015) and older adults (Learmonth et al., 2017) also indicated a critical time-window, starting as early as 139 ms after the stimulus presentation. This effect was observed until 400 ms after the stimulus onset. In addition, an age-dependent time window, ranging from 280 to 400 ms, has been reported (Learmonth et al., 2017), which also coincides with the start of the critical time-window in the present study.

In the present work, other factors such as subjective alertness, handedness, or gender did not significantly influence the observed spatial bias. In fact, participants in this study were not specifically recruited to increase variability in the aforementioned factors, with only a limited variance with regards to subjective alertness as well as handedness. Moreover, my sample was not controlled for the years of education and this variable was, therefore, not analyzed. However, future studies should also investigate the effects of cultural factors, including the reading direction (Chokron & Imbert, 1993), by testing, for instance, the temporal development of spatial asymmetries in right-to-left readers (e.g., Hebrew speaking individuals as in Rinaldi et al., 2014) of different ages. This approach would help characterize the complex interaction between “nature and nurture” in determining asymmetries of visuospatial attention.

In conclusion, the present study revealed that, during visual exploration of naturalistic everyday scenes, there is a critical time window within the first second of visual exploration in which age is a predictor of the attenuation of this leftward bias. Furthermore, a significant correlation between line bisection bias and spatial bias during visual exploration was found, i.e., the stronger the leftward bias in line bisection, the stronger the leftward deviation during visual exploration. Hence, this work concurs with previous research by providing evidence that free visual exploration of naturalistic scenes generally starts within the left side of an image, but it extends it in two important ways. First, by providing a systematic and detailed time-course investigation of spatial asymmetries during naturalistic scene perception; second, by directly comparing the outcome of two attentional tasks of visuospatial nature (i.e., free visual exploration and line bisection task) in a sample of neurologically healthy participants ranging from young adults to elderly.

CHAPTER 3

3. Modulation of visuospatial orienting by means of conventional tDCS and HD-tDCS of frontoparietal circuits: Study 2[2]

3.1. Aim of the study

As discussed in the introduction, tDCS has attracted a lot of interest as for its potential to modulate visuospatial processes in the healthy brain and for possible clinical applications in the context of acquired attentional disorders following brain damage, such as neglect. However, more research is needed to figure out the effects and variability of tDCS in experimental tasks which are closer to everyday life experience. In this direction, the FVE represents a good candidate to shed more light on this issue. Accordingly, the present work aims at investigating to what extent anodal conventional tDCS (Experiment 1) and HD-tDCS (Experiment 2) can modulate visuospatial orienting and asymmetries in an FVE task. In a within-participant, sham-controlled approach, offline anodal tDCS was applied in different sessions over the right PPC and right FEF. I tested whether leftward asymmetries could be induced and possible differences between parietal and frontal stimulation may emerge. Moreover, in the experiment 1, attentional orienting and disengagement were also tested

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[2] Preliminary results of this study were published in a conference paper (Diana et al., 2021). Results about the effects of conventional tDCS and HD-tDCS on FVE were published in Diana et al. 2022.

by means of a saccadic task, i.e., the gap-overlap paradigm. Importantly, in light of the well-known state-dependency of NIBS, the effects of tDCS were also investigated with baseline-corrected models (Masina et al., 2021)

3.2. Experiment 1 – Conventional tDCS

3.2.1. Materials and methods

Participants and sample size estimation

As I expected a significant level of inter-participant variability of response to tDCS, I planned to analyze the effects of stimulation by means of mixed models. Despite possible methods to estimate sample size for mixed models exist, (see e.g., Brysbaert & Stevens, 2018), it is challenging to retrieve all needed parameters for a proper *a priori* analysis because previous works on tDCS and visuospatial attention did not employ this statistical approach. Therefore, the sample size was estimated with an *a priori* power analysis (G*Power 3.1.9.6; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) for a repeated-measures analysis of variance (ANOVA), assuming it may yield a sufficient approximation of the needed sample size. As suggested by Minarik et al. (2016), I specified a medium-small effect size, i.e., $f = .2$ ($d = .4$), $\alpha = .05$, $1\text{-}\beta = .08$, correlation among measures = .05, sphericity correction = 1, and number of measurements = 6), as each participant carried out the experimental task six times (i.e., before and after three different tDCS stimulations). According to the results of the analyses, 28 participants (18 female, mean age = 25 y ± 3 years) were recruited at the University of Milano-Bicocca. Inclusion criteria for the study were: right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971), normal or corrected-to-normal visual acuity, and absence of contraindications to tDCS (Bikson et al., 2016; Thair et al., 2017). The study was approved by the Ethics Committee of the University of Milano-Bicocca (Protocol 457 – 27/11/2019) and was conducted in accordance with the ethical standards of the Declaration of Helsinki. All participants provided their written informed consent to the experiment.

Stimuli and Materials

Experimental Setup

The experimental tasks were both programmed with SR Research Experiment Builder 2.3.1 (SR Research Ltd., Canada) and were performed in a dark room. Participants were seated in front of a monitor (Acer HN274H 27”) aligned with their participant’s mid-sagittal plane at a viewing distance of 83 cm, which was kept constant by means of a chin-and-head rest. Eye movements were recorded by means of an EyeLink 1000 (SR Research Ltd., Canada). At the beginning of the task, the eye tracker was calibrated using a 9-point grid and the mean gaze accuracy was kept, on average, around .5° of visual angle.

Free Visual Exploration Task

The task consisted in the free exploration of sets of 12 naturalistic pictures (1680 x 1050 pixels, 35°x22° degrees of visual angle, presentation time = 7 s), interleaved by a black screen with a fixation cross lasting 1.5 s. As the participants performed the task six times (i.e. before and after tDCS in three different sessions; see below), I made sure they explored different pictures in each experimental session and that these blocks were comparable in terms of left and right saliency. Specifically, a total of 108 pictures were selected from a previously used database (Hartmann et al., 2019; Chiffi et al., 2021). A saliency matrix - based on several features such as orientation, color, and intensity - was obtained for each picture with a MATLAB (R2019b) algorithm (Itti et al., 1998). Subsequently, the ratio between mean left-right saliency was calculated and pictures were randomly assigned to nine different blocks. A one-way Analysis of variance (ANOVA) confirmed there was no significant difference between blocks in terms of mean left-right saliency ratio ($F_{8,99} = .78$; $p = .618$). Therefore, each participant was randomly assigned to 6 out of 9 possible blocks. Moreover, to further reduce the impact of pictures content on visuospatial asymmetries, the same blocks were mirrored along the vertical midline for half of participants.

Gap-Overalp Task

Participants were asked to perform saccades from a central fixation point towards a lateral target as quickly and accurately as possible (Saslow, 1967; Paladini et al., 2016). Target appeared randomly in two positions: 10° to the right or to the left of the central fixation point. In the gap trials the fixation point disappeared 200 ms before the appearance of the target whereas in the overlap trials the fixation remained present when the target appeared. The duration of central fixation varied between 1200 ms and 1500 ms. Each trial was separated by a 1700 ms black screen. A schematic depiction is represented in Figure 5. The task involved 64 trials for a total duration of 4 minutes. Thirty-two trials were gap and 32 were overlap. In half trials the target appeared to the left and in the remaining trials to the right of the central fixation. A short break was allowed in the middle of the task to avoid excessive eye fatigue.

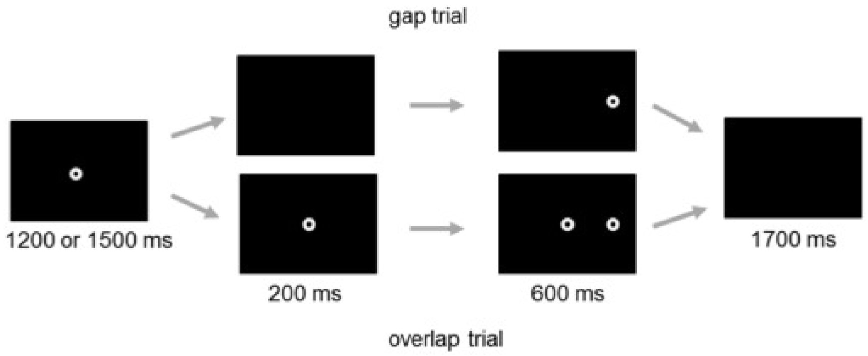

Figure 5. Time-course of gap and overlap trials.

tDCS protocol and experimental procedure

tDCS was delivered by a battery-driven current stimulator (BrainSTIM device, E.M.S., Bologna, Italy) through two electrodes inserted into saline-soaked sponges (target electrode: 5x5 cm^2 and reference electrode: 7x5 cm^2). Anodal tDCS was applied to the target areas (i.e., right FEF and right PPC) for a duration of 10 minutes at 1 mA intensity (Sparing et al., 2009), with 10 s fade-in and fade-out. In the case of sham tDCS, the stimulator was turned off after 30 s (i.e., 10 s fade-in, 10 seconds of stimulation, 10 seconds fade-out). Each participant underwent three experimental tDCS sessions on three different days; in each session, tDCS was applied over the right FEF, over the right PPC, or it was delivered as sham stimulation (the sham tDCS was for half of the participants over the FEF and for the other half over PPC). The order of 3 experimental tDCS sessions was counterbalanced across participants. Target areas were marked on an elastic cap that was centered on participants' head. FEF and PPC had been previously identified by means of a neuronavigation procedure (Softaxic 2.0, E.M.S., Bologna, Italy) on 10 healthy volunteers. The stereotaxic MNI coordinates were: 44, -66, 43 for right PPC (corresponding to P4 of the 10-20 system, Koessler et al., 2009) and 23, -13, 59 for right FEF (Kincade et al., 2005). The anode was placed over the right FEF or PPC (at the center of the 10 marks identified by means of neuronavigation) depending on the condition, whereas the cathode (i.e., the reference electrode), was always located over the left forehead, in a supraorbital position. The electrodes were secured by means of two elastic bands. Figure 6 depicts a simulation of the induced electrical field, calculated with SimNIBS 3.2 (Thielscher et al., 2015). More details about the procedure are reported in the Appendix A.

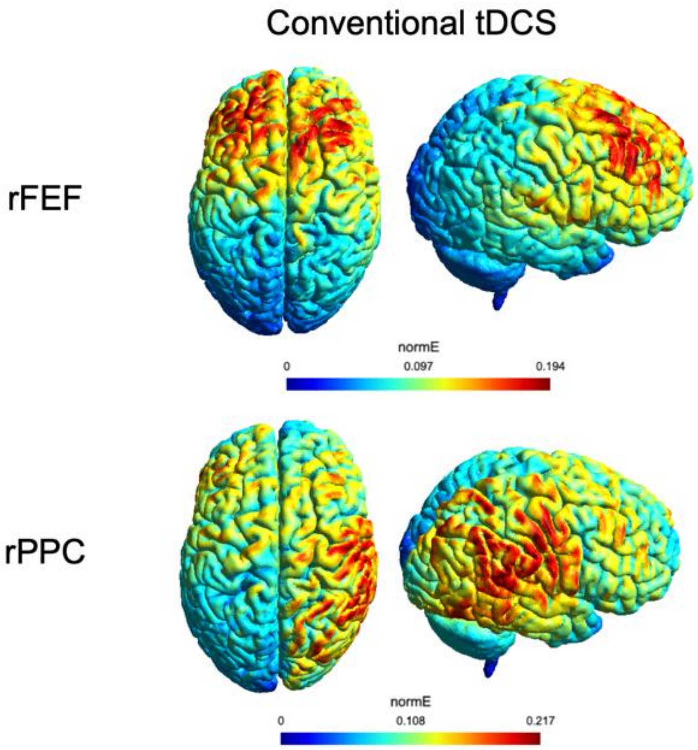

Figure 6. Simulation of the electric field (normE - V/m) performed with SimNIBS. Side and top views of right posterior parietal cortex (rPPC) and right frontal eye field (rFEF).

During each experimental session, participants performed the experimental tasks before and right after tDCS. During the stimulation, they were asked to relax and look at a blank screen. Each session took place at the same time of the day and was separated by at least 24 hours to avoid any possible carry-over effects. At the end of the session, a questionnaire was administered to collect sensations experienced during the stimulation (Fertonani et al., 2017). At the end of the last session, participants were also asked to report whether they received real or sham stimulations and when. See Figure 7, for a schematic representation of the experimental procedure.

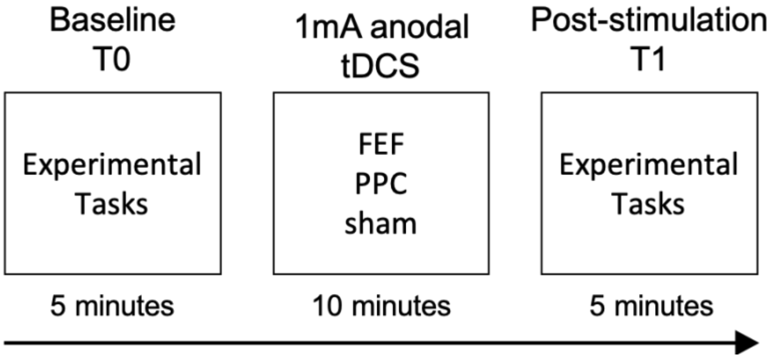

Figure 7. Experimental Procedure

Overall, tDCS was well tolerated and no serious adverse effects occurred. The most-reported sensation was head itching of mild intensity, which began at stimulation onset and quickly stopped. In general, the total score at the questionnaire was higher for both PPC tDCS (p = .013) and FEF tDCS (p = 0.032), as compared to sham tDCS. With respect to the blinding to stimulation, only 7 out of 28 participants correctly identified all three stimulations (see Appendix B for more details).

Data Analyses

Eye movements were automatically parsed into fixations and saccades according to the eye-tracking manufacturer's standard thresholds for velocity and acceleration, that is, 30°/s and 8000°/s^2. This setup is reported to be the best for cognitive research, as it reduces the number of microsaccades and the number of short fixations (<100 ms). Fixations and saccades parameters were computed by and exported from the software SR Research Data Viewer (SR Research Ltd., Canada. Data processing, analysis and visualization were realized using R 3.6.2 (R Core Team, 2021) and specific packages (Bates et al., 2015; Wickham, 2009; Wickham et al., 2019; Kuznetsova et al., 2017; Lenth, 2020; Frossard & Renaud, 2018) within R-Studio 1.2.5033 (RStudio Team, 2020) and jamovi 1.6.9.0 (the jamovi project, 2020) *via* its GAMLj module (Gallucci, 2019). Distributional assumptions checks were performed by means of descriptive and test statistics, as well as visual inspections (Ghasemi & Zahediasl, 2012; Kim, 2013). α was set at .05.

Free Visual Exploration Task

After the exclusion of fixations falling outside of the picture area (.35 %), the final dataset included 54,163 fixations. To analyze the effects of tDCS modulation on the free visual exploration pattern, I adopted an integrated spatial-temporal approach. In fact, previous research (e.g. Chiffi et al., 2021; Paladini et al., 2019; Delazer et al., 2018; Kaufmann et al., 2020) showed a characteristic time-course of visual asymmetries during free visual exploration characterized by an initial exploration of the left side of the pictures – interpreted as pseudoneglect - followed by the exploration of the right side with a final tendency towards the center of the picture. In other words, I aimed to investigate whether and when could tDCS modulate this typical pattern of free visual exploration.

Thus, I firstly tested the effects of tDCS on the average horizontal fixation position, irrespective of the viewing time, whereas, as next step, I employed a nonparametric random permutation procedure to get insights into the effect of time (Hartmann et al., 2019). In order to investigate left-right asymmetries, I calculated the average fixation position on the horizontal axis in pixels – henceforth, the average gaze position - for each participant, considering as main factors: Stimulation (FEF, PPC, and sham), and Timepoint (baseline - T0 and post-tDCS - T1). Moreover, as some participants explored the pictures more actively than others (i.e., more saccades/shorter fixations vs. fewer saccades/longer fixations), the average number of fixations was calculated for each Stimulation and Timepoint, and considered for the analyses.

As first step, I followed a classic "pre-post" approach, that is, comparing the baseline performance (T0) with post-tDCS (T1) performance, for each Stimulation. To this aim, I ran a Linear Mixed Model (LMM) with the average gaze position as dependent variable; fixed effects were tested for Stimulation (FEF, PPC, and sham), Timepoint (T0 and T1), their interaction, and the average number of fixations. Random intercepts were allowed for Stimulation and Timepoint. Significance of the fixed effects were evaluated by means of F-tests with Satterthwaite's method. In case of significant interaction, post-hoc contrasts were defined a priori, by comparing T0 and T1 within each Stimulation.

Afterwards, the effects of tDCS were investigated by means of a baseline-dependent analysis. Indeed, it has been reported that pre-post approaches, as well as correlational ones between baseline and change of performance, may overlook some potential statistical issues such as the regression to the mean (Clifton & Clifton, 2019; Masina et al., 2021). Therefore, I ran an LMM with the average gaze position after tDCS (at T1) as dependent variable; fixed effects were tested for Stimulation (FEF, PPC, and sham), with the baseline performance (i.e. the average gaze position at T0), the interaction between Stimulation and the baseline. The average number of fixations was not included because there was no effect in the previous model (See Results). Random intercepts were allowed for Participants only, because the addition of "Stimulation" yielded a singular fit. Significance of the fixed effects were evaluated by means of F-tests with Satterthwaite's method. Post-hoc contrasts were corrected with Bonferroni's method. The interaction between the baseline performance and Stimulation were decomposed by analyzing the simple effects.

The effects of tDCS on visual exploration patterns from a temporal perspective

In order to investigate *when* (i.e., at which time of the 7s exploration) may tDCS have had an effect, I adopted a similar approach as in Chiffi et al. (2021): the average gaze position was calculated for each participant, stimulation (FEF, PPC, and sham), Timepoint (T0 and T1) over bins of 100 ms, namely 70 bins for 7 s. For each time-bin, it was tested whether the interaction between Stimulation and Timepoint was a significant predictor of the average gaze position. To account for the problem of multiple comparisons, I implemented the nonparametric random permutation procedure suggested by Maris and Oostenveld (2007). Accordingly, adjacent 100 ms bins found significant for a predictor (p<.05) formed a cluster; Fisher's F values of all bins within a cluster were summed up, resulting in "cluster mass values". These values were then compared to a "random distribution" of mass values obtained from randomly permutated bins for 5000 times. Stimulation and Timepoint were included as random terms. Permutations, as well as the corresponding p values, were obtained using the R-package *permuco* (Frossard & Renaud, 2018). Finally, in case the previous analyses indicated significant time cluster for the Stimulation by Timepoint interaction, the horizontal gaze position was averaged for the time period of those significant clusters and an LMM was calculated with Stimulation X Timepoint as factor, and random intercepts for Stimulation and Timepoint. Significance of the fixed effects was evaluated by means of F-test with the Satterthwaite method. In case of significant interaction, post-hoc contrasts were calculated, by comparing T0 and T1 within each Stimulation.

Gap-Overlap Task - Saccadic Reaction Times

Analyses were performed on saccadic reaction times (SRTs), reflecting the saccadic latency from target appearance. Anticipatory/express saccades (i.e., SRTs < 80 ms), multiple-step saccades, as well as saccades in the wrong direction with respect to the target were excluded, as in Paladini et al. (2016). Overall, this procedure led to the exclusion of 2.71% of data, of which 2.29% were gap .42% were overlap.

As non-aggregated raw SRTs for were heavily right-skewed, I adopted a generalized linear mixed model (GLMM) assuming a Gamma distribution. In the first "pre-post" model, I tested a 4-way Stimulation (levels: FEF, PPC, and sham)*Timepoint (levels: baseline T0 and post-stimulation T1)*Trial Type (levels: gap and overlap)*Side (Left and right saccades) term regarding participants as clusters. A random intercept was fitted Stimulation and Timepoint. Bonferroni-corrected comparisons were also performed.

Subsequently, I performed a baseline-corrected analyses on SRTs. Specifically, median SRTs were calculated for each Stimulation, Timepoint (T0 and T1), Side (Left and right saccades), and Trial Type (gap and overlap). Median post-stimulation SRTs (i.e., at T1) were used as dependent variable of an LMM), testing for Stimulation*Side*Trial Type and Stimulation*baseline SRTs interactions (i.e., at T0), with median SRTs at baseline as covariate. Random intercepts were included for participants. Bonferroni-corrected post-hocs were calculated.

Gap-Overlap Task – Gap Effect

GE was calculated for each participant, stimulation, timepoint, and side of saccade by subtracting median gap SRTs from median overlap SRTs. Therefore, bigger values (i.e., bigger differences between gap and overlap SRTs) were interpreted as higher costs of disengagement, whereas lower values as lower costs. As GE values were judged as being Normally distributed, I tested a three-way Stimulation*Timepoint *Side term employing an LMM, with Satterthwaite method for degrees of freedom. Participants were regarded as clusters and a random intercept only was fitted in the model. Bonferroni-corrected post-hoc comparisons were performed.

A “baseline” LMM was also performed, with the median GE at T1 as dependent variable and the Stimulation*Side interaction as factor; median GE at T0 was inserted as covariate and random intercepts were included for participants.

Correlations between tDCS-induced asymmetries in the two tasks

Finally, for each stimulation, Spearman correlations were used to test relationships between tDCS-induced asymmetries in the two tasks. For the FVE, I considered the change of average gaze position (i.e., post-tDCS mean gaze position *minus* pre-tDCS mean gaze position), whereas for the gap overlap paradigm, I first calculated an asymmetry index (AI) of SRTs (i.e., median left SRTs/right SRTs) and then the post stimulation change (post-tDCS AI *minus* pre-tDCS AI) for gap and overlap trials. In general, negative values reflected post-tDCS leftward asymmetries, whereas positive values indicated post-tDCS rightward asymmetries.

3.2.2. Results

Free Visual Exploration Task

The "pre-post" LMM yielded a significant Stimulation by Timepoint interaction ($F_{2,58.8} = 3.91$; $p = .026$). Post-hoc comparisons showed a small leftward deviation (17.7 pixels, .37° of visual angle, $t = 2.55$, $p = .025$) after PPC stimulation as compared to its baseline. No effect of the average number of fixations was found ($F_{1,118.4} = 1.9$; $p = .17$). All results are reported in the Table A3 and Table A4 of the Appendix B. Results are depicted in Figure 7a.

The "baseline" LMM indicated no effect of Stimulation on the average gaze position after tDCS ($F_{2,60.34} = .19$; $p = .825$). I only found a significant effect of the baseline ($F_{1,66.04} = 52.98$; $b = .073$; $p < .001$) indicating a positive association with post-tDCS average gaze position. No interaction between the baseline and Stimulation was observed ($F_{2,60.38} = .2$; $p = .82$). See Figure 7b for a graphical representation of the baseline effect.

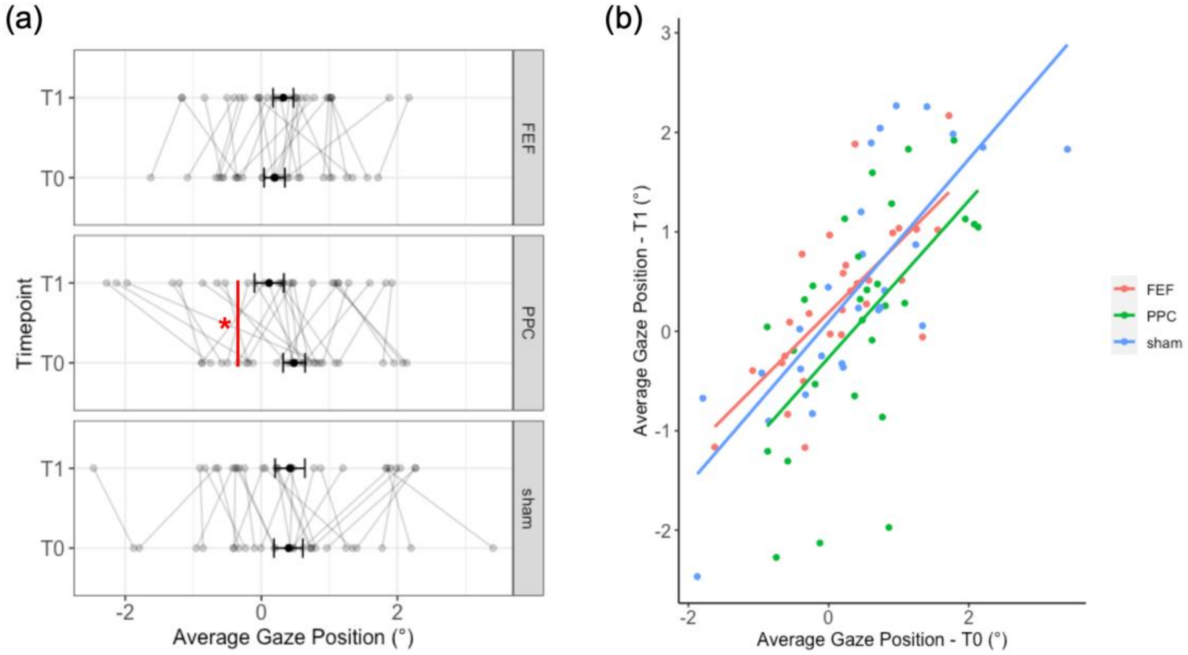

Figure 7. a) Average gaze position relative to the center of the picture for each stimulation session and timepoint. Bold black lines represent the mean values with the standard errors, while individual performances are depicted with grey lines. The red line represents the significant post-hoc comparisons (pre-post LMM). After PPC tDCS (T1), as compared to its baseline (T0), participants' gaze position shifted slightly to the left. b) Regression lines for each stimulation on the baseline performance, as from the "baseline" LMM; * p = .024.

The non-parametric random permutation procedure revealed no significant clusters of time-bins for Stimulation, Timepoint, or their interaction. Therefore, I did not conduct any further analysis. More details are reported in the Table A5 in the Appendix B.

Gap-Overlap Saccadic Reaction Times

The GLMM "pre-post" model revealed a significant main effect of Timepoint (χ^2_1=5.62; p = .018), Trial Type (χ^2_1=5053.51; p<.001), and Side (χ^2_1=5.51; p = .019). As expected, overlap trials were associated with slower SRTs (*M*=175 ms; *SE*=2.86 ms) than gap trials (*M*=234 ms; *SE*=2.85 ms). Notably, we observed a significant Stimulation*Timepoint interaction (χ^2_2=8.86; p = .013): SRTs were significantly faster after tDCS delivered to PPC (ΔPre-Post, i.e., pre *minus* post tDCS = 8.7 ms; p = .008), but not after either FEF (ΔPre-Post = 3.44 ms; p = .1) and sham stimulation (ΔPre-Post = 3.32 ms; p = .1). Finally, the interaction Trial Type*Timepoint (χ^2_1=10.94; p<.001) showed a significant post-stimulation reduction in SRTs for gap trials (ΔPre-Post = 8.81 ms; p<.001) but not for overlap trials (ΔPre-Post= 2.45 ms; p = 1). See Figure 8, for a graphical representation of the main interactions.

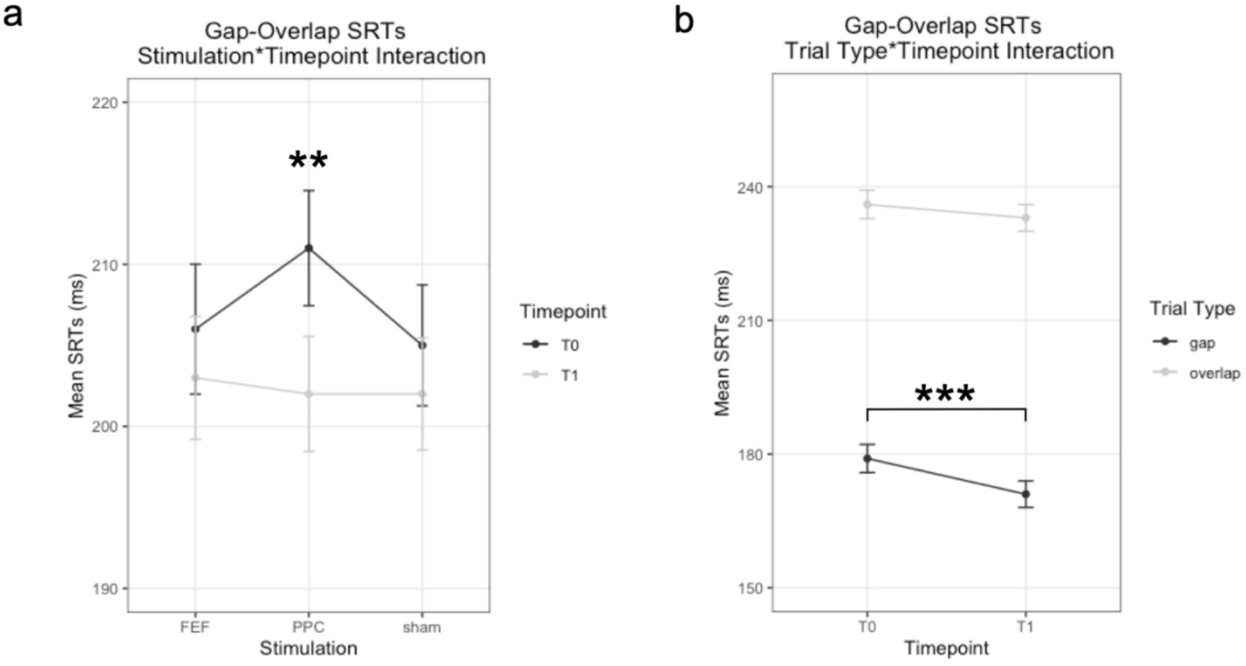

Figure 8. Relevant interactions of the analyses of saccadic reaction times (SRTs). a) Stimulation*Timepoint interaction showing a significant decrease of SRTs after PPC tDCS; b) Trial Type*Timepoint interaction showing a significant post-stimulation decrease for gap trials, only. FEF= frontal eye field; PPC= posterior parietal cortex; T0=before tDCS; T1=after tDCS ;****p* <.001; ***p* <.01

As for the baseline model, the analyses of post-stimulation SRTs could only highlight a significant effect of Trial Type ($F_{1,304.9}$=155.17; p<.001) and a positive association with the baseline values ($F_{1,297}$=154.18; p<.001), indicating a stability of SRTs at baseline (T0) and after (T1) stimulation. The baseline did not interact with Stimulation ($F_{2,307}$=.718 p=.489). All results are reported in the Table A6 and Table A7 of the Appendix B.

Gap Effect (GE)

The analyses did not yield any effect of tDCS. Significant effects of Timepoint ($F_{1,297}$=3.56; p = .007) and Side ($F_{1,297}$=6.99; p = .009) were found: the GE at T0 was lower (*M*=55.1 ms; *SE*=3.7 ms) than at T1 (*M*=62.2 ms; *SE*=3.7 ms), and left GE (*M*=62 ms; *SE*=3.7 ms) was higher than right GE (*M*=55.2 ms; *SE*=3.7 ms). No other effects reached the significance level. All results are reported in Table A8 and Table A9 of the Appendix B and depicted in Figure 9.

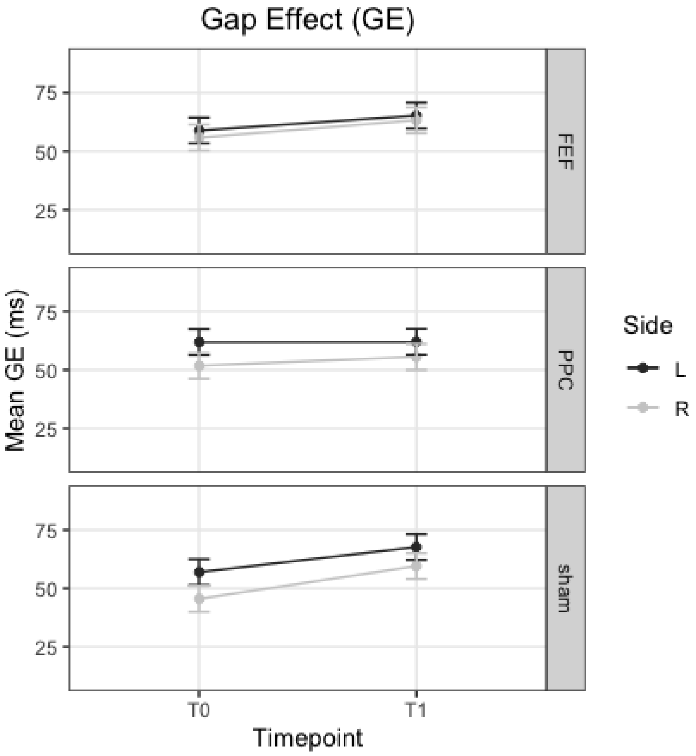

Figure 9. Gap effect (GE) for each stimulation, timepoint and side of saccade. FEF= frontal eye field; PPC= posterior parietal cortex; L= left; R= right.

With respect to the baseline model, the analyses of post-stimulation GE only highlighted a positive association with the baseline values at T0 ($F_{1,131}$=375.49; p<.001), but no effects of tDCS.

Correlations between tDCS-induced asymmetries in the two tasks

No significant correlations between tDCS-induced asymmetries in the two tasks were observed (all ρs < |.3|; all *ps* > .121).

3.2.3. Discussion of the Experiment 1

In this first experiment, I tested the effects of conventional tDCS over right PPC or FEF on overt orienting of visuospatial attention. I investigated whether anodal tDCS, which is thought to increase the excitability of the stimulated area, could induce a contralateral shift of the attentional focus, measured with the FVE task, an ecological, eye-tracking-based paradigm. I adopted a spatio-temporal perspective, namely, I sought to unravel not only *whether*, but also *when* (i.e. at which time point of 7s of exploration) may tDCS have had an effect. Additionally, the effects of tDCS on visuospatial orienting and disengagement were studied within a saccadic perspective, by means of the gap-overlap task.

Free Visual Exploration Task

Interestingly, the first LMM, named the "pre-post" model, indicated a very small (around 17 pixels) leftward shift of the average gaze position only after PPC stimulation, but not after FEF or sham. However, the non-parametric random permutation approach did not reveal a particular time window where this effect could take place, suggesting it may be different for different participants. Overall, these results concur with previous evidence (Sparing et al., 2009; Bolognini et al., 2010; Roy et al., 2015) showing a benefit for attentional orienting towards contralateral stimuli brought about the anodal stimulation of the right PPC. These findings are in line with the model of interhemispheric rivalry by Kinsbourne (1987), according to which, an increased activity of the right-hemisphere vector (as achieved by means of anodal tDCS) would increase its inhibitory effect over the left one, biasing the attention towards the left hemispace.

However, by analyzing the same data with a different statistical approach, a different conclusion may be drawn. Indeed, when the baseline performance was considered to predict tDCS effects (i.e. the average gaze position post-stimulation), no behavioral modulation was found after tDCS. Several studies have previously shown the impact of the baseline level of performance and of brain activation on tDCS efficacy (Learmonth et al., 2015; Masina et al., 2021; Splittgerber et al., 2020). Here, I found a positive association between the baseline attentional bias (leftward or rightward) and post-tDCS performances (indicating a stability of such bias), but regardless of the type of stimulation (real or sham) and the target area (FEF, PPC). Notably, though, by using the change of average gaze position

(T1-T0) in a second model (see Appendix B), the relationship becomes negative, suggesting a reversal of the attentional bias post-stimulation: those participants with a baseline rightward bias are more likely to show a leftward shift at T1, and vice versa. It is worth mentioning, however, that using the baseline to predict a score change often leads to negative associations (Clifton & Clifton, 2019) and even distorted results because of statistical phenomena, such as the regression to the mean. Indeed, some authors (Masina et al., 2021) suggest that the best approach should be the one I followed in the “baseline” model.

Moreover, as can be seen from individual data illustrated in Figure 7, the individual performance on the task is quite variable both before and after brain stimulation. On the one hand, the task has an intrinsic variable nature, as each participant was let free to explore the picture by following any internal personal strategy or preference. One could argue that any observable change is due to such variability. Nonetheless, I tried to control for intrinsic picture saliency variability by creating blocks of picture balanced for left-right saliency and by mirroring these blocks for half of participants. Furthermore, aware that some participants may employ more active exploration strategies, rather than spending more time on single elements of the picture, I included the average number of fixations in the first LMM and found no effect.

Gap-Overlap Task

With respect to the Gap-Overlap task, I observed a general enhancement of saccadic performance (i.e., faster SRTs for both left and right saccades) following PPC stimulations, but not after FEF or sham tDCS. Concerning PPC, to my knowledge, this is the first study to apply neuromodulation over parietal areas to influence saccades. With respect to saccadic eye movements, the right PPC plays an important role in the generation of exogenous saccades as those in our task (Müri & Nyffeler, 2008). Indeed, here I found that tDCS over this area brought about the largest SRTs reduction but without differences between left and right saccades. With respect to this point, from a broader perspective of lateralization and balance of attentional networks, one may have expected a facilitation for leftward saccades following right parietal anodal stimulation, thus paralleling the results of the pre-post analyses of the FVE task. However, it is important to note, that, whereas the gap-overlap task featured a visual scene with no sensory competition and reduced top-down task demands, the FVE task included more complex visual scenes and an interaction of bottom-up and top-down processes, possibly leading to tDCS-induced upregulation of partially different cortico-subcortical networks and lateralized processes (Ptak & Müri, 2013). Nonetheless, there are other possible explanations for such non-lateralized, bilateral decrease of SRTs.

Firstly, although a practice effect must be considered, it is possible that anodal stimulation brought about an additive effect by means of an up-regulation of right-hemispheric circuits of tonic alertness, thus leading to generally faster SRTs (Sturm et al. 1999; Petersen & Posner, 2012). This hypothesis could be explored by analyzing tDCS effects on pupil size as a proxy of arousal (Morad et al. 2000; Paladini et al. 2017). Furthermore, our finding may also reflect what is found in human lesion studies. For example, Pierrot-Deseilligny (1991) found that brain-damaged patients with right parietal lesions showed a bilateral increase of saccadic latency.

Regarding the statistical analyses, the pre-post analysis highlighted significant differences by directly comparing SRTs before (T0) and after (T1) PPC stimulation. One could argue that this effect was driven by relatively slower SRTs before PPC tDCS, however 1) baseline SRTs did not differ significantly among stimulations, and 2) slower SRTs associated to PPC session (reflecting intra-individual variability on different days/sessions) should have been observed even after PPC tDCS, but this was not the case. The "baseline" model, however, by using a different outcome variable, i.e., post-tDCS SRTs, and by taking the individual baseline performance directly into account, did not show significant differences among stimulations. Therefore, before concluding for an actual modulation of SRTs by anodal PPC tDCS, a further replication of this result is warranted. Other important aspects and possible improvements regarding the stimulation protocol will be addressed in the general discussion.

With respect to FEF stimulation, we did not observe an actual modulation brought about by tDCS. Those few works attempting to modulate saccadic parameters by applying FEF tDCS showed mixed results (Kanai et al., 2012; Tseng et al., 2018; Reteig et al., 2018). Whereas Kanai et al (2012) found stimulation- and task- specific effects on saccades directed to the contralateral visual hemifield, Tseng and colleagues (2018) observed that the effects of anodal tDCS over the right FEF depended on the probability of target location and the individual level of performance. On the other hand, Reteig et al (2018), by replicating and improving Kanai’s (2012) experiment, found no effects of either anodal or cathodal stimulation. Our results, despite some methodological differences regarding tDCS montage and stimulation protocol, concur with the null findings of Reteig et al. (2018).

The gap-overlap paradigm also allowed to investigate the effects of tDCS on attentional disengagement, by including both trials with lower (gap) and higher (overlap) disengagement requires. Overall, gap trials were faster than overlap ones, thus confirming the validity of the experimental paradigm (Saslow, 1967). I subsequently calculated the gap effect (GE) to obtain a measure of disengagement costs (Paladini et al., 2016). Both pre-post and baseline-corrected analyses showed that GE was not affected by anodal tDCS. I only observed an increase of GE, irrespective of the type stimulation, which seemed primarily driven by a reduction of SRTs in gap trials (as indicated by the pre-post model, see Figure 8b), rather than by a SRTs slowdown in overlap trials. In other words, after active or sham tDCS participants showed a greater benefit of the fixation offset of the gap trials rather than an increase cost of the disengagement.

A final critical factor, potentially explaining the present mixed findings of both tasks, is the low spatial resolution of the conventional tDCS. The simulation of the electrical field computed with SimNIBS (see Figure 6), clearly shows that PPC tDCS is associated with a widespread diffusion of current over a large portion of right temporal and frontal cortex, with current peaks outside of the target areas. Moreover, FEF tDCS was associated to significant stimulation of left frontal areas, a well-known issue of classic tDCS montages positioning the reference electrodes in contralateral supraorbital positions (see e.g. Thair et al., 2017). Therefore, in Experiment 2, I employed HD-tDCS with concentric electrodes (Bortoletto et al., 2016; Martin et al., 2017), focusing more specifically on the FVE task, to test whether: 1) a more focal current could induce more specific and reliable effects on visuospatial asymmetries , 2) the effects would peak later, by introducing a third time-point (i.e, T2) at 30 minutes after the stimulation (Kuo et al., 2013), and 3) the tDCS effects were dependent on the viewing time, by replicating the random permutation analyses on the time bins.

3.3. Experiment 2 - HD-tDCS

3.3.1. Materials and methods

Participants and sample size estimation

To estimate the sample size for Experiment 2, I replicated the same procedure as in the Experiment 1, but the number of measurements was set to 9, as participants carried out the experimental task 9 times (i.e., three stimulations by three timepoints). According to the results, I recruited 22 right-handed participants (14 females, mean age = 23 y ± 3 years). They all complied with inclusion criteria for brain stimulation and provided written informed consent.

Stimuli and Materials

Free Visual Exploration Task

Task parameters and experimental setting were the same as for Experiment 1, except that in this experiment I created nine new blocks of 25 randomly assigned pictures, for a total of 225 pictures. 120 pictures taken from the database already used in the Experiment 1 and 115 new pictures of naturalistic and urban landscapes were downloaded from Pixabay.com). The choice of increasing the number of pictures was motivated by the high performance variability observed in Experiment 1. In the attempt to reduced it, in Experiment 2, I additionally balanced more thoroughly blocks presentation across experimental sessions and timepoints. A one-way ANOVA confirmed the absence of between-block difference in the ratio between left and right saliency ($F_{8, 216} = .87$; $p = .547$). The order of blocks was counterbalanced so that, across participants, every block was presented at least once for each combination of Stimulation and Timepoint. Moreover, half of participants were administered the same combination of blocks in the same order, but pictures were mirrored along the vertical midline.

HD-tDCS Protocol and Experimental Procedure

The tDCS protocol was the same as for the Experiment 1 in terms of intensity, duration, and localization of target areas, but the current was delivered through two concentric rubber electrodes (neuroCare Group GmbH, Germany), i.e., a round target electrode (diameter = 25 mm) and a reference ring electrode (outer diameter = 100 mm, inner diameter = 75 mm) positioned around the target one. This kind of configuration was first used by Bortoletto et al. (2016) on the motor cortex showing a high spatial accuracy. Compared to 4x1 HD-tDCS setups, a setup with concentric electrodes is more affordable and compatible with classical stimulators. To reduce impendence, ten20 paste (Weaver and Co., US) was applied on both electrodes. Moreover, I employed an elastic tubular net to keep the electrodes in place. Figure 10 depicts a simulation of the induced electrical field, calculated with SimNIBS 3.2 (Thielscher et al., 2015). More details about the procedure are reported in the Appendix A.

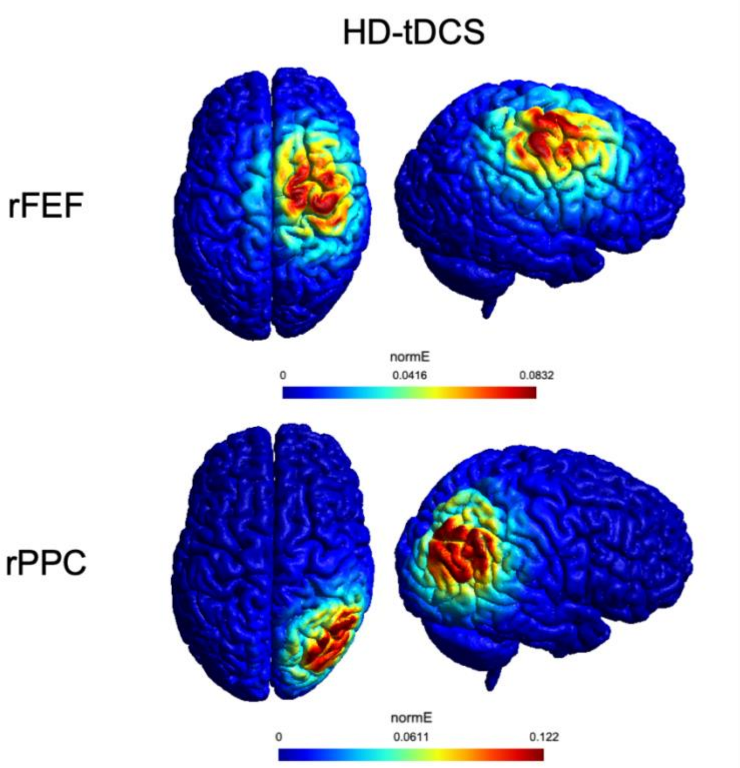

Figure 10. Simulation of the electric field induced by HD-tDCS (normE - V/m) performed with SimNIBS. Side and top views of right posterior parietal cortex (rPPC) and right frontal eye field (rFEF).

Overall, the most reported sensation was head itching of mild intensity, which began at stimulation onset and quickly stopped. Moreover, more frequent and intense sensations were associated with PPC HD-tDCS, as compared to sham stimulation ($p = 0.048$). Full results from the questionnaires assessing the sensations experienced during the stimulation and the sham blinding are reported in Appendix C. The experimental procedure was the same as that of the Experiment 1, but a third assessment was included, T2, delivering the FVE task also 30 minutes after the end of the stimulation.

Data Analysis

Analyses were conducted on 109,267 fixations, excluding those outside of the picture perimeter (i.e., .26%). The mean number of fixations per image was 22.1 (SD = 4.5; range = 12–31). I replicated the same analyses as in the Experiment 1. I first calculated a “pre-post” LMM with the average gaze position as dependent variable, predicted by the Stimulation (FEF, PPC, and sham) by Timepoint (T0, T1, T2) interaction, and the average number of fixations as in index of “exploration strategy”. Random intercepts were participants, only. Bonferroni-corrected post-hoc comparisons were run within each Stimulation.

Subsequently, I ran a “baseline” LMM with the average gaze position after tDCS. Fixed effects were tested for the interaction between Stimulation (FEF, PPC, and sham) and Timepoint (T1 and T2) and the baseline performance. Random intercepts were allowed for Participants. Significance of the fixed effects were evaluated by means of F-test - Satterthwaite method. In case of significant Stimulation by Timepoint interaction, Bonferroni-corrected post-hocs were used. The interactions with the baseline performance and Stimulation were decomposed by analyzing the simple effects.

Employing nonparametric random permutation procedure, I tested for each time-bin of 100 ms the interaction of Stimulation (FEF, PPC, and sham) and Timepoint (T0, T1, and T2). In case of significant time clusters for the Stimulation by Timepoint interaction, the horizontal gaze position was averaged for the time period of those significant clusters and an LMM was calculated with Stimulation by Timepoint as factor and random intercepts for the participants. Significance of the fixed effects was evaluated by means of F-tests - Satterthwaite method and in case of significant interaction, Bonferroni-corrected post-hoc comparisons were run for each Stimulation session.

3.3.2. Results

Overall, the “pre-post” LMM showed no significant effects: Stimulation ($F_{2,167.66}$= .59; p = .558), Timepoint ($F_{2,167.78}$ = 1.29; p = .28), Stimulation x Timepoint ($F_{4,167.78}$ = .61; p = .659), average number of fixations ($F_{1,116.72}$ = .81; p = .37). Averaged and individual data are reported in Figure 11.

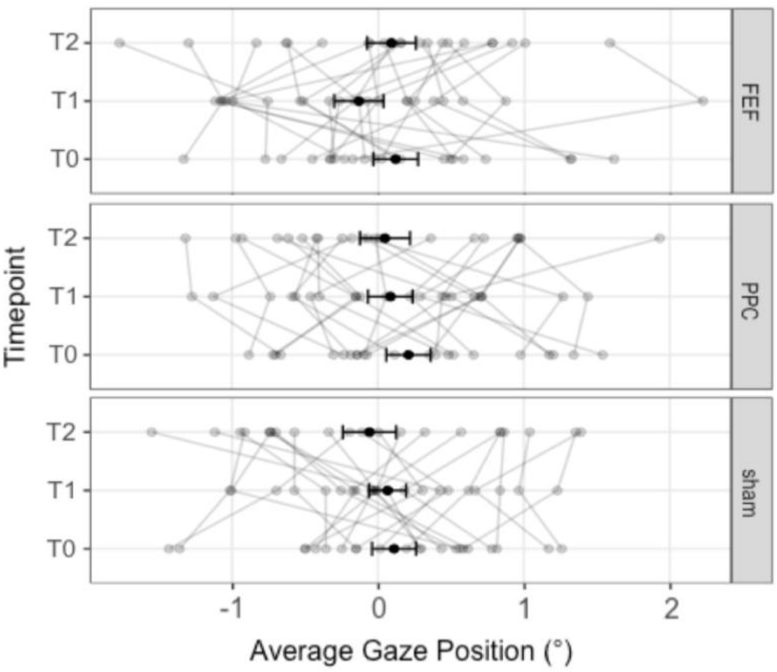

Figure 11. Average gaze position relative to the center of the picture for each stimulation and timepoint. Bold black lines represent the mean values and the standard errors. Individual performances are depicted with grey lines. FEF: Frontal Eye Field; PPC: Posterior Parietal Cortex.

Likewise, the "baseline" LMM yielded no significant effects of Stimulation, Timepoints, the baseline or their interactions (all *ps* > .101). See also the table A12 and A13 of the Appendix C.

Interestingly, the temporal analysis on time-bins by means of non-parametric permutations revealed a small significant cluster of 200 ms (i.e., between 5700 ms and 5900 ms, cluster mass = 9.46; *p* = .005) during which the interaction between Stimulation and Time had a significant effect. The LMM calculated on the average fixation position within this time-frame, indeed, showed a significant Stimulation x Timepoint interaction ($F_{4,168}$ = 5.07; *p* < .001): a more pronounced leftward bias was found immediately after FEF stimulation (i.e., T1) as compared to the baseline (T0 = -37.58 pixels, −0.78° of visual angle; *t* = -2.54; *p* = .036) and the 30-min assessment (T2 = -55.26 pixels, - 1.15° of visual angle; *t* = -3.738; *p* < .001). No significant differences emerged for sham or PPC tDCS (all *ps* > .05). Main results are depicted in Figure 12.

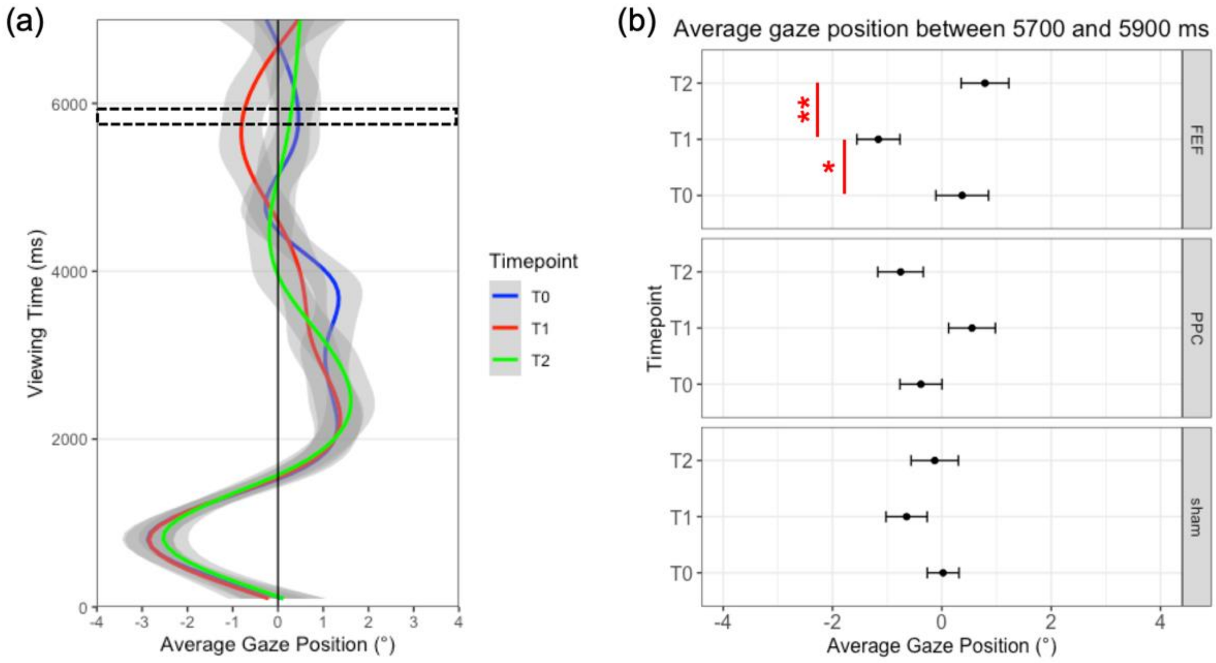

Figure 12. **a)** Time-course of visual exploration at different timepoints for FEF HD-tDCS. The black dotted box represents the time window of interest between 5700 and 5900 ms. **b)** Average gaze position relative to the center of the picture, between 5700 and 5900 ms, for each stimulation and timepoint. Red lines represent significant differences. Error bars= standard error. FEF= Frontal Eye Field; PPC = Posterior Parietal Cortex; * $p < .05$; ** $p < .001$.

3.3.3. Discussion of the Experiment 2

Results of the experiment 2 showed that concentric HD-tDCS did not modulate the average gaze position (without the viewing time), not replicating the trend observed in Experiment 1 with conventional tDCS, namely, a small leftward shift after PPC stimulation. Nevertheless, a more fine-grained analysis of the time-bins, revealed a significant Stimulation by Timepoint interaction around 5800 ms: within this time-window, participants showed an overall leftward shift after FEF stimulation (T1), as compared to the baseline performance (T0) and the performance after 30 minutes from the end of the stimulation (T2).

These findings could be driven by a tDCS-induced up-regulation of the dorsal frontoparietal network involved top-down attentional orienting, which comprises FEF (Corbetta & Shulman, 2002). Indeed, this effect takes place at a later stage of the exploration behavior, namely when participants have already explored both sides of the picture. That is, the FEF-tDCS effect emerged at a time where exploration is more likely to be driven by internal, top-down mechanisms, with respect to the initial phases. In future studies, more structured tasks with a proper “goal” (such as a visual search) could be implemented within the FVE (Nuthmann & Matthias, 2014) to verify such hypothesis.

As previously described, previous works applying tDCS over the right FEF mainly investigated attentional orienting in terms of saccadic latency for peripheral targets, obtaining mixed results (Kanai et al., 2012; Tseng et al., 2018; Reteig et al., 2018). The involvement of FEF in overt attention assessed with an FVE task was also investigated in a study by Cazzoli et al. (2015): by applying inhibitory TMS over right FEF, they found a reduction of exploration times in both hemifields, at the level of the peripheral parts of pictures. However, the authors did not explore the temporal dimension (i.e., the viewing time) as in the present research.

Further methodological reflections will be exposed in the general discussion.

CHAPTER 4

4. General Discussion and Conclusions

The aim of the present PhD thesis was to extend our comprehension of everyday-life visuospatial attention and the temporal evolution of its asymmetries, through the lenses of eye movements and non-invasive brain stimulation. To this aim, I took advantage of a computerized task, i.e., the Free Visual Exploration, an eye-tracking based paradigm that have been used to characterize visuospatial processes in the healthy brain, as well as alterations of such processes in brain-damaged patients with hemispatial neglect. In two studies, I tried to answer some open questions regarding the influence of individual variables on FVE-based asymmetries, its relationship with line bisection – a visuospatial task widely used both in clinical and research setting – and the value of a fine-grained spatio-temporal approach. Moreover, I addressed some crucial aspects of tDCS modulation by comparing anodal modulation of PPC and FEF, and by exploring the complex relationship of baseline-dependent effects and different tDCS focality.

Specifically, in Study 1, I investigated the temporal dynamics of free visual exploration in a sample of 60 younger and older adults, aiming to elucidate the influence of age on typical asymmetries, such as pseudoneglect, and to determine whether pseudoneglect, as assessed by a classic paper-and-pencil line bisection task, would correlate with pseudoneglect observed in a free visual exploration task. Moreover, I tested whether additional factors such as sex, handedness, and subjective alertness would influence the visual exploration behavior. Firstly, results showed the typical pattern of fixation distribution, i.e., an initial pseudoneglect indexed by a leftward bias during the initial phase of the free visual exploration, followed by the exploration of the right part of the picture. This finding is in agreement with previous studies that employed visual exploration to study lateralized biases (Ossandon et al., 2014), even in specific settings (e.g., within far/near space in Hartmann et al., 2019), and under different task requirements (e.g., visual search or memory task in Nuthmann & Matthias, 2014). Secondly, and more importantly, I found a critical time window in the early phase of exploration (between 260 and 960 ms) that was modulated by age: the leftward bias was attenuated with increasing age. To my knowledge, this is the first evidence of the effect of age on FVE-based pseudoneglect in an ecological setting, extending previous finding on reduced hemispheric asymmetries with increasing age (e.g., Schmitz & Peigneux, 2011; Benwell et al., 2014). By contrast, I did not find any effects of sex, handedness or alertness, however future studies should also investigate these aspects by recruiting more balanced sample with respect to these variables.

Furthermore, I found a significant correlation between the line bisection bias and the spatial bias in the FVE, by which a stronger leftward bias in the line bisection task correlated with a stronger leftward deviation in the visual exploration task. As for age, this association takes place within a specific time window. These findings bring additional validity to the usage of FVE paradigms to study visuospatial asymmetries and I believe they may promote future normative studies in order to use FVE more extensively in research and, especially, clinical settings; as previously discussed, FVE tasks are more sensitive to spatial asymmetries than paper-pencil tests such as the line bisection, which is also featured by a high interindividual variability in performance (Mitchell et al., 2020). Moreover, FVE tasks could be used to reliable measures other visuo-spatial disorders, beyond the syndrome of neglect, such as oculomotor visual field exploration in hemianopia and related central visual field disorders (e.g., Bolognini et al., 2005). Taken together, these results also provide a methodological advance in the study of attentional biases and visual exploration strategies, proving the importance of studying the deployment of visuospatial orienting within a temporal perspective; ecological explortion tasks are well suited to this aim.

After the first behavioral study, I decided to test whether the explorative asymmetries could be modulated by means of tDCS applied over frontoparietal circuits of the right hemisphere. Several studies, mostly focusing on the right PPC (e.g., Sparing et al., 2009; Giglia et al., 2011; Bolognini et al., 2013; Benwell et al., 2015), showed that it is possible to modulate visuospatial attention processes - facilitating or inhibiting them - with important potential clinical implications to promote brain plasticity in the treatment of hemispatial neglect. However, the effects of tDCS on visuospatial asymmetries were never tested with ecological paradigms such as the FVE, that may add further evidence about the efficacy of the technique. Furthermore, the outcomes of tDCS applied on frontal areas have been less investigated (Ball et al., 2013; Roy et al., 2015), with most studies focusing on basic saccadic metrics (e.g., saccadic latency; Kanai et al. 2012; Tseng et al. 2018; Reteig et al. 2018), and, overall, yielded conflicting results. Lastly, in light of the reported variability of tDCS results (Horvath et al., 2015), it is important to address two crucial aspects of NIBS, namely, the effect of reduced current spread achieved by focal montages, and, importantly, the effects of state-dependents phenomena, such as the individual baseline performance. Therefore, in Study 2 I investigated to what extent anodal conventional tDCS (Experiment 1) and HD-tDCS (Experiment 2) can modulate visuospatial orienting asymmetries in an FVE task. In a within-participant, sham-controlled approach, offline anodal tDCS was applied over the right PPC and right FEF. I tested whether leftward asymmetries could be induced and possible differences between parietal and frontal stimulation may emerge. Moreover, in Experiment 1, I studied study attentional orienting and disengagement with another experimental task, i.e., the gap-overlap paradigm, a saccadic task under different condition of disengagement from central fixation. Importantly, the effects of tDCS were also tested by means of baseline-corrected models (Masina et al., 2021), and from a fine-grained spatio-temporal perspective.

In Experiment 1, I found a small leftward shift of the average gaze position (FVE task) after PPC stimulation with the conventional tDCS, in line with previous findings (e.g., Sparing et al., 2009); however, such effect was not observed when the post-stimulation gaze position was corrected by its baseline. Likewise, regarding the gap-overlap, I found that PPC, but not FEF or sham, stimulation seemed to induce a bilateral enhancement of SRTs, which, however, was not confirmed by a baseline-corrected model. Taken together, these results concur with previous literature reporting mixed or null findings (Horvath et al., 2015) of single tDCS applications on healthy individuals' cognitive functions. However, as shown by the simulation of the induced current field (Fig. 5), conventional tDCS is associated with a large current spread with current peaks beyond the target area, possibly explaining some variability in my results. For this reason, in Experiment 2, I tested whether the higher spatial resolution of concentric HD electrodes could induce more consistent behavioral changes of exploration behavior. I also explored whether these effects could emerge at a different time post stimulation, i.e., after 30 min as shown by Kuo et al. (2013) in an HD-tDCS study on the motor cortex. Even the more focal HD-tDCS was ineffective in modulating visuospatial asymmetries, regardless of the statistical approach (i.e., pre- and post-stimulation comparisons or data corrected for the baseline performance). However, by looking at the temporal pattern of visuospatial exploration, a tDCS-induced leftward shift emerged after the stimulation of FEF with HD-tDCS; this effect emerged towards the end of pictures exploration, around 6 s.

Overall, the results of Experiment 1 and 2 do not provide definitive conclusions about the effectiveness of offline anodal tDCS over the right FEF or the right PPC on visuospatial orienting, suggesting that the direction of the neuromodulation effects depends on different, potentially interacting, factors. Firstly, the choice of the statistical approach (i.e., comparison between baseline and post-tDCS performance vs. controlling for individual baseline performance) plays a main role in influencing the results. Indeed, in line with the literature about the state-dependency of tDCS effects (Learmonth et al., 2015; Masina et al., 2021; Splittgerber et al., 2020), the baseline level of performance impacts on the direction of the tDCS effects, both by "correcting" post-stimulation effects (thus preventing "false positives") and by showing under which circumstance tDCS is most effective (thus preventing "false negatives" from group-averaged analysis).

A second factor affecting tDCS modulation of free visual exploration is related to the time window of the analysis: I indeed found that time-dependent effects interact with the spatial aspects. This evidence suggests that fine-grained methods, such as the present spatiotemporal approach, may reveal subtle, but significant, effects of neuromodulation, not detectable with gross measures such as the analysis of overall reaction time or response accuracy, at least in the healthy population. On the other hand, this could also imply that, under some experimental conditions, or with respect to some cognitive domains, tDCS effects on healthy human performance could be negligible (Horvath et al., 2015).

The present findings are also of relevance with respect to the putative advantage of using more focal electric stimulations. A lower current spread by using HD electrodes may have diminished the variability the effects variability of the conventional tDCS, thus inducing more reliable behavioral changes. This was not the case in the present study, where we found mixed-to-null effects after conventional tDCS of the right PPC, and a very small, but viewing time-dependent, effect after HD-tDCS applied over the right FEF, but not over the right PPC. Overall, these results do not support a substantial advantage of HD-tDCS over the conventional tDCS, at least for modulating overt visuospatial attention. Rather, with the FVE paradigm, a focal electrical stimulation seems to induce different behavioral effects than the standard tDCS. In this regard, Masina and co-workers (2021) found different electrophysiological changes in EEG frequency bands linked to the focality of the stimulation, showing that alpha power was selectively affected by HD-tDCS, whereas beta power was modulated by conventional tDCS.

However, some methodological differences should be noted in the present tDCS experiments. Firstly, the conventional tDCS and the HD-tDCS electrodes differed both for shape and size. With respect to the size, the reduced area of the target electrode of the HD-tDCS (4.9 vs. 25 cm^2 of the conventional tDCS electrode) also implies an increase of current density (i.e., 0.2 vs. 0.04 mA/cm^2) along with a reduced strength of the electrical field, in turn, possibly inducing different patterns of neurophysiological effects. Indeed, the reported behavioral and physiological effects of different current intensities (e.g., 1 vs. 2 mA) are directly linked to current density (e.g. Batsikadze et al., 2013; Chew et al., 2015). Although some works showed enhanced behavioral effects with higher intensities (e.g., 2 vs. 1 mA HD-tDCS; Fiori et al., 2019), other studies showed more robust effects with lower current intensity (1 vs. 2 mA; Papazova et al., 2018) and even differences in the effect direction, with cathodal tDCS at 2 mA increasing motor cortex excitability, but decreasing it at 1 mA (Batsikadze et al., 2013). Therefore, the focality of stimulation is only one of the factors shaping the complexity of tDCS outcomes.

Additionally, whereas conventional tDCS electrodes are often placed on both hemispheres, the HD-tDCS electrodes are typically confined to one hemisphere. These different montages likely affect the excitability of different intra- and inter-hemispheric networks, a non-trivial aspect in the field of visuospatial orienting (Corbetta & Shulman, 2002; Thiebaut de Schotten et al., 2011). tDCS can modulate long-range activity of areas functionally connected with target one (Pisoni et al., 2018), hence it cannot be excluded that even a focal modulation of parietal areas can affect the functioning of frontal nodes, such as the FEF. Future studies are required to compare the effect of conventional tDCS and HD-tDCS from the perspective of connectivity of task-related brain networks, for example, by means of TMS-EEG (Romero Lauro et al., 2014; Pisoni et al., 2018).

Another limit of the present study is the absence of a within-subject design that would have allowed a direct comparison between HD-tDCS and conventional tDCS, along with the intrinsic differences between Experiment 1 and 2 with respect to sample sizes and to the different number of stimuli presented during the FVE task. These methodological differences may have further impacted the intrinsic inter-individual variability stemming from tasks and from the two neuromodulation techniques, but they also have precluded a between-experiment comparison. Therefore, I cannot exclude the possibility that all these factors could have played a role in my findings.

A final consideration regards the present tDCS protocol. Here I applied tDCS offline, at rest, in the absence of a concurrent task, using a stimulation protocol proved to be effective in modulating visuospatial attention (Sparing et al., 2009). However, as previously said, the behavioral and neurophysiological effects of tDCS are state-dependent (Fertonani

& Miniussi, 2017), with target networks more effectively modulated when they are engaged in a task. Instead, offline neuromodulation protocols seem to primarily affect the Default Mode Network (Li et al., 2019). Future investigations should explore whether the online approach could be more appropriate to reduce variability, giving rise to more reliable effects at the FVE task.

Despite such potential limits, results from the present set of experiments expand the current knowledge of eye tracking- based spatial asymmetries, particularly through the FVE, an ecological task of visual exploration. Taken together, my results provide a behavioral and neuromodulatory characterization of overt attentional orienting in the healthy brain from a spatio-temporal perspective.

This work encourages future adoptions of FVE tasks to study the spatial orienting under ecological conditions, to further confirm its usefulness as a neuropsychological task to assess visuospatial disorders. Moreover, given the increasing interest in NIBS techniques, the present results stimulate further research into the complex relationship among target areas, focality of stimulation, spatiotemporal aspects of deployment of attention, and the role of the individual baseline performance in shaping tDCS effects. All these reflections will be helpful to design future neuromodulation studies on visuospatial attention, with the final goal of confirming the efficacy of tDCS as neuromodulatory technique of cognitive functioning and optimizing its protocols to study human brain plasticity in healthy and pathological populations.

References

Alam, M., Truong, D. Q., Khadka, N., & Bikson, M. (2016). Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). *Physics in Medicine & Biology,* 61(12), 4506.

Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., ... & Corbetta, M. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain*, 137(12), 3267-3283.

Ball, K., Lane, A. R., Smith, D. T., & Ellison, A. (2013). Site-dependent effects of tDCS uncover dissociations in the communication network underlying the processing of visual search. *Brain Stimulation*, *6*(6), 959-965.

Bartolomeo, P., Thiebaut de Schotten, M., & Chica, A. B. (2012). Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience*, 6, 110.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. *arXiv preprint arXiv:1406.5823*.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of Physiology*, *591*(7), 1987-2000.

Beauchamp, M. S., Petit, L., Ellmore, T. M., Ingeholm, J., & Haxby, J. V. (2001). A parametric fMRI study of overt and covert shifts of visuospatial attention. *NeuroImage*, *14*(2), 310-321.

Belopolsky, A. V., & Theeuwes, J. (2012). Updating the premotor theory: the allocation of attention is not always accompanied by saccade preparation. *Journal of Experimental Psychology: Human Perception and Performance*, *38*(4), 902.

Benwell, C. S., Harvey, M., Gardner, S., & Thut, G. (2013). Stimulus-and state-dependence of systematic bias in spatial attention: additive effects of stimulus-size and time-on-task. *Cortex*, *49*(3), 827-836.

Benwell, C. S., Harvey, M., & Thut, G. (2014). On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length. *NeuroImage*, *86*, 370-380.

Benwell, C. S., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*, *69*, 152-165.

Beste, C., Hamm, J. P., & Hausmann, M. (2006). Developmental changes in visual line bisection in women throughout adulthood. *Developmental Neuropsychology*, *30*(2), 753-767.

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., ... & Woods, A. J. (2016). Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimulation,* 9(5), 641-661.

Bolognini, N., Olgiati, E., Rossetti, A., & Maravita, A. (2010). Enhancing multisensory spatial orienting by brain polarization of the parietal cortex. *European Journal of Neuroscience*, *31*(10), 1800-1806.

Bolognini, N., Rasi, F., Coccia, M., & Ladavas, E. (2005). Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain*, *128*(12), 2830-2842.

Bortoletto, M., Rodella, C., Salvador, R., Miranda, P. C., & Miniussi, C. (2016). Reduced current spread by concentric electrodes in transcranial electrical stimulation (tES). *Brain Stimulation*, *9*(4), 525-528.

Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: Effects of hemispace on a tactile line bisection task. *Neuropsychologia*, *18*(4-5), 491-498.

Brooks, J. L., Darling, S., Malvaso, C., & Della Sala, S. (2016). Adult developmental trajectories of pseudoneglect in the tactile, visual and auditory modalities and the influence of starting position and stimulus length. *Brain and Cognition*, *103*, 12-22.

Bruce, C. J., Goldberg, M. E., Bushnell, M. C., & Stanton, G. (1985). Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *Journal of Neurophysiology*, *54*(3), 714-734.

Brysbaert, M., & Stevens, M. (2018). Power analysis and effect size in mixed effects models: A tutorial. *Journal of Cognition*, *1*(1).

Bueno, A. P. A., Sato, J. R., & Hornberger, M. (2019). Eye tracking–The overlooked method to measure cognition in neurodegeneration?. *Neuropsychologia*, *133*, 107191.

Bultitude, J. H., & Davies, A. M. A. (2006). Putting attention on the line: Investigating the activation–orientation hypothesis of pseudoneglect. *Neuropsychologia*, *44*(10), 1849-1858.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage*, *17*(3), 1394-1402.

Cai, Q., Van der Haegen, L., & Brysbaert, M. (2013). Complementary hemispheric specialization for language production and visuospatial attention. *Proceedings of the National Academy of Sciences*, *110*(4), E322-E330.

Casteau, S., & Smith, D. T. (2019). Associations and dissociations between oculomotor readiness and covert attention. *Vision*, *3*(2), 17.

Casteau, S., & Smith, D. T. (2020). Covert attention beyond the range of eye-movements: Evidence for a dissociation between exogenous and endogenous orienting. *Cortex*, *122*, 170-186.

Cazzoli, D., Jung, S., Nyffeler, T., Nef, T., Wurtz, P., Mosimann, U. P., & Müri, R. M. (2015). The role of the right frontal eye field in overt visual attention deployment as assessed by free visual exploration. *Neuropsychologia*, *74*, 37-41.

Chew, T., Ho, K. A., & Loo, C. K. (2015). Inter-and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. *Brain Stimulation*, *8*(6), 1130-1137.

Chieffo, R., Arcari, C., Comi, G., Comola, M., & Leocani, L. (2019). Effects of tDCS in modulating the after-effect of prismatic lenses training in stroke patients with neglect. *Clinical Neurophysiology,* 130(1), e15.

Chiffi, K., Diana, L., Hartmann, M., Cazzoli, D., Bassetti, C. L., Müri, R. M., & Eberhard-Moscicka, A. K. (2021). Spatial asymmetries ("pseudoneglect") in free visual exploration—modulation of age and relationship to line bisection. *Experimental Brain Research*, *239*(9), 2693-2700.

Chokron, S., Bartolomeo, P., Perenin, M. T., Helft, G., & Imbert, M. (1998). Scanning direction and line bisection: A study of normal subjects and unilateral neglect patients with opposite reading habits. *Brain Research. Cognitive Brain Research*, 7(2), 173–178.

Chokron, S., & Imbert, M. (1993). Influence of reading habits on line bisection. *Brain Research: Cognitive*, 1(4), 219–222.

Clifton, L., & Clifton, D. A. (2019). The correlation between baseline score and post-intervention score, and its implications for statistical analysis. *Trials*, *20*(1), 1-6.

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., ... & Shulman, G. L. (1998). A common network of functional areas for attention and eye movements. *Neuron*, *21*(4), 761-773.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201-215.

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569-599.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., & Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*, *2*(4), 201-207.

De Haan, B., Morgan, P. S., & Rorden, C. (2008). Covert orienting of attention and overt eye movements activate identical brain regions. *Brain Research*, *1204*, 102-111.

Delazer, M., Sojer, M., Ellmerer, P., Boehme, C., & Benke, T. (2018). Eye-tracking provides a sensitive measure of exploration deficits after acute right MCA stroke. *Frontiers in Neurology*, *9*, 359.

Diana, L., Pilastro, P., N. Aiello, E., K. Eberhard-Moscicka, A., M. Müri, R., & Bolognini, N. (2021, May). Saccades, attentional orienting and disengagement: the effects of anodal tDCS over right posterior parietal cortex (PPC) and frontal eye field (FEF). In *ACM Symposium on Eye Tracking Research and Applications* (pp. 1-7).

Diana, L., Scotti, G., Aiello, E. N., Pilastro, P., Eberhard-Moscicka, A. K., Müri, R. M., & Bolognini, N. (2022). Conventional and HD-tDCS May (or May Not) Modulate Overt Attentional Orienting: An Integrated Spatio-Temporal Approach and Methodological Reflections. *Brain Sciences*, 12(1), 71.

Dickinson, C. A., & Intraub, H. (2009). Spatial asymmetries in viewing and remembering scenes: Consequences of an attentional bias?. *Attention, Perception, & Psychophysics*, *71*(6), 1251-1262.

Doesburg, S. M., Bedo, N., & Ward, L. M. (2016). Top-down alpha oscillatory network interactions during visuospatial attention orienting. *NeuroImage*, *132*, 512-519.

Dolcos, F., Rice, H. J., & Cabeza, R. (2002). Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neuroscience & Biobehavioral Reviews*, *26*(7), 819-825.

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, *12*(3), 99-105.

Ehrhardt, S. E., Filmer, H. L., Wards, Y., Mattingley, J. B., & Dux, P. E. (2021). The influence of TDCS intensity on decision-making training and transfer outcomes. *Journal of Neurophysiology*, *125*(2), 385-397.

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2020). Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. *Cochrane Database of Systematic Reviews*, (11).

End, A., & Gamer, M. (2017). Preferential processing of social features and their interplay with physical saliency in complex naturalistic scenes. *Frontiers in Psychology*, *8*, 418.

Geng, J. J., & Vossel, S. (2013). Re-evaluating the role of TPJ in attentional control: contextual updating?. *Neuroscience & Biobehavioral Reviews*, *37*(10), 2608-2620.

Goldberg, M. E., & Bruce, C. J. (1985). Cerebral cortical activity associated with the orientation of visual attention in the rhesus monkey. *Vision Research*, *25*(3), 471-481.

Greene, D. J., Barnea, A., Herzberg, K., Rassis, A., Neta, M., Raz, A., & Zaidel, E. (2008). Measuring attention in the hemispheres: The lateralized attention network test (LANT). *Brain and Cognition,* 66(1), 21-31.

Grosbras, M. H., Laird, A. R., & Paus, T. (2005). Cortical regions involved in eye movements, shifts of attention, and gaze perception. *Human Brain Mapping*, *25*(1), 140-154.

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*(3), 340-347.

Ferrier, D. (1874). The localization of function in the brain. *Proceedings of the Royal Society of London*, *22*(148-155), 228-232.

Fertonani, A., Ferrari, C., & Miniussi, C. (2015). What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. *Clinical Neurophysiology*, *126*(11), 2181-2188.

Fertonani, A., & Miniussi, C. (2017). Transcranial electrical stimulation: what we know and do not know about mechanisms. *The Neuroscientist*, *23*(2), 109-123.

Fink, G. R., Marshall, J. C., Weiss, P. H., & Zilles, K. (2001). The neural basis of vertical and horizontal line bisection judgments: an fMRI study of normal volunteers. *NeuroImage*, *14*(1), S59-S67.

Fiori, V., Nitsche, M. A., Cucuzza, G., Caltagirone, C., & Marangolo, P. (2019). High-definition transcranial direct current stimulation improves verb recovery in aphasic patients depending on current intensity. *Neuroscience*, *406*, 159-166.

Foulsham, T., Gray, A., Nasiopoulos, E., & Kingstone, A. (2013). Leftward biases in picture scanning and line bisection: A gaze-contingent window study. *Vision Research*, *78*, 14-25.

Foxe, J. J., McCourt, M. E., & Javitt, D. C. (2003). Right hemisphere control of visuospatial attention: line-bisection judgments evaluated with high-density electrical mapping and source analysis☆. *NeuroImage*, *19*(3), 710-726.

Friedrich, T. E., Hunter, P. V., & Elias, L. J. (2016). Developmental trajectory of pseudoneglect in adults using the greyscales task. *Developmental Psychology*, *52*(11), 1937.

Friedrich, T. E., Hunter, P. V., & Elias, L. J. (2018). The trajectory of pseudoneglect in adults: a systematic review. *Neuropsychology Review*, *28*(4), 436-452.

Friesen, C. K., & Kingstone, A. (1998). The eyes have it! Reflexive orienting is triggered by nonpredictive gaze. *Psychonomic Bulletin & Review*, *5*(3), 490-495.

Frischen, A., Bayliss, A. P., & Tipper, S. P. (2007). Gaze cueing of attention: visual attention, social cognition, and individual differences. *Psychological Bulletin*, *133*(4), 694.

Gallea, C., Wicki, B., Ewenczyk, C., Rivaud-Péchoux, S., Yahia-Cherif, L., Pouget, P., ... & Hainque, E. (2021). Antisaccade, a predictive marker for freezing of gait in Parkinson's disease and gait/gaze network connectivity. *Brain*, *144*(2), 504-514.

Gallucci, M. (2019). GAMLj: General analyses for linear models.[jamovi module].

Gaymard, B., Ploner, C. J., Rivaud-Pechoux, S., & Pierrot-Deseilligny, C. (1999). The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Experimental Brain Research*, *129*(2), 288-301.

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: a guide for non-statisticians. *International Journal of Endocrinology and Metabolism*, *10*(2), 486.

Giglia, G., Mattaliano, P., Puma, A., Rizzo, S., Fierro, B., & Brighina, F. (2011). Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects. *Brain Stimulation,* 4(4), 294-299.

Girotti, F., Casazza, M., Musicco, M., & Avanzini, G. (1983). Oculomotor disorders in cortical lesions in man: the role of unilateral neglect. *Neuropsychologia*, *21*(5), 543-553.

Gooding, D. C., & Basso, M. A. (2008). The tell-tale tasks: a review of saccadic research in psychiatric patient populations. *Brain and Cognition*, *68*(3), 371-390.

Golinkoff, R. M., Ma, W., Song, L., & Hirsh-Pasek, K. (2013). Twenty-five years using the intermodal preferential looking paradigm to study language acquisition: What have we learned?. *Perspectives on Psychological Science*, *8*(3), 316-339.

Gruber, N., Müri, R. M., Mosimann, U. P., Bieri, R., Aeschimann, A., Zito, G. A., ... & Nef, T. (2014). Effects of age and eccentricity on visual target detection. *Frontiers in Aging Neuroscience*, *5*, 101.

Frossard, J., & Renaud, O. (2018). Permuco: Permutation tests for regression,(repeated measures) ANOVA/ANCOVA and comparison of signals (R version 1.0. 1).
Hallett, P. E., & Adams, B. D. (1980). The predictability of saccadic latency in a novel voluntary oculomotor task. *Vision Research*, *20*(4), 329-339.

Hartmann, M., Sommer, N. R., Diana, L., Müri, R. M., & Eberhard-Moscicka, A. K. (2019). Further to the right: viewing distance modulates attentional asymmetries (‘pseudoneglect’) during visual exploration. *Brain and Cognition*, *129*, 40-48.

Hatin, B., Tottenham, L. S., & Oriet, C. (2012). The relationship between collisions and pseudoneglect: Is it right?. *Cortex*, *48*(8), 997-1008.

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*(6), 905-918.

Heilman, K. M. and Van Den Abell, T. (1980) ‘Right hemisphere dominance for attention: The mechanism underlying hemispheric asymmetries of inattention (neglect)’, Neurology. Neurology, 30(3), pp. 327–330. doi: 10.1212/wnl.30.3.327.

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2019). Impact of concurrent task performance on transcranial direct current stimulation (tDCS)-Induced changes in cortical physiology and working memory. *Cortex*, *113*, 37-57.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, *3*(3), 284-291.

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimulation*, *8*(3), 535-550.

Itti, L., Koch, C., & Niebur, E. (1998). A model of saliency-based visual attention for rapid scene analysis. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *20*(11), 1254-1259.

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental Brain Research*, *216*(1), 1-10.

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia*, *38*(1), 93-110.

Jonides, J. (1981). Voluntary versus automatic control over the mind's eye's movement. *Attention and Performance*, 187-203.

Kanai, R., Muggleton, N. G., & Walsh, V. (2012). Transcranial direct current stimulation of the frontal eye fields during pro-and antisaccade tasks. *Frontiers in Psychiatry*, *3*, 45.

Kaufmann, B. C., Cazzoli, D., Pflugshaupt, T., Bohlhalter, S., Vanbellingen, T., Müri, R. M., ... & Nyffeler, T. (2020). Eyetracking during free visual exploration detects neglect more reliably than paper-pencil tests. *Cortex*, *129*, 223-235.

Kim, H. Y. (2013). Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. *Restorative Dentistry & Endodontics*, *38*(1), 52-54.

Kincade, J. M., Abrams, R. A., Astafiev, S. V., Shulman, G. L., & Corbetta, M. (2005). An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. *Journal of Neuroscience*, *25*(18), 4593-4604.

Kinsbourne, M. (1987). Mechanisms of unilateral neglect. In *Advances in Psychology* (Vol. 45, pp. 69-86). North-Holland.

Kinsbourne, M. (1994). Mechanisms of neglect: implications for rehabilitation. *Neuropsychological Rehabilitation*, *4*(2), 151-153.

Klein, R. (1980). Does oculomotor readiness mediate cognitive control of visual attention?. *Attention and Performance*, 8, 259-276.

Koessler, L., Maillard, L., Benhadid, A., Vignal, J. P., Felblinger, J., Vespignani, H., & Braun, M. (2009). Automated cortical projection of EEG sensors: anatomical correlation via the international 10–10 system. *NeuroImage*, *46*(1), 64-72.

Kortman, B., & Nicholls, K. (2016). Assessing for unilateral spatial neglect using eye-tracking glasses: A feasibility study. *Occupational Therapy in Health Care*, *30*(4), 344-355.

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study. *Brain Stimulation*, *6*(4), 644-648.

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. (2017). lmerTest package: tests in linear mixed effects models. *Journal of Statistical Software*, *82*(1), 1-26.

Ladavas, E., Giulietti, S., Avenanti, A., Bertini, C., Lorenzini, E., Quinquinio, C., & Serino, A. (2015). a-tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment in neglect. *Restorative Neurology and Neuroscience*, *33*(5), 647-662.

Learmonth, G., Benwell, C. S., Thut, G., & Harvey, M. (2017). Age-related reduction of hemispheric lateralisation for spatial attention: An EEG study. *NeuroImage*, *153*, 139-151.

Learmonth, G., Gallagher, A., Gibson, J., Thut, G., & Harvey, M. (2015). Intra-and inter-task reliability of spatial attention measures in pseudoneglect. *PloS One*, *10*(9), e0138379.

Learmonth, G., & Papadatou-Pastou, M. (2021). A meta-analysis of line bisection and landmark task performance in older adults. *Neuropsychology Review*, 1-20.

Learmonth, G., Thut, G., Benwell, C. S., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. *Neuropsychologia*, 74, 108-119.

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., ... & Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, *128*(1), 56-92.

Lenth, R., Singmann, H., Love, J., Buerkner, P., & Herve, M. (2018). Emmeans: Estimated marginal means, aka least-squares means. *R package version*, *1*(1), 3.

Li, L. M., Violante, I. R., Leech, R., Ross, E., Hampshire, A., Opitz, A., ... & Sharp, D. J. (2019). Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human Brain Mapping*, *40*(3), 904-915.

Loftus, A. M., & Nicholls, M. E. (2012). Testing the activation–orientation account of spatial attentional asymmetries using transcranial direct current stimulation. *Neuropsychologia*, *50*(11), 2573-2576.

Longo, M. R., Trippier, S., Vagnoni, E., & Lourenco, S. F. (2015). Right hemisphere control of visuospatial attention in near space. *Neuropsychologia*, *70*, 350-357.

Luh, K. E. (1995). Line bisection and perceptual asymmetries in normal individuals: What you see is not what you get. *Neuropsychology*, *9*(4), 435.

Lupiáñez, J., Klein, R. M., & Bartolomeo, P. (2006). Inhibition of return: Twenty years after. *Cognitive Neuropsychology*, *23*(7), 1003-1014.

Machado, L., & Rafal, R. D. (2004). Control of fixation and saccades during an anti-saccade task: an investigation in humans with chronic lesions of oculomotor cortex. *Experimental Brain Research,* 156(1), 55-63.

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG-and MEG-data. *Journal of Neuroscience Methods*, *164*(1), 177-190.

Martin, A. K., Huang, J., Hunold, A., & Meinzer, M. (2017). Sex mediates the effects of high-definition transcranial direct current stimulation on “mind-reading”. *Neuroscience*, *366*, 84-94.

Masina, F., Arcara, G., Galletti, E., Cinque, I., Gamberini, L., & Mapelli, D. (2021). Neurophysiological and behavioural effects of conventional and high definition tDCS. *Scientific Reports*, *11*(1), 1-11.

McCourt, M. E., & Garlinghouse, M. (2000). Asymmetries of visuospatial attention are modulated by viewing distance and visual field elevation: Pseudoneglect in peripersonal and extrapersonal space. *Cortex*, 36(5), 715-731.

Meehan, T. P., Bressler, S. L., Tang, W., Astafiev, S. V., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2017). Top-down cortical interactions in visuospatial attention. *Brain Structure and Function*, *222*(7), 3127-3145.

Mengotti, P., Käsbauer, A. S., Fink, G. R., & Vossel, S. (2020). Lateralization, functional specialization, and dysfunction of attentional networks. *Cortex*.

Milner, A. D., Brechmann, M., & Pagliarini, L. (1992). To halve and to halve not: an analysis of line bisection judgements in normal subjects. *Neuropsychologia*, *30*(6), 515-526.

Minarik, T., Berger, B., Althaus, L., Bader, V., Biebl, B., Brotzeller, F., ... & Sauseng, P. (2016). The importance of sample size for reproducibility of tDCS effects. *Frontiers in Human Neuroscience*, *10*, 453.

Mitchell, A. G., Harris, J. M., Benstock, S. E., & Ales, J. M. (2020). The reliability of pseudoneglect is task dependent. *Neuropsychologia*, *148*, 107618.

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimulation*, *6*(3), 424-432.

Moore, T., Armstrong, K. M., & Fallah, M. (2003). Visuomotor origins of covert spatial attention. *Neuron*, 40(4), 671-683.

Morad, Y., Lemberg, H., Yofe, N., & Dagan, Y. (2000). Pupillography as an objective indicator of fatigue. *Current Eye Research*, *21*(1), 535-542.

Müller, H. J., & Rabbitt, P. M. (1989). Spatial cueing and the relation between the accuracy of “where” and “what” decisions in visual search. *The Quarterly Journal of Experimental Psychology*, *41*(4), 747-773.

Munoz, D. P., & Wurtz, R. H. (1992). Role of the rostral superior colliculus in active visual fixation and execution of express saccades. *Journal of Neurophysiology*, *67*(4), 1000-1002.

Müri, R. M., & Nyffeler, T. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain and Cognition*, *68*(3), 284-292.

Nicholls, M. E., Bradshaw, J. L., & Mattingley, J. B. (1999). Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. *Neuropsychologia*, *37*(3), 307-314.

Nicholls, M. E., Hobson, A., Petty, J., Churches, O., & Thomas, N. A. (2017). The effect of cerebral asymmetries and eye scanning on pseudoneglect for a visual search task. *Brain and Cognition*, *111*, 134-143.

Niemeier, M., & Karnath, H. O. (2000). Exploratory saccades show no direction-specific deficit in neglect. *Neurology*, *54*(2), 515-515.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901.

Nobre, A. C., Gitelman, D. R., Dias, E. C., & Mesulam, M. M. (2000). Covert visual spatial orienting and saccades: overlapping neural systems. *NeuroImage*, *11*(3), 210-216.

Nuthmann, A., & Matthias, E. (2014). Time course of pseudoneglect in scene viewing. *Cortex*, *52*, 113-119.

Nyffeler, T., Cazzoli, D., Wurtz, P., Lüthi, M., Von Wartburg, R., Chaves, S., ... & Müri, R. M. (2008). Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. *European Journal of Neuroscience*, *27*(7), 1809-1813.

Ohmatsu, S., Takamura, Y., Fujii, S., Tanaka, K., Morioka, S., & Kawashima, N. (2019). Visual search pattern during free viewing of horizontally flipped images in patients with unilateral spatial neglect. *Cortex, 13*, 83-95.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.

Ossandón, J. P., Onat, S., & König, P. (2014). Spatial biases in viewing behavior. *Journal of Vision*, *14*(2), 20-20.

Paladini, R. E., Diana, L., Nyffeler, T., Mosimann, U. P., Nef, T., Müri, R. M., & Cazzoli, D. (2016). The asymmetrical influence of increasing time-on-task on attentional disengagement. *Neuropsychologia*, 92, 107-114.

Paladini, R. E., Müri, R. M., Meichtry, J., Nef, T., Mast, F. W., Mosimann, U. P., ... & Cazzoli, D. (2017). The influence of alertness on the spatial deployment of visual attention is mediated by the excitability of the posterior parietal cortices. *Cerebral Cortex*, *27*(1), 233-243.

Paladini, R. E., Wyss, P., Kaufmann, B. C., Urwyler, P., Nef, T., Cazzoli, D., ... & Müri, R. M. (2019). Re-fixation and perseveration patterns in neglect patients during free visual exploration. *European Journal of Neuroscience*, *49*(10), 1244-1253.

Papazova, I., Strube, W., Becker, B., Henning, B., Schwippel, T., Fallgatter, A. J., ... & Hasan, A. (2018). Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. *Schizophrenia Research*, *202*, 203-209.

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience*, 35, 73-89.

Pflugshaupt, T., Bopp, S. A., Heinemann, D., Mosimann, U. P., von Wartburg, R., Nyffeler, T., ... & Müri, R. M. (2004). Residual oculomotor and exploratory deficits in patients with recovered hemineglect. *Neuropsychologia*, *42*(9), 1203-1211.

Pierrot-Deseilligny, C., Milea, D., & Müri, R. M. (2004). Eye movement control by the cerebral cortex. *Current Opinion in Neurology*, *17*(1), 17-25.

Pierrot-Deseilligny, C. H., Rivaud, S., Gaymard, B., & Agid, Y. (1991a). Cortical control of reflexive visually-guided saccades. *Brain*, *114*(3), 1473-1485.
Pierrot-Deseilligny, C. H., Rivaud, S., Gaymard, B., & Agid, Y. (1991b). Cortical control of memory-guided saccades in man. *Experimental Brain Research*, *83*(3), 607-617.

Pisoni, A., Mattavelli, G., Papagno, C., Rosanova, M., Casali, A. G., & Romero Lauro, L. J. (2018). Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. *Cerebral Cortex*, *28*(4), 1132-1140.

Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*, *32*(1), 3-25.

Posner, M. I., & Cohen, Y. (1984). Components of visual orienting. *Attention and performance X: Control of language processes*, *32*, 531-556.

Posner, M. I., Nissen, M. J., & Ogden, W. C. (1978). Attended and unattended processing modes: The role of set for spatial location. *Modes of perceiving and processing information*, *137*(158), 2.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*(1), 25-42.

Proskovec, A. L., Wiesman, A. I., Heinrichs-Graham, E., & Wilson, T. W. (2018). Beta oscillatory dynamics in the prefrontal and superior temporal cortices predict spatial working memory performance. *Scientific Reports*, *8*(1), 1-13.

Ptak, R., Schnider, A., Golay, L., & Müri, R. (2007). A non-spatial bias favouring fixated stimuli revealed in patients with spatial neglect. *Brain*, *130*(12), 3211-3222.

R Core Team. (2021). R: *A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2021

Radant, A. D., Dobie, D. J., Calkins, M. E., Olincy, A., Braff, D. L., Cadenhead, K. S., ... & Tsuang, D. W. (2007). Successful multi-site measurement of antisaccade performance deficits in schizophrenia. *Schizophrenia Research*, 89(1-3), 320-329.

Ramsey, L. E., Siegel, J. S., Baldassarre, A., Metcalf, N. V., Zinn, K., Shulman, G. L., & Corbetta, M. (2016). Normalization of network connectivity in hemispatial neglect recovery. *Annals of Neurology*, *80*(1), 127-141.

Reteig, L. C., Knapen, T., Roelofs, F. J., Ridderinkhof, K. R., & Slagter, H. A. (2018). No evidence that frontal eye field tDCS affects latency or accuracy of prosaccades. *Frontiers in Neuroscience*, *12*, 617.

Reuter-Lorenz, P. A., Hughes, H. C., & Fendrich, R. (1991). The reduction of saccadic latency by prior offset of the fixation point: an analysis of the gap effect. *Perception & Psychophysics*, *49*(2), 167-175.

Rinaldi, L., Di Luca, S., Henik, A., & Girelli, L. (2014). Reading direction shifts visuospatial attention: An interactive account of attentional biases. Acta Psychologica, 151, 98–105.

Rizzolatti, G., Riggio, L., Dascola, I., & Umiltá, C. (1987). Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia*, 25(1), 31-40.

Roig, M., & Cicero, F. (1994). Hemisphericity style, sex, and performance on a line-bisection task: An exploratory study. *Perceptual and Motor Skills*, *78*(1), 115-120.

Romero Lauro, L. J., Rosanova, M., Mattavelli, G., Convento, S., Pisoni, A., Opitz, A., ... & Vallar, G. (2014). TDCS increases cortical excitability: direct evidence from TMS–EEG. *Cortex*, *58*, 99-111.

Roy, L. B., Sparing, R., Fink, G. R., & Hesse, M. D. (2015). Modulation of attention functions by anodal tDCS on right PPC. *Neuropsychologia*, *74*, 96-107.

RStudio Team. (2020). RStudio: Integrated Development for R; RStudio, PBC: Boston, MA, USA,

Sadaghiani, S., & D'Esposito, M. (2015). Functional characterization of the cingulo-opercular network in the maintenance of tonic alertness. *Cerebral Cortex*, *25*(9), 2763-2773.

Salazar, A. P. S., Vaz, P. G., Marchese, R. R., Stein, C., Pinto, C., & Pagnussat, A. S. (2018). Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *99*(2), 355-366.

Saslow, M. G. (1967). Effects of components of displacement-step stimuli upon latency for saccadic eye movement. *Josa*, *57*(8), 1024-1029.

Schall, J. D. (2009). Frontal Eye Fields. Encycl. Neurosci. 2009, 367–374.

Schenkenberg, T., Bradford, D. C., & Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509-509.

Schmitz, R., & Peigneux, P. (2011). Age-related changes in visual pseudoneglect. *Brain and Cognition*, *76*(3), 382-389.

Smith, D. T., & Schenk, T. (2012). The premotor theory of attention: time to move on?. *Neuropsychologia*, 50(6), 1104-1114.

Sparing, R., Thimm, M., Hesse, M. D., Küst, J., Karbe, H., & Fink, G. R. (2009). Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. *Brain*, *132*(11), 3011-3020.

Splittgerber, M., Salvador, R., Brauer, H., Breitling-Ziegler, C., Prehn-Kristensen, A., Krauel, K., ... & Siniatchkin, M. (2020). Individual baseline performance and electrode montage impact on the effects of anodal tDCS over the left dorsolateral prefrontal cortex. *Frontiers in Human Neuroscience*, *14*.

Störmer, V. S., Li, S. C., Heekeren, H. R., & Lindenberger, U. (2013). Normal aging delays and compromises early multifocal visual attention during object tracking. *Journal of Cognitive Neuroscience*, *25*(2), 188-202.

Stuart, S., Parrington, L., Martini, D., Peterka, R., Chesnutt, J., & King, L. (2020). The measurement of eye movements in mild traumatic brain injury: a structured review of an emerging area. *Frontiers in Sports and Active Living*, *2*, 5.

Sturm, W., De Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., ... & Willmes, K. (1999). Functional anatomy of intrinsic alertness: evidencefor a fronto-parietal-thalamic-brainstem network in theright hemisphere. *Neuropsychologia*, *37*(7), 797-805.

Sunwoo, H., Kim, Y. H., Chang, W. H., Noh, S., Kim, E. J., & Ko, M. H. (2013). Effects of dual transcranial direct current stimulation on post-stroke unilateral visuospatial neglect. *Neuroscience Letters*, *554*, 94-98.

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Frontiers in Neuroscience*, *11*, 641.

The jamovi project (2020). jamovi (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org

Thiebaut De Schotten, M., Dell'Acqua, F., Forkel, S., Simmons, A., Vergani, F., Murphy, D. G., & Catani, M. (2011). A lateralized brain network for visuo-spatial attention. *Nature Precedings*, 1-1.

Thiebaut de Schotten, M., Tomaiuolo, F., Aiello, M., Merola, S., Silvetti, M., Lecce, F., ... & Doricchi, F. (2014). Damage to white matter pathways in subacute and chronic spatial neglect: a group study and 2 single-case studies with complete virtual "in vivo" tractography dissection. *Cerebral Cortex*, *24*(3), 691-706.

Thiebaut de Schotten, M., Urbanski, M., Duffau, H., Volle, E., Lévy, R., Dubois, B., & Bartolomeo, P. (2005). Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science*, *309*(5744), 2226-2228.

Thielscher, A., Antunes, A., & Saturnino, G. B. (2015, August). Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS?. In *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 222-225). IEEE.

Tseng, P., Wang, M. C., Lo, Y. H., & Juan, C. H. (2018). Anodal and cathodal tDCS over the right frontal eye fields impacts spatial probability processing differently in pro-and anti-saccades. *Frontiers in Neuroscience*, *12*, 421.

Urwyler, P., Gruber, N., Müri, R. M., Jäger, M., Bieri, R., Nyffeler, T., ... & Nef, T. (2015). Age-dependent visual exploration during simulated day-and night driving on a motorway: a cross-sectional study. *BMC Geriatrics*, *15*(1), 1-12.

Veldema, J., Bösl, K., Neumann, G., Verheyden, G., & Nowak, D. A. (2020). Noninvasive brain stimulation in rehabilitation of hemispatial neglect after stroke. *CNS Spectrums*, *25*(1), 38-49.

Vernet, M., Quentin, R., Chanes, L., Mitsumasu, A., & Valero-Cabré, A. (2014). Frontal eye field, where art thou? Anatomy, function, and non-invasive manipulation of frontal regions involved in eye movements and associated cognitive operations. *Frontiers in Integrative Neuroscience*, *8*, 66.

Vossel, S., Weidner, R., Driver, J., Friston, K. J., & Fink, G. R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *Journal of Neuroscience, 32(31), 10637-10648.*

Weiss, M., & Lavidor, M. (2012). When less is more: evidence for a facilitative cathodal tDCS effect in attentional abilities. *Journal of Cognitive Neuroscience*, *24*(9), 1826-1833.

Wickham, H. (2009). Elegant graphics for data analysis. *Media*, *35*(211), 10-1007.

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L. D. A., François, R., ... & Yutani, H. (2019). Welcome to the Tidyverse. *Journal of Open Source Software*, *4*(43), 1686.

Appendixes

Appendix A. Electric field Simulation with SimNIBS 3.2.4

Current distribution was simulated on the head model provided with the software (i.e. “Ernie”). First, MNI coordinates of target areas were transformed into the subject space by means of a dedicated MATLAB function (*mni2subject_coords*), i.e., 38.3, -70.2, 59.9 for PPC and 20.8, -17.5, 82 for FEF. In fact, the software auto-adjusted these values, thus resulting in 50.1, -82.74, 66.82 for PPC and 34.76, -12.11, 107.4 for FEF.

For the conventional tDCS montage, the target electrode was assigned a current value of +1mA, electrode size = 5 cm x 5 cm, electrode thickness = 1 mm, sponge thickness = 2 mm; sponge size = 6 cm x 5 cm. The reference electrode was located over the contralateral supraorbital position at -31.46, 81.07, 48.78 for both PPC and FEF simulation. It was assigned a current value of -1mA, electrode size = 7 cm x 5 cm, electrode thickness = 1 mm, sponge thickness = 2 mm; sponge size = 8 cm x 6 cm.

For the HD-tDCS montage, we used the same coordinates and current intensity for the target electrode, but we specified: elliptical electrode size = 2.5 cm x 2.5 cm, electrode thickness = 1 mm, gel thickness = 1 mm. As for the reference ring electrode, in absence of a proper setup, we simulated 8 small circular electrodes (elliptical electrode size = 1.25 cm x 1.25 cm - corresponding to the width of the ring electrode; thickness = 1 mm, gel thickness = 1 mm), positioned around an imaginary circle of 7.5 cm of diameter – the inner diameter of the ring electrode – centered to the target electrode position. See Figure A1 for an example. Each of the 8 small electrodes were assigned a current value of -.125 mA, resulting in a total current of -1mA.

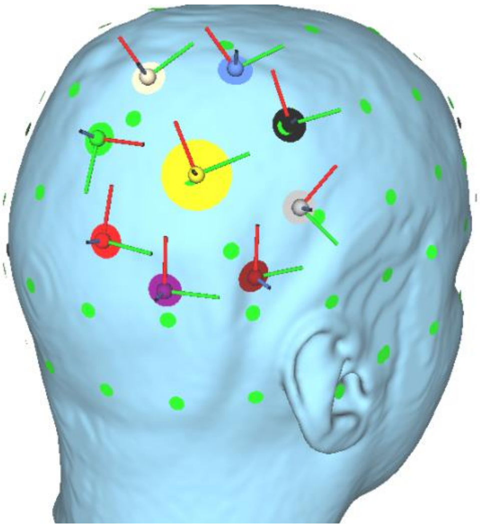

Figure A1. Example of electrodes configuration for the simulation of PPC HD-tDCS. In yellow, the target electrode. The colored, small, electrodes around the target one represent an approximation of the ring-shaped, return electrode.

Appendix B. Study 2 - Experiment 1 (Conventional tDCS)

Appendix B.1. tDCS-related sensations and sham blinding

At the end of each tDCS session, we administered a 7-item questionnaire (adapted from Fertonani et al., 2015) to evaluate the potential adverse effects of tDCS. Participants were asked to report whether they felt 1) itching, 2) pain, 3) burning, 4) heat, 5) pinching, 6) metallic taste, or 7) fatigue, rating the intensity of their sensations using a 5-point scale (i.e., 0=absent, 1=Mild, 2=Moderate, 3=Considerable, 4=Strong). Moreover, they had to indicate when the feeling/discomfort began, when it stopped, where it was localized, and whether the it affected their performance. The reported sensations, their frequencies and the most reported intensities can be found in Table A1.

Table A1. tDCS-related sensations, their frequency and the most reported intensity after frontal eye field (FEF), posterior parietal cortex (PPC), and sham stimulations.

	FEF		PPC		sham	
Item	*N*	Most reported	*N*	Most reported	*N*	Most reported
Itching	23	Mild	25	Mild	20	Mild
Pain	2	Mild, Moderate	2	Mild	0	
Burning	18	Mild	17	Mild	12	Mild
Heat	11	Mild	11	Mild	12	Mild
Pinching	25	Mild	24	Mild	18	Mild
Metallic Taste	1	Moderate	0		0	
Fatigue	8	Moderate	5	Mild	5	Mild

Overall, all participants localized the sensations on the head and these sensations were never rated as “Strong”. Only one participant reported considerable pinching, burning, and itching after PPC stimulation.

For FEF stimulation, 27 participants experienced these sensations at the beginning of the stimulation, whereas only one participant at the end of the stimulation. Most participants, i.e., 21, reported that these sensations stopped quickly or in the middle of the stimulation, whereas for 7 participants these sensations stopped at the end of the stimulation. With respect to the influence on the task, only two participants reported that the feelings may have had a mild effect on the performance. Regarding PPC stimulation, the sensations started at the beginning of the stimulation for all participants and stopped quickly or in the middle of the stimulation for most of them (24), whereas for 4 participants at the end of the stimulation. With respect to the influence on the task, only one participant reported that the feelings may have had a mild effect on the performance. For sham stimulation, 4 participants reported no feelings. 23 participants experienced these sensations at the beginning of the stimulation, 1 participant in the middle. For 22 participants the sensations stopped quickly, whereas for 2 of them at the end of the stimulation. No participants reported that these sensations might have had an effect on the performance.

Responses to the questionnaire were statistically analyzed to explore differences among sessions. Participants’ total score at the questionnaire (maximum score = 28, indexing that each of the seven questionnaire items was rated as “Strong”, obtaining a score of 4) in each tDCS session was analyzed by means of an LMM analysis with “Stimulation” as a factor; random intercepts were considered for participants. The significance of the fixed effects was evaluated by means of an F-test with Satterthwaite’s method and Bonferroni-corrected post-hoc contrasts were used whenever necessary. A significant difference emerged between tDCS sessions (F_{254} = 5.34; *p* = .008): as compared to sham tDCS (mean total score = 2.46, SE = .4), higher scores were reported for both FEF (mean total score = 4, SE = .4; *p* = .013) and PPC tDCS (mean total score = 3.82, SE = .4; *p* = .032), with no differences between them (*p* = .9).

Concerning the blinding to sham stimulation, a chi-square analysis was performed to test the ability to discriminate between real and sham stimulation. As shown in the table of contingence (see Table A2), whereas most of participants would correctly identify FEF and PPC stimulations as real, sham stimulation was correctly identified by less than half of participants ($\chi^2(2) = 9.58$; $p = .008$). However, only 7 participants correctly identified all three stimulations.

Table A2. Blinding to conventional sham stimulation.

	FEF		PPC		sham	
	Count	Adapted residuals	Count	Adapted residuals	Count	Adapted residuals
Correct	23	1.3	21	1.8	11	-3.1
Wrong	5	-1.3	7	-1.8	17	3.1

Appendix B.2. Free Visual Exploration task - Detailed Statistics

Detailed results of the pre-post model (Table A3), the Stimulation*Timepoint interaction (Table A4), and time-bin clusters of the random permutation model (Table A5).

Table A3: Free Visual Exploration task – pre-post GLM

Factor	Sum Sq	MeanSq	df	*F*	*p*-value
Stim	461.8	230.90	2, 26.79	.45	.641
Timepoint	371.6	371.63	1, 27.58	.73	.401
No. of Fixations	973.5	973.52	1, 118.44	1.9	.17
Stim*Timepoint	3998.4	1999.18	2, 53.81	3.9	.026

Note: Stim: Stimulation

Table A4. Free Visual Exploration task - Post-hoc comparisons of the significant Stimulation*Timepoint interaction

Comparisons	estimate	SE	df	*t* ratio	*p*-value
FEF T0 – FEF T1	2.58	3.48	73.2	.45	.922
PPC T0 – PPC T1	-8.84	3.46	72.5	.73	.026
Sham T0 – Sham T1	.02	3.58	73.3	1.9	1

Note: comparisons between post-stimulation (T1) and baseline (T0) average gaze position (in pixels) for posterior parietal cortex (PPC), frontal eye field (FEF), and sham conventional tDCS.

Table A5. Free Visual Exploration task - Random permutation model of the viewing time analysis (time-bins)

Factor	Start	End	Cluster mass	*p* (> mass)
Stimulation	62	62	4.88	.491
Timepoint	3	3	5.70	.73
	19	19	5.3	.79

Factor	Start	End	Cluster mass	*p* (> mass)
	24	24	4.13	.95
	30	30	5.04	.83
	44	44	4.25	.93
	53	53	4.41	.92

Note: Cluster of time-bins with mass value > 4 for Stimulation and Timepoint

Appendix B.3. Free Visual Exploration task - The relationship between the baseline and the change in gaze position

An LMM was run with the "shift of average gaze position after tDCS" (i.e. T1-T0) as dependent variable; fixed effects were tested for Stimulation (FEF, PPC, and sham), with the baseline performance (i.e. the average gaze position at T0), and the interaction between Stimulation and the baseline. Random intercepts were allowed for participants. Significance of the fixed effects were evaluated by means of F-test with Satterthwaite's method. Post-hoc contrasts were corrected with Bonferroni's approach. The interaction between the baseline performance and Stimulation were decomposed by analyzing the simple effects.

The model yielded no effect of Stimulation tDCS ($F_{2,60.34}$ = .19; *p* = .825), but a significant effect of the baseline ($F_{1,66.04}$ = 7.15; *b* = -.27; *p* = .009) - indicating a negative association with the shift of average gaze position –, but no baseline by Stimulation interaction ($F_{2,60.38}$ = .2; *p* = .82). Figure A2 represents the associations between baseline and shift of average gaze position.

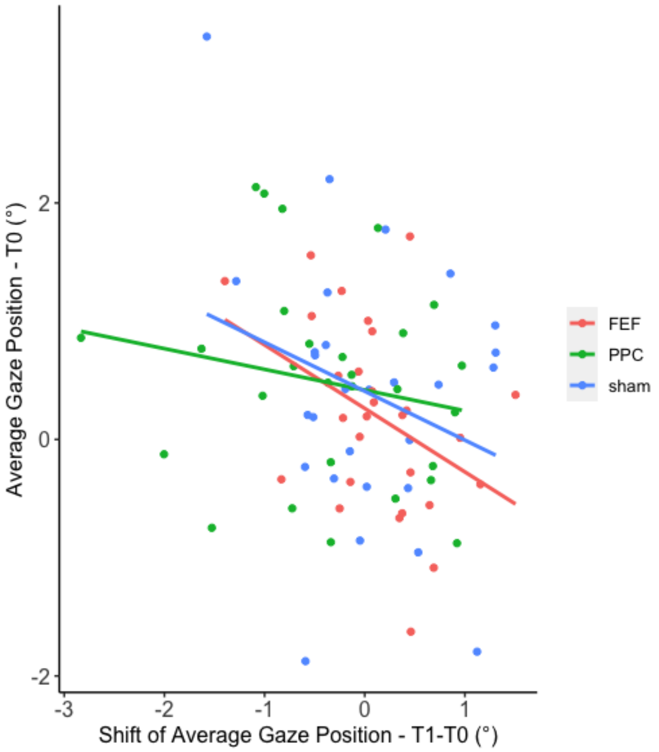

Figure A2. Regression lines of the shift of average gaze position (T1-T0) on the baseline performance (T0) for Frontal Eye Field (FEF), Posterior Parietal Cortex (PPC), and sham stimulation.

Appendix B.4. Gap-Overlap task - Analyses of saccadic reaction times

Main effects and interactions of the pre-post and baseline analyses are reported in Table A6 and Table A7, respectively.

Table A6. Gap-Overlap task - Main effects and interactions of the pre-post model

Factors	X^2	df	*p-value*
Stimulation	.487	2	.784
Timepoint	5.618	1	.018
Side	5.52	1	.019
Trial Type	5053.51	1	<.001
Stimulation * Timepoint	8.76	2	.013
Stimulation * Side	.541	2	.763
Timepoint * Side	.344	1	.557
Stimulation * Trial Type	.215	2	.898
Timepoint * Trial Type	10.94	1	<.001
Side * Trial Type	17.48	1	<.001
Stimulation * Timepoint * Side	.133	2	.936

Stimulation * Timepoint * Trial Type	.803	2	.669
Stimulation * Side * Trial Type	2.493	2	.287
Timepoint * Side * Trial Type	.893	1	.345
Stimulation * Timepoint * Side * Trial Type	.09	2	.957

Table A7. Gap-Overlap task - Main effects and interactions of the baseline model

Factors	*F*	df	*p-value*
Stimulation	.234	2, 26.1	.793
Side	.263	1, 243.7	.608
Trial Type	1551.715	1, 304.9	<.001
Baseline	1540.968	1, 262.1	<.001
Stimulation * Trial Type	.675	2, 243.2	.510
Stimulation * Side	14.391	2, 243.3	.239
Stimulation * Baseline	.718	2, 307	.489
Side * Trial Type	.173	1, 244.3	.678
Stimulation * Side * Trial Type	.025	2, 243.2	.975

Appendix B.5. Gap-Overlap task - Analyses of the Gap Effect

Main effects and interactions of the pre-post and baseline analyses of the Gap Effect (GE) are reported in Table A8 and Table A9, respectively.

Table A8. Main effects and interactions of GE pre-post analyses

Factors	*F*	df	*p-value*
Stimulation	.68	2, 297	.506
Timepoint	7.46	1, 297	.007
Side	6.99	1, 297	.009
Stimulation * Timepoint	1.35	2, 297	.262
Stimulation * Side	.73	2, 297	.482
Timepoint * Side	.26	1, 297	.609
Stimulation * Timepoint * Side	.03	2, 297	.973

Table A9. Main effects and interactions of the baseline model of the GE effect

Factors	*F*	df	*p-value*
Baseline	375.485	1, 131	<.001
Side	.368	1, 127	.545
Stimulation	14.088	2, 126	.248
Side * Stimulation	.047	2, 125	.954

Appendix C. Study 2 - Experiment 2 (HD-tDCS)

Appendix C.1. HD-tDCS-related sensations and sham-blinding

As in the Experiment 1, at the end of each tDCS session a 7-item questionnaire evaluating potential adverse effects of tDCS) was administered. The reported sensations, their frequencies and the most reported intensities can be found in Table A10.

Table A10. HD-tDCS-related sensations, their frequency and the most reported intensity after frontal eye field (FEF), posterior parietal cortex (PPC), and sham stimulations

	FEF		PPC		sham	
Item	*N*	Most reported	*N*	Most reported	*N*	Most reported
Itching	17	Mild	16	Moderate	15	Mild
Pain	9	Mild	8	Mild	7	Mild
Burning	15	Mild	14	Mild	12	Mild
Heat	8	Mild	13	Mild	8	Mild
Pinching	20	Mild	18	Mild	17	Mild
Metallic Taste	0		1	Mild	0	
Fatigue	4	Mild	5	Mild	7	Mild

All participants localized the sensations on the head and these sensations were never rated as “Strong”. Only one participant reported “Considerable” burning and heat after FEF stimulation.

For FEF stimulation, all participants experienced tDCS-related sensations at the beginning of the stimulation. Nineteen participants reported that these sensations stopped quickly or in the middle of the stimulation, whereas for three participants they stopped at the end of the stimulation. Five participants reported that tDCS-related sensations had a mild effect on their performance. Regarding PPC stimulation, the sensations started at the beginning of the stimulation for all participants and stopped quickly or in the middle of the stimulation for most of them (N = 18), whereas for three participants these sensations stopped at the end of the stimulation. One participant did not report any sensation. Three participants reported that the feelings may have had a mild effect on the performance. For sham stimulation, one participant reported no feelings. Twenty participants experienced these sensations at the beginning of the stimulation, one participant at the end. For all participants, the sensations stopped quickly. Four participants reported that tDCS-related sensations could have influenced their performance. LMM analyses conducted on the questionnaire total scores (see Appendix B) showed a significant difference between stimulations ($F_{242} = 3.7$; $p = .033$): PPC HD-tDCS was associated with more frequent and intense sensations (mean total score = 4.68, SE = .49) as compared to sham HD-tDCS (total score = 3.36, SE = .49; $p = .048$). No significant differences emerged between PPC and FEF HD-tDCS (mean total score = 4.5, SE = .49; $p = .1$) or between FEF and sham HD-tDCS ($p = .109$).

With respect to the blinding to sham stimulation, the chi-square analysis indicated no significant association between the type of stimulation and the correctness of the guess

($\chi^2(2) = 5.96$; *p* = .051). See also Table A11. Of note, only three participants correctly identified all three stimulation.

Table A11. Blinding to HD sham stimulation.

	FEF		PPC		sham	
	Count	Adapted residuals	Count	Adapted residuals	Count	Adapted residuals
Correct	14	1.3	14	1.8	7	-3.1
Wrong	8	-1.3	8	-1.8	15	3.1

Appendix C.2. Free Visual Exploration task - Detailed Statistics

Table A12 report detailed statistics of the FVE baseline-corrected analyses, respectively.

Table A12. Free Visual Exploration task -HD-tDCS - baseline-model

Factor	Sum Sq	MeanSq	df	*F*	*p*-value
Stim	482.22	241.11	2, 101.96	.39	.676
Timepoint	120.33	120.33	1, 95.5	.2	.659
Baseline	808.69	808.69	1, 117.91	1.32	.254
Stim*Timepoint	2779.49	1389.74	2, 95.5	2.27	.11
Stim*Baseline	507.20	253.60	2, 101.96	.41	.663
Timepoint*baseline	127.11	127.11	1, 95.5	.21	.65
3-ways interaction	2885.26	1442.63	2, 95.5	2.35	.101

Note: Stim: Stimulation.