

Dissecting visual attention

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Dissecting visual attention: on the origin of attentional bias, alerting, and orienting effects

Ting Wang



Maastricht University

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Dissecting visual attention: on the origin of attentional bias, alerting, and orienting effects

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Ting Wang

born on 5 December 1993
in Hubei, China

Supervisor

Prof. Dr. Alexander T. Sack

Co-supervisor

Dr. Felix Duecker

Assessment Committee

Prof. Dr. Peter de Weerd (Chair)

Prof. Dr. Caroline van Heugten

Prof. Dr. Vincenzo Romei (University of Bologna, Italy)

Dr. Fren Smulders

Dr. Paul Taylor (Ludwig Maximilian University of Munich, Germany)

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Chapter 1

General introduction

1.0 General introduction

Visual attention is an omnipresent aspect of our daily experiences that allows us to navigate a world rich with stimuli. However, our attention capacity is limited, which therefore necessitates a selection process that filters the most pertinent information from an overwhelming array of options. The process of visual selection, akin to a mental spotlight, enables us to efficiently process and prioritize the visual information that matters most at any given moment. This process plays an essential role in our daily interactions, helping us navigate complex scenes, quickly identify important cues, and make sense of our surroundings in a streamlined manner. One critical aspect of visual attention is visual spatial attention. Just as a spotlight focuses on a specific area on a stage, spatial attention directs our cognitive resources to particular locations within our visual field or physical space. This selective focus on spatial information allows us to enhance the processing of objects, events, or regions in our environment, while temporarily reducing our awareness of other areas. This feature becomes especially evident when people have deficits in spatial attention control, as in the case of spatial neglect. Neglect is a condition in which individuals, often due to brain injury, are unable to process one side of their visual field, typically the left side. In daily life, this might manifest as a person exclusively consuming food from the right side of their plate or only attending to the right side of their body.

Here, it may be illuminating to consider how the experience of spatial neglect affects the attention of those with the condition. Imagine a neglect patient, Z, walking down a corridor with doorways on both sides. Because of spatial neglect, Z's **attention is biased** toward the right side while ignoring the left side. As Z continues to walk down the corridor, he/she might maintain close proximity to the right wall, disregarding everything on the left. Suddenly, the lights in the corridor extinguish, enveloping the surroundings in darkness. This abrupt change alarms the senses and provokes a heightened physiological response, such as an increased heart rate and alertness. The sudden darkness is interpreted as an **alerting** signal to respond to any potential changes that may ensue. At this precise moment, a person steps out from a doorway on Z's left and remarks, "It is so dark here," creating an auditory cue. The **orienting** effect of attention immediately comes into play, causing Z's attention to shift toward the source of the sound. Despite the spatial neglect bias, the cognitive system still rapidly orients to the auditory stimulus, showcasing its capacity to process and respond to new information.

These attention phenomena exist everywhere, and not only for spatial neglect patients. The work presented in this thesis will focus on the phenomena of attention bias and attentional effects, including alerting and orienting effects, through the use of diverse methods. The overall objective is to obtain a deeper understanding of these phenomena. As a first step in this project, this introduction delves into various aspects of (spatial) attention.

1.1 Attention bias

As an example of how a spatial neglect patient perceives the world, they may focus their attention on the right side but ignore the left one. For instance, they might eat food from only the right side of their plate or dress only the right side of their body. Spatial neglect, a severe disorder characterized by a significant deficit in attending to and perceiving stimuli presented on one side of space (Corbetta & Shulman, 2011), occurs more commonly and severely after damage to the brain's right hemisphere, particularly the parietal lobe (Corbetta et al., 2005). Individuals with spatial neglect after right hemisphere damage may ignore people or objects or be unaware of sensory inputs from the left side of their environment.

Certain tasks, such as line bisection and landmark tasks, which require patients to indicate the perceived midpoint of horizontal lines (or differentiate whether lines are bisected based on existing marks), serve as valuable tools for evaluating spatial neglect resulting from stroke or other brain injuries (Sack, 2010; Schuhmann et al., 2022). These tasks also serve as helpful experimental paradigms in healthy individuals, as they accurately reveal spatial attention biases (Benwell et al., 2013; Learmonth & Papadatou-Pastou, 2022; Okon-Singer et al., 2011). In these paradigms, individuals consistently misjudge the midpoint of a horizontal line, showing a tendency to favor the left side (see Fig. 1). This intriguing pattern has captured many researchers' interest and is referred to as "pseudoneglect" (Bowers & Heilman, 1980; Jewell & McCourt, 2000). This phenomenon is believed to stem from the functional lateralization of the brain, in which case the right hemisphere plays a greater role in processing spatial information, resulting in a slight preference for the left visual field (Vogel et al., 2003).

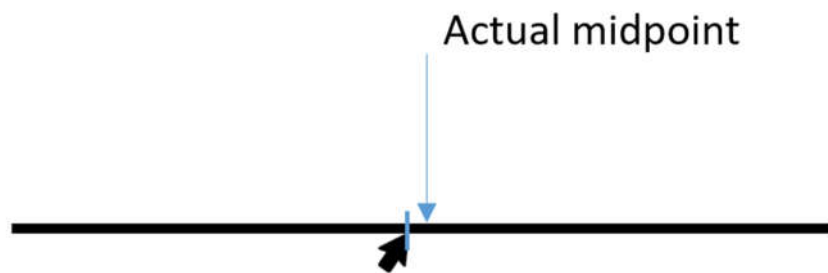


Fig. 1. In the line bisection task, we showed the participants a horizontal line and asked them to cross it with a vertical line at its center. Most participants crossed the line a bit to the left of the actual midpoint, which is indicative of leftward attention bias.

Another task that is closely related to spatial neglect and attention bias is the visual detection task. In this case, stimuli are presented on either the left or right side of a central fixation point, or bilaterally, and participants report whether they perceive stimuli on the left, right, or both sides (e.g., Pascual-Leone et al., 1994). The bilateral condition relates to the extinction phenomenon, which means that there is a failure to perceive a stimulus in the contralesional hemifield when a second competing stimulus is simultaneously presented in the ipsilesional hemifield (Riddoch et al., 2009). This condition can be interpreted as somewhat analogous to the line bisection task mentioned earlier. However, what sets it apart is the unilateral condition. This means that changes in target detection are assessed independently in both hemifields, allowing for more informative results. By including all three conditions (left/right unilateral and bilateral conditions), these tasks still enable the calculation of attention bias (i.e., via the difference in detection performance between left and right for unilateral stimuli or the proportion of left versus right responses in the case of bilateral stimuli). Moreover, they offer the opportunity to evaluate detection rates in each hemifield in isolation (i.e., detection rates of stimuli on the left or right considered independently).

1.2 Visuospatial attention

Transitioning from the traditional concept of attention biases, researchers have come to appreciate that attention is not fixed, but rather highly flexible and adaptable. Attention can be manipulated using various cues and stimuli, and it can be intentionally directed, leading to changes in how cognitive resources are allocated. The ability to manipulate attention provides valuable opportunities to investigate the underlying mechanisms of attentional processes.

Specifically, it allows researchers to explore how particular cues or stimuli influence attention and what factors modulate attentional shifts.

One especially intriguing aspect of attention is the alerting effect, which is manipulated by alerting cues, much like the case of lights suddenly going out. An alerting cue is a sensory signal or stimulus that serves as a trigger that signals the imminent appearance of a target stimulus. These cues are signals that can capture our attention and prepare our cognitive system for an upcoming event. The alerting effect pertains to the enhancement of attention in response to cues that signal the imminent arrival of a target stimulus. This heightened state of attention, triggered by alerting cues, makes us more efficient and responsive to incoming information. It prepares our cognitive resources, rendering us more vigilant and prepared to process relevant stimuli. Consequently, we can react more swiftly and accurately when completing tasks or in response to events, thereby enhancing our overall performance.

Another striking aspect of attention is the orienting effect, which is manipulated by orienting cues, akin to a voice on the left side. Orienting cues are sensory signals or stimuli that provide information about the spatial location of a target stimulus. These cues direct our attention to a particular region in space, thereby guiding our gaze and focus toward relevant information. Orienting cues can be either exogenous or endogenous (see Fig. 2A & 2B). An exogenous orienting cue is an external stimulus that automatically captures our attention without conscious effort. These cues are typically salient and stand out from the background, thus grabbing our attention involuntarily. Examples of exogenous cues include sudden flashes of light, a loud noise, or a fast-moving object in the periphery of our vision. An endogenous orienting cue is an internal signal or symbolic cue that requires conscious processing and voluntary effort. These cues are typically informative and provide spatial information about the location of a target. Endogenous cues are often arrows or other visual symbols that indicate where the target will appear. The orienting effects refer to the changes in attention that occur in response to orienting cues. When presented with an orienting cue, our attention shifts toward the cued location, resulting in an attentional shift to that specific region in space.

In summary, the alerting effect enhances attention in response to cues by signaling the imminent arrival of a target stimulus, while the orienting effect involves the allocation of attention based on prior spatial information. Exogenous cueing tasks investigate the attentional orienting driven

by external cues, whereas endogenous cueing tasks focus on attentional orienting driven by internal cues or voluntary shifts of attention. Together, these attentional effects provide valuable insights into the dynamic nature of cognitive processes and the mechanisms behind attentional control.

One of the most famous experimental paradigms designed to understand the exogenous and endogenous manipulation of attention is the spatial cueing task (Posner et al., 1980). In this task, the participants fixate their gaze on a central point on the screen, and a cue (exogenous or endogenous) is presented. Following the cue, a target stimulus appears in the periphery, either on the left or right side of the fixation point. Participants are then required to discriminate the target stimulus and respond accordingly (see Fig. 2C & 2D). The manipulation of attention comes from cues that provide different information, such as by indicating the location (where) or timing (when) of the upcoming stimulus. This manipulation leads to what are known as alerting (when) and orienting effects (where), respectively (Posner and Cohen, 1984; Posner et al., 1980).

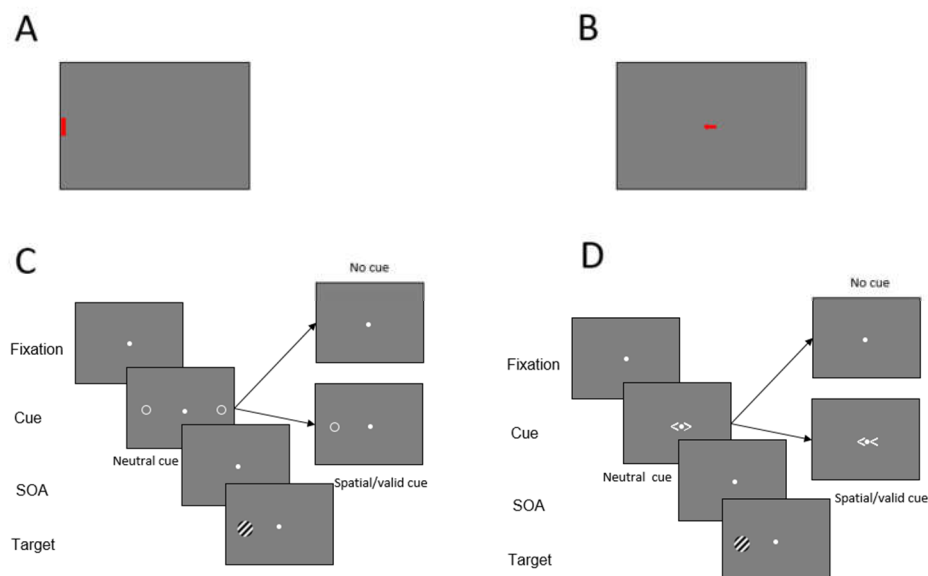


Fig. 2. (A) An example of visuospatial attention being automatically manipulated with a target location cue. (B) An example of visuospatial attention voluntarily being manipulated with a center location cue. (C) An example of an exogenous cueing task. A peripheral cue (which could be nothing/no cue, a neutral cue, or a spatial/valid cue) is briefly presented, after which the target stimulus is presented in the left or right hemifield. (D) An example of an endogenous cueing task. A center cue (which could be nothing/no cue, a neutral cue, or a spatial/valid cue) is briefly presented, after which the target stimulus is presented in the left or right hemifield.

1.3 Brain networks and the neural basis of attention

1.3.1 Neuroanatomical network of attention

The phenomena of spatial attention bias and spatial neglect find their neural basis in the interplay of attentional networks and hemisphere asymmetry (Corbetta et al., 2005). These networks comprise the interconnected brain regions responsible for regulating attentional processes and directing cognitive resources toward relevant stimuli.

Functional magnetic resonance imaging (fMRI) studies in healthy human participants (Corbetta & Shulman, 2002) have revealed the existence of multiple fronto-parietal networks for spatial attention: the dorsal attention network (DAN) and ventral attention network (VAN). The DAN, often termed the “top-down” attention network, is primarily associated with spatial processing and goal-directed attention. It includes certain brain regions, such as the intraparietal sulcus (IPS) and frontal eye fields (FEF), that constitute a bilateral network. The VAN, also known as the “bottom-up” attention network, specializes in detecting salient or behaviorally relevant stimuli in the visual field. Core regions, including the temporo-parietal junction (TPJ) and the ventral frontal cortex, exhibit right-lateralized dominance (see Fig. 3A).

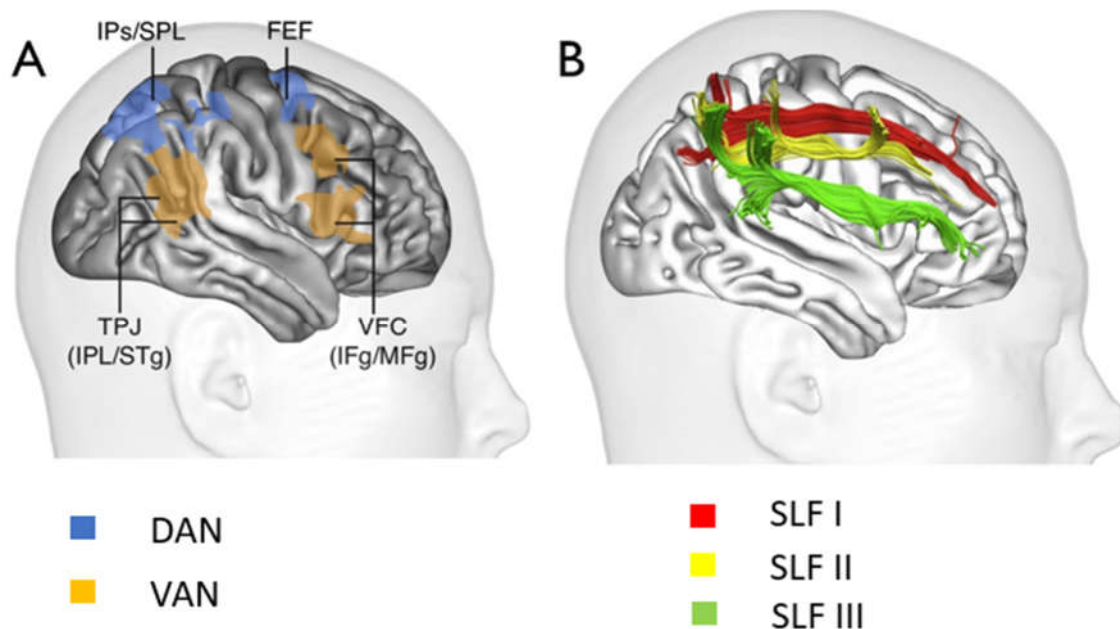


Fig. 3. (A) Right hemisphere networks of visuospatial attention (DAN and VAN), according to Corbetta and Shulman (2002). (B) Three branches of the superior longitudinal fasciculus (SLF), according to Thiebaut de Schotten et al. (2011). These figures are adapted from Chica, Bartolomeo, and Lupiáñez (2013).

The core nodes of the DAN and VAN are not only functionally connected, but also structurally connected through anatomical pathways, specifically the superior longitudinal fasciculus (SLF) branches (see Fig. 3B). Thiebaut de Schotten et al. (2011) demonstrated that the SLF III connects brain regions within the VAN, whereas the DAN is connected by the human homologue of the SLF I. The SLF II connects the parietal component of the VAN to the prefrontal component of the DAN, thereby facilitating direct communication between the VAN and DAN. Importantly, in concurrence with the asymmetries of blood-oxygen-level-dependent (BOLD) response during fMRI—with a larger right hemisphere response for the VAN and more symmetrical activity for the DAN (Corbetta & Shulman, 2002)—the SLF III (connecting the VAN) is anatomically larger in the right hemisphere than in the left hemisphere. In contrast, the SLF I (connecting the DAN) is more symmetrically organized. The lateralization of the SLF II strongly correlates with behavioral indicators of right hemisphere specialization for visuospatial attention, such as pseudoneglect in line bisection (Bowers & Heilman, 1980; Jewell & McCourt, 2000; Toba et al., 2011) and asymmetries in the speed of detection between the right and left hemifields (de Schotten et al., 2011).

It is generally accepted that attention involves a bilaterally distributed network with asymmetrically represented components in the two hemispheres (Greene et al., 2008; Shulman et al., 2010). At the neural level, the alerting of visuospatial attention has been linked with more widespread neural activation in the right hemisphere (Corbetta et al., 2000; Corbetta & Shulman, 2011; Petersen & Posner, 2012; Sturm & Willmes, 2001). The orienting of visuospatial attention selectively engages the right parietal cortex (Corbetta et al., 2000), a core node in the DAN. It has been proposed that the sub-regions of the DAN control the visuospatial focus of attention via interhemispheric competition. According to this view, an overactivation in one hemisphere relative to the other leads to a shift in visuospatial attention toward the hemifield contralateral to that hemisphere (Kinsbourne, 1977; Szczepanski & Kastner, 2013). For both alerting and orienting effects, right hemispheric dominance may induce attentional lateralization to the left.

1.3.2 Temporal processing characteristics of attention

While researchers have investigated the neuroanatomical foundations of attention, they have also emphasized unraveling the temporal dynamics inherent in attention.

Electroencephalography (EEG) is a powerful tool for studying the neural dynamics of attention due to its excellent temporal resolution in the order of milliseconds (Gazzaniga and Mangun, 2014). Among the various oscillatory brain activities, alpha oscillations (7 – 13 Hz) have been recognized as playing a crucial role in visual perception and attention (de Graaf et al., 2020; Klimesch, 2012; Nelli et al., 2017; Ruzzoli et al., 2019; van Diepen et al., 2016). Studies have shown that posterior alpha oscillatory brain activity is closely related to both explicit and implicit attentional processes. The role of posterior oscillatory brain activity within the alpha range (7 – 13 Hz) is focused either on tasks explicitly requiring voluntary shifts of spatial attention (Dombrowe and Hilgetag, 2014; Rihs et al., 2009; Sauseng et al., 2005; Worden et al., 2000; Yamagishi et al., 2005) or on implicitly assessing attentional processes by probing variations in perceptual performance (Hanslmayr et al., 2007; Lange et al., 2013; van Dijk et al., 2008). Pre-stimulus alpha power has been shown to predict general task performance (Händel et al., 2011; Hanslmayr et al., 2007; Thut et al., 2006; van Dijk et al., 2008), while also being linked to the spatially specific attentional biases that spontaneously occur in visual tasks (Boncompagni et al., 2016).

Event-related potential (ERP) studies have corroborated the fact that spatial attention can evoke an increase in the amplitude of the posterior P1 and N1 components, particularly in the bilateral occipital region. P1 has been explained in terms of reflecting sensory selection (e.g., Heinze et al., 1990) via top-down suppression (Hillyard et al., 1998), whereas N1 has been attributed to indexing the orienting of attention (Luck et al., 1990; Natale et al., 2006) via neural activation amplification (Hillyard et al., 1998). In contrast to the attentional operations attributed to P1 and N1, various findings indicate that the P2 component in the parieto-occipital regions (Freunberger et al., 2007) indexes working memory function (Lefebvre et al., 2005; Taylor et al., 1990; Wolach & Pratt, 2001), particularly by encoding for attentional stimuli (Chapman et al., 1978; Dunn et al., 1998). A negative component N2 peaking at 240 ms at the posterior electrodes has been found to show differences in attentional attribution (Busch & VanRullen, 2010). Moreover, the anterior P2 has also been reported as an index of feature detection processes (Luck and Hillyard, 1994) for attentional stimuli.

These findings indicate that EEG signals can serve as a valuable tool for detecting the neural dynamics of visuospatial attention, including the processing of alerting and orienting effects.

1.4 Visuospatial attention theories

Despite the extensive efforts invested by researchers to understand the neural basis of right hemispheric dominance in attention bias, theoretical debates in this domain still persist. There are two widely supported theories of attention (Duecker & Sack, 2015; Gallotto et al., 2020): Heilman's hemispacial theory (Heilman & Abell, 1980) and Kinsbourne's interhemispheric competition theory (Kinsbourne, 1977). These theories offer valuable perspectives on how imbalances in attentional processing and disruptions in specific brain regions contribute to observed attentional biases. Both theories conclude that the right hemisphere causes more pronounced functional attention effects. However, they offer differing explanations for this asymmetry by attributing the attentional control contributions of each hemisphere to two fundamentally different processes.

Heilman's hemispacial theory postulates that the right hemisphere is not necessarily "stronger," but rather has an expanded function. Specifically, the right hemisphere shifts attention to both visual hemifields, while the left hemisphere is only able to shift attention to the right visual hemifield (Heilman & Abell, 1980). Thus, under normal circumstances, the right hemisphere exhibits dominance, resulting in a leftward bias. Once the left parietal is damaged, the function of attention on the right side may experience only a minor impact, because the intact right hemisphere can compensate for the left hemisphere's function, thereby assisting in attention shifts to the right side. In this case, the right hemisphere can partially take over the attentional control that would have been primarily handled by the left hemisphere. In contrast, if the right parietal region is damaged, the function of attention on the left side may be significantly affected. This is because the left hemisphere mediates attention shifts to the right side, and if it is damaged, there is no intact hemisphere to compensate for this function. As a result, attentional control toward the left side of space may be more severely impaired.

As an alternative point of view, Kinsbourne's interhemispheric competition theory comprises two main proposals. First, it suggests that the left hemisphere is dominant in contralateral hemifield bias. Second, this theory posits that both hemispheres induce an attentional bias toward their respective contralateral visual hemifield. This leads to reciprocal inhibition between the hemispheres, as they work together to maintain a balance within the attentional

system (Kinsbourne, 1977). In this theory, the left hemisphere-induced bias toward the right hemifield is somewhat stronger, and once disinhibited after a right hemispheric lesion (i.e., a loss of interhemispheric balance), this stronger functional spatial attention bias toward the right side of space causes left hemineglect.

These different theories attempt to elucidate the intricate operations of a healthy brain and shed light on how attention can falter following brain damage. Despite substantial advancements in our understanding, the complexities of hemispheric asymmetries continue to evade complete comprehension, even after several decades of investigation. However, these challenges were brought into new light with the invention of the new technology of transcranial magnetic stimulation (TMS), which can mimic brain damage in the normal brain.

TMS is a non-invasive brain stimulation technique that allows for the manipulation of brain activity in humans by exposing specific brain areas to a rapidly changing magnetic field (Hallett, 2000; Pascual-Leone, 2000; Sack, 2006; Walsh & Cowey, 2000). TMS involves placing a coil over the scalp to generate magnetic pulses. When a brief, intense current passes through the coil, it induces a magnetic field that penetrates the skull and influences the underlying brain tissue (Cukic et al., 2009). TMS can create what is known as a “virtual lesion” in the brain (Bien et al., 2012; Siebner et al., 2009; Silvanto & Cattaneo, 2017), which refers to the transient disruption of neural activity in a specific brain region induced by TMS. By targeting a particular area with magnetic pulses, researchers can temporarily interfere with its normal function, effectively “turning off” or impairing the activity in that region (Walsh & Pascual-Leone, 2003). This virtual lesion approach allows researchers to mimic brain injury and observe changes in behavioral performance (Hilgetag et al., 2001). Studies using inhibitory TMS on parietal regions of the healthy brain, combined with the performance of a line bisection task, can evaluate its effect on attentional bias shift and determine whether this pattern is similar to that found in neglect patients (Bagattini et al., 2015; Salatino et al., 2014, 2019; Szczepanski & Kastner, 2013). While many studies in this field have been conducted, the data from the last two decades have not yet been aggregated in meta-analyses.

The hemispheric asymmetries could be evaluated by comparing the aggregated effect between the left and right hemisphere TMS stimulations. To differentiate the Heilman and Kinsbourne models, a comparison of the effects on the left and right hemifields after left and right

hemisphere TMS is essential, as these two models make different predictions. In Heilman's model, what can be strongly predicted is a contralateral deficit after right or left stimulation. While the theory arose to explain why neglect after right hemisphere damage is more common and severe (Beis et al., 2004; Corbetta et al., 2005; Suchan et al., 2012), it is unclear how strongly we should expect similar results in TMS-induced "impairments" in otherwise healthy brains. A soft supposition might have a larger contralateral impairment effect after right as compared to left parietal TMS. Kinsbourne's model offers further predictions, particularly about the effects of TMS on ipsilateral visual detection. Once the left or right parietal cortex is inhibited, this should not only impair the contralateral hemifield but also, owing to the altered interhemispheric balance/competition, enhance detection in the ipsilateral hemifield. Thus, a meta-analysis examining the effects of TMS on the parietal cortex after the left and right hemispheres is needed to evaluate hemispheric asymmetry. Also, a meta-analysis of the visual detection tasks for checking TMS effects on the parietal cortex would be helpful to evaluate the accuracy of Heilman's and Kinsbourne's theoretical predictions.

While a meta-analysis can typically uncover patterns and associations within existing data, computational models allow us to delve deeper by simulating and testing various hypotheses. This latter approach enables us to dissect the underlying cognitive mechanisms governing different aspects of attention, thus extending our insights beyond those limited to attentional bias.

1.5 Drift diffusion model

To return back to alerting and orienting effects, reaction times (RTs) and accuracy are typically used to assess cue-related effects by computing differences between cue conditions. However, relying solely on RTs or accuracy as outcome measures has its limitations (Voss et al., 2013). Simple tasks can involve multiple cognitive processes, from early visual processing and decision making to motor response preparation and execution. All of these processes can influence the final RT. While differences in the final RT can provide valuable information, which specific cognitive (sub) processes have contributed to these RT differences between cue conditions often remains unclear. Consequently, these RT measures may not offer a more specific understanding of the cognitive processes involved, and they are limited in explaining the origins of alerting and orienting effects.

To overcome these limitations, attentional tasks need to combine approaches, including the use of neuroimaging techniques and computational modeling, and thus consider a wide range of cognitive processes.

The drift diffusion model (DDM) is a computational model in psychology and neuroscience that is widely used to explain decision-making processes in tasks involving perceptual judgments. The DDM conceptualizes decision making as a diffusion process, through which evidence accumulates over time until a decision threshold is reached. It assumes that evidence accumulation is noisy and influenced by various factors, including sensory input and cognitive biases (see Fig. 4).

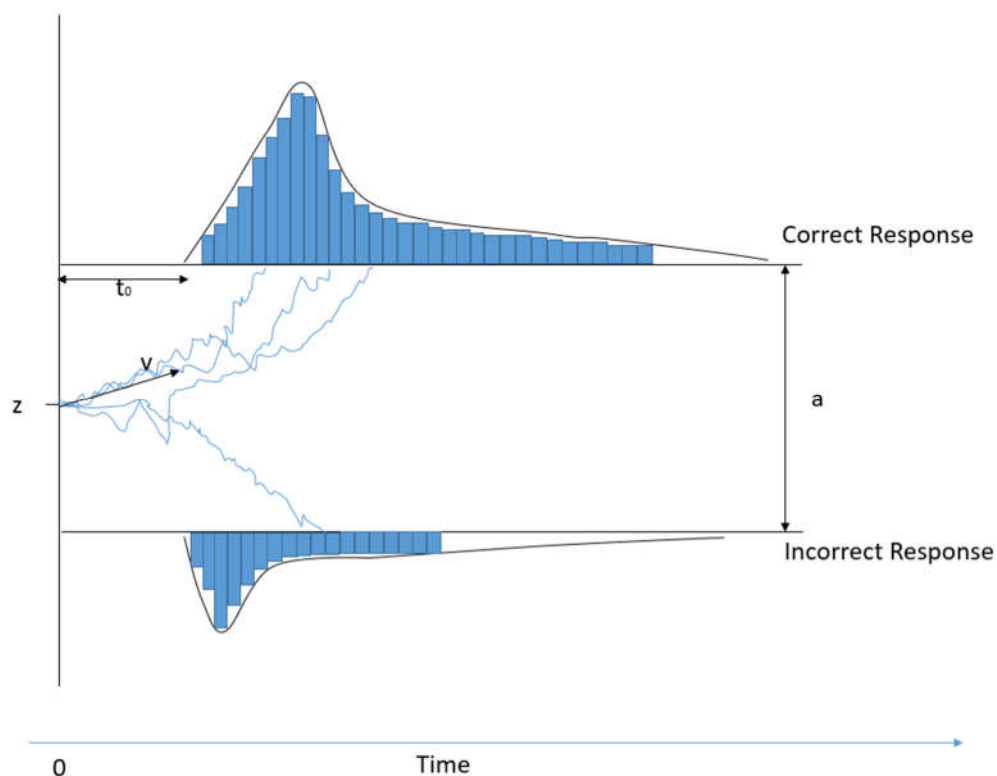


Fig. 4. Example of a drift diffusion model. All of these blue squares represent the cumulated reaction times and the resulting distributions (black curve lines). An information accumulation process starts at point z and runs over time with the mean slope v until it hits an upper (correct response) or lower threshold (incorrect response) with the entire separation threshold a . Because of random noise, the process durations and outcomes vary from trial to trial. The non-decisional time t_0 refers to the time span from 0 to the start time of the distribution.

The DDM estimates several parameters from the RT distributions in binary response paradigms (Ratcliff, 1978; Ratcliff & Tuerlinckx, 2002; Voss et al., 2004). The parameters of the DDM include the non-decisional time (t_0), which incorporates various components before

and after the decision process, including early visual processing and button press execution. The drift rate (v) reflects the speed of uptake of information about the stimuli and maps the cognitive or perceptual speed of information processing. The separation threshold (a) represents the amount of information considered for a decision and reflects how conservative an individual is in terms of their decision boundary, which can also account for the speed-accuracy tradeoff. The starting point (z) represents a priori biases in the decision thresholds.

In the context of alerting and orienting, the DDM can offer valuable insights into how attentional cues impact these (sub) processes by comparing the parameter differences between various conditions. It thus provides a way of understanding the asymmetry involved in alerting and orienting at the cognitive process level.

By integrating the DDM with experimental data, we can quantitatively assess how alerting and orienting cues modulate attentional processes. Conducting both an exogenous spatial orienting task and an endogenous one in combination with DDM analysis can provide a more specific understanding of the attentional (sub)processes involved in alerting and orienting in bottom-up and top-down attention as separate processes. Additionally, the DDM combined with neural-related techniques, like EEG and ERPs, can, as a model-based approach to neuroscience, link neuroscientific measurements and underlying multifaceted cognitive architectures, thereby providing insights into how neural activity represents task or stimulus information and further enhancing our understanding of attentional effects (Barber & Kutas, 2007; Forstmann et al., 2016; Ratcliff et al., 2016). In this sense, the DDM could also help with EEG signals by finding the linkage between DDM cognitive processes and EEG signal neural processes; thus, decoding brain activity by using EEG and DDM to predict the attention itself would open up a range of new possibilities for determining how neural activity represents the information related to a task or stimulus.

1.6 Outline of the thesis

The work described in this thesis is divided into three parts. Part I aims to provide a deeper understanding of attention bias based on meta-analyses of landmark/line bisection tasks and visual detection/extinction tasks. Part II seeks to explore TMS localization techniques utilizing MRI data. Part III focuses on illuminating the alerting and orienting effect in attention based on

the DDM model on exogenous and endogenous cueing tasks at the cognitive process level (see Fig. 5).

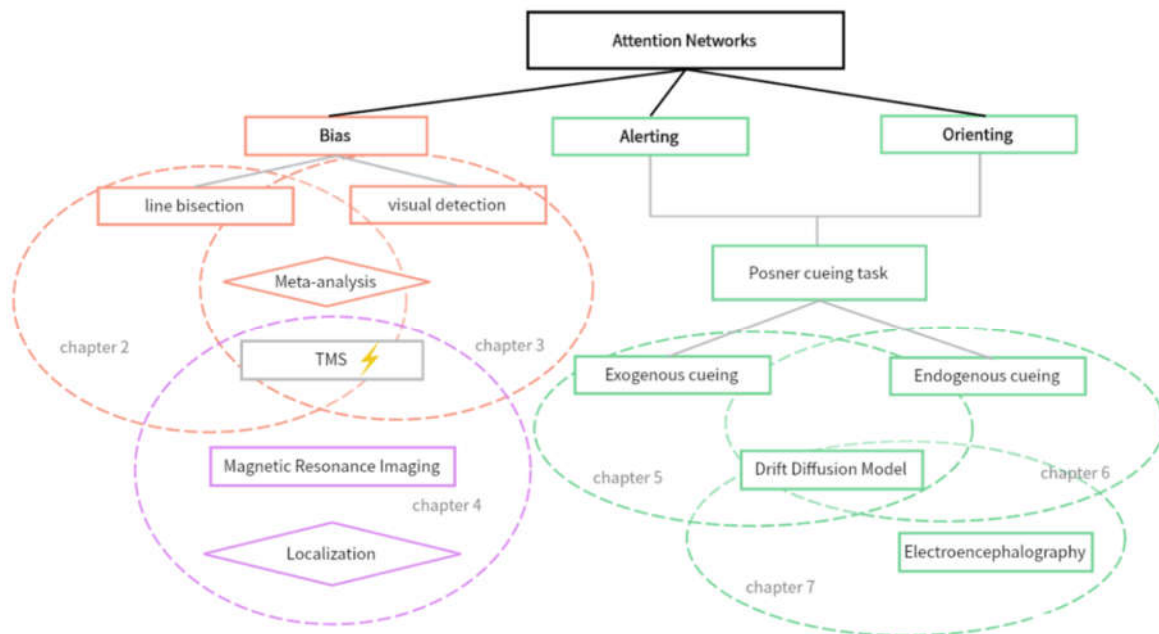


Fig. 5. General overview of this thesis; the squares represent key concepts and methods. When a circle includes several squares, it implies a combination of these concepts and methods for a particular study (or chapter). Red refers to Part I, which focuses on attentional bias. Purple refers to Part II, which focuses on TMS localization. Green refers to Part III, which covers alerting and orienting effects. **Part I:** *Chapter 2* consists of a meta-analysis of research on the inhibitory TMS effect on the left and right parietal cortex based on line bisection task performance. This was done to determine whether TMS could mimic the case of neglect patients and to compare the left and right hemisphere effects in attentional bias shifting. *Chapter 3* contains a meta-analysis of the findings pertaining to the inhibitory effect of TMS on the left and right parietal cortex based on visual detection performance, which separated attentional bias into the left and right hemifields to evaluate the left and right hemisphere asymmetry mechanism and further assess the related visuospatial attention theories. **Part II:** *Chapter 4* explores and compares various MRI-guided TMS target localization approaches for the core nodes of the DAN and the VAN. **Part III:** *Chapter 5* describes the performance of an exogenous cueing task using a DDM to examine the cognitive mechanisms associated with the alerting and orienting effects on visual spatial attention. Along similar lines, *Chapter 6* describes an endogenous cueing task but also evaluates the alerting and orienting hemifield lateralization that might be caused by hemispheric asymmetries. *Chapter 7* uses the same endogenous cueing task, but with EEG recordings, to find the link between neural dynamics and cognitive processes in alerting and orienting.

Part I. Dissecting spatial attentional bias

The first part of this thesis explores how attention bias shifts after inhibitory TMS targeting the posterior parietal cortex and compares the effects on the left and right hemispheres. In **Chapter 2**, we assess the functional relevance of the left and right parietal cortex in attention control, as measured by line bisection and landmark tasks, in a meta-analysis of all existing TMS studies. We explicitly wanted to aggregate all the studies targeting either the left hemisphere or right hemisphere or both to evaluate (1) whether right or left PPC TMS could indeed induce an

attentional bias on landmark/line bisection task, (2) whether there is any difference in the effect size between these two hemispheres, and (3) whether this pattern between the left and right hemispheres is similar to what is typically observed in neglect patients. Based on these evaluations, we were able to determine whether TMS could mimic the case of neglect patients and compared the left and right hemisphere effects in attentional bias shifting.

In **Chapter 3**, we focus on TMS studies in the context of visual detection paradigms, which allowed us to analyze the separate functional roles of each hemisphere and determine the hemisphere-specific attention biases, gains, and costs associated with the ipsilateral versus contralateral sides of space. This, in turn, allowed for a systematic assessment of detection performance in each hemifield in isolation (Duecker & Sack, 2015). Based on the aggregated data, we aimed to objectify the current empirical evidence base and obtain reliable TMS-induced i) contralateral impairment, ii) ipsilateral enhancement, and iii) attentional selection in visual detection paradigms. As a result, we were able to assess the evidence for visuospatial attention theories.

Part II. TMS localization with different MRI methods

In the second part of this thesis, we focus on finding alternative TMS positioning methods based on individual and group MRI data for the core nodes of attention networks. In **Chapter 4**, we compare various MRI-guided TMS target localization approaches for the core nodes of the DAN and VAN. Here, we aimed to determine whether group data can provide effective alternatives when individual task data are unavailable. The findings contribute to refining the accuracy and efficiency of TMS target localization methods.

Part III. Dissecting alerting and orienting effects

In the third part of this thesis, we turn to visuospatial attention and try to separate alerting and orienting effects into different (sub) processes. In **Chapter 5**, we describe how we performed an exogenous spatial orienting task combined with DDM analysis to gain insights into the attentional (sub) processes linked to alerting and orienting. By analyzing the effects of spatial orienting manipulations on DDM parameters, such as drift rate and non-decisional time (t_0), we intended to uncover the underlying cognitive mechanisms.

In **Chapter 6**, building upon Chapter 5, we apply a similar design to an endogenous cueing task. This task allowed us to not only investigate alerting and orienting effects, but also to explore the hemispheric lateralization of these effects. By analyzing the drift rate and non-decisional time (t_0), we aimed to uncover the roles of each hemisphere in alerting and orienting.

In **Chapter 7**, we integrate EEG signals, including oscillations and ERPs, with DDM parameters to establish links between neural dynamics and cognitive processes. We expected that specific parameters, including the drift rate and the non-decisional time (t_0), would be correlated to specific EEG signals, including cue-related oscillation, such as alpha power, and target-locked modes, like P1, N1, P2 amplitudes, thereby enhancing our understanding of the neural underpinnings of alerting and orienting.

Finally, **Chapter 8** summarizes the main findings of this thesis, discusses their implications within a broader context, and highlights potential avenues for future research.

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Chapter 2

Hemispheric Asymmetry in TMS-induced effects on spatial attention: a Meta-Analysis

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Abstract

Hemispheric asymmetry is a fundamental principle in the functional architecture of the brain. It plays an important role in attention research where right hemisphere dominance is core to many attention theories. Lesion studies seem to confirm such hemispheric dominance with patients being more likely to develop left hemineglect after right hemispheric stroke than vice versa. However, the underlying concept of hemispheric dominance is still not entirely clear. Brain stimulation studies using transcranial magnetic stimulation (TMS) might be able to illuminate this concept. To examine the putative hemispheric asymmetry in spatial attention, we conducted a meta-analysis of studies applying inhibitory TMS protocols to the left or right posterior parietal cortices (PPC), assessing effects on attention biases with the landmark and line bisection task. A total of 18 studies including 222 participants from 1994 to February 2022 were identified. The analysis revealed a significant shift of the perceived midpoint towards the ipsilateral hemifield after right PPC suppression (Cohen's $d = 0.52$), but no significant effect after left PPC suppression (Cohen's $d = 0.26$), suggesting a hemispheric asymmetry even though the subgroup difference do not reach significance ($p = .06$). A complementary Bayesian meta-analysis revealed a high probability of at least a medium effect size after right PPC disruption, versus a low probability after left PPC disruption. This is the first quantitative meta-analysis supporting right hemisphere-specific TMS-induced spatial attention deficits, mimicking hemineglect in healthy participants. We discuss the result in the light of prominent attention theories, ultimately concluding how difficult it remains to differentiate between these theories based on attentional bias scores alone.

Keywords: hemispheric asymmetry; transcranial magnetic stimulation; spatial attention; landmark; line bisection; meta-analysis

2.1 Introduction

Hemispheric asymmetry is a key concept in the functional architecture of the brain and plays a core role in many spatial attention theories. This is also, and maybe even primarily, based on the hemispacial neglect phenomenon, a syndrome where patients struggle to allocate attention to, or even simply detect, stimuli in the left hemifield. It is more common and severe after right hemisphere damage (Beis et al., 2004; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Suchan, Rorden, & Karnath, 2012). This consistent evidence has inspired different ideas about the contribution of the right versus the left hemisphere to attentional processing (e.g., Mennemeier, Vezey, Chatterjee, Rapcsak, & Heilman, 1997; Mesulam, 1981). An early intuitive idea based on this functional asymmetry seen in neglect patients is that the right hemisphere of the human brain is dominant for relevant attention processes. This right hemispheric dominance in attention (e.g., Shulman et al., 2010), would thus represent a general principle of the brain similar to the left hemispheric dominance in language processing regions (Geschwind, 1972).

There are two widely supported theories of attention, the Heilman's hemispacial theory and the Kinsbourne's interhemispheric competition theory (Duecker & Sack, 2015). Both theories conclude that the right hemisphere causes more pronounced functional attention effects, however, they both explain this asymmetry very differently by accounting for the contribution of each hemisphere to attentional control in fundamentally different ways. The Heilman's hemispacial theory postulates that the right hemisphere is not necessarily 'stronger', but rather has an expanded function. Namely, the right hemisphere shifts attention to both visual hemifields, while the left hemisphere is only able to shift attention to the right visual hemifield (Heilman & Van Den Abell, 1980). In this model, left parietal lesions can be compensated for by the right hemisphere but not vice versa. Kinsbourne's interhemispheric competition theory, on the other hand, postulates that the left hemisphere is dominant, but that, importantly according to the interhemispheric competition model, both hemispheres induce attentional bias toward their respective contralateral visual hemifield, exerting reciprocal inhibition over one another to maintain system balance (Kinsbourne, 1977). In this theory, the left hemisphere-induced bias towards the right hemifield is somewhat stronger and once disinhibited after right hemispheric lesion (loss of interhemispheric balance), this stronger functional spatial attention bias towards the right side of space causes left hemineglect.

Additionally to neuropsychological evidence of hemispheric asymmetries in the functional relevance of left versus right parietal cortex, a more rigorous and controlled experimental investigation of these asymmetries in healthy volunteers using neuroscientific research tools is paramount. Although extensive neuroimaging work on human visual attention has investigated the involvement of the right and left hemisphere during the execution of various attention tasks (e.g., Corbetta & Shulman, 2002; Driver, Vuilleumier, & Husain, 2004; Serences & Yantis, 2006), standard neuroimaging studies are not sufficient on their own to address hemispheric differences (Ruff et al., 2009). Transcranial magnetic stimulation (TMS), as a functional intervention, allows the temporary modulation of local neural activity in healthy individuals (Pascual-Leone, 2000), revealing a subsequent inability to perform a particular behavior, TMS can thus be regarded as a unique research tool for the investigation of causal structure–function relationships (Sack, 2006). TMS modulates behavior depending on the used protocols (Silvanto & Muggleton, 2008), but in general terms TMS is often conceptualized as inducing a change of excitability (offline protocols) or a disruption of ongoing processing (online protocols) (Veniero, Strüber, Thut, & Herrmann, 2016). Several studies used TMS to induce “virtual lesions” in parietal nodes of the visuospatial attention network in healthy volunteers to induce transitory biases simulating symptoms of spatial neglect (Babiloni et al., 2007; Chambers, Payne, Stokes, & Mattingley, 2004; Esterman, Verstynen, & Robertson, 2007; Fuggetta, Pavone, Walsh, Kiss, & Eimer, 2006; Harris, Benito, Ruzzoli, & Miniussi, 2008; Koch, Oliveri, Torriero, & Caltagirone, 2005; Rounis, Yarrow, & Rothwell, 2007; Rushworth, Ellison, & Walsh, 2001; Sack, 2010). Importantly, inducing neglect-like attentional deficits in healthy volunteers using TMS in a well-controlled laboratory settings holds the promise of gaining more specific insights into hemispheric asymmetries in attention (Salatino, Poncini, George, & Ricci, 2014; Szczepanski & Kastner, 2013). While the exact nature of the effects induced by TMS may not directly mirror the deficits observed in neglect patients, studying the effects of TMS on spatial attention provides valuable insights into the underlying neural mechanisms and potential functional contributions of different brain regions. By manipulating neural activity in specific brain areas, TMS allows us to investigate the causal relationship between brain regions and cognitive processes. By exploring the relative effects of stimulating the left versus right hemisphere, we contribute to the understanding of the hemispheric dominance in spatial attention and provide insights into the predictions of attention theories.

The line bisection (LB) and landmark (LM) tasks have played prominent roles in assessing attentional bias in neglect patients as well as TMS-induced attentional bias in healthy volunteers (Fierro et al., 2006; Giardina, Caltagirone, Cipolotti, & Oliveri, 2012; Mahayana, Tcheang, Chen, Juan, & Muggleton, 2014). Both tasks require individuals to judge the midpoint of a line. However, in the LB task, participants mark the judged midpoint themselves, whereas in the LM task the line is pre-bisected and participants have to judge whether this bisection is correct (Cicek, Deouell, & Knight, 2009; Learmonth & Papadatou-Pastou, 2022; Strappini, Ben-Nun, & Pecchinenda, 2023). Patients with right posterior parietal lesions tend to judge the middle-point of the line to be slightly right of true center, indicating a rightward shift of attention (Chatterjee, Thompson, & Ricci, 1999; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). A leftward-shift is substantially less likely to emerge following left-parietal damage (Karnath & Rorden, 2012). Several studies have successfully employed the LB and LM task also in healthy volunteers using TMS to inhibit their left and/or right posterior parietal cortex (PPC; left PPC: LPPC; right PPC: RPPC) and assessing the behavioral consequences on attention task performance in a controlled experimental setting (Bagattini, Mele, Brignani, & Savazzi, 2015; Brighina et al., 2002; Cazzoli & Chechlacz, 2017; Ellison, Schindler, Pattison, & Milner, 2004; Giglia et al., 2015; Salatino et al., 2019; Salatino, Poncini, George, & Ricci, 2014; Szczepanski & Kastner, 2013). However, a systematic investigation of the existing TMS literature is still missing. TMS effects are often small, studies notoriously underpowered, and findings often not replicable across laboratories (Gilmore, Diaz, Wyble, & Yarkoni, 2017). The question, thus, whether TMS is indeed capable of reliably producing significant spatial attention effects in healthy volunteers is far from being settled, and even less so the question whether such effects are more pronounced after left or right hemispheric TMS interventions, thus either mimicking or contradicting the deficits seen in hemineglect patients.

Here, we assessed the functional relevance of left and right parietal cortex in attention control, as measured by LB and LM tasks, in a meta-analysis of all existing TMS studies. We explicitly wanted to aggregate all the studies targeting either the left hemisphere or right hemisphere or both to evaluate: (1) whether right or left PPC TMS could indeed induce an attentional bias on landmark/ line bisection task, (2) whether there is any difference of effect size between those two hemispheres, and (3) whether this pattern between left and right hemisphere is similar to what is typically observed in neglect patients.

2.2 Methods

2.2.1 Study Selection

The current review was not registered but followed the PRISMA guidelines. The literature search was conducted on PubMed, Web of Science, and Elsevier databases using the search codes: (TMS OR “transcranial magnetic stimulation”) AND (PPC OR “parietal”) AND (“landmark” OR “bisection” OR “spatial attention” OR “neglect”). The search was restricted to journal articles written in English, between 1994 and February 2022. Two researchers searched articles fully independently according to the PRISMA guideline and inconsistencies in the search results were resolved in team discussions.

2.2.2 Inclusion and Exclusion Criteria

Search results were imported into Endnote and passed through three screening rounds. Duplicates were removed in the first screening round. The two researchers conducted the abstract and full-text review in the second and third rounds. The inclusion criteria were: (1) at least 5 healthy human participants; (2) TMS targeting any regions of the PPC; (3) using the LM and/or LB tasks; (4) comparison between active and baseline conditions. Baseline conditions could be in the form of no TMS, sham TMS, or stimulation over a control site (e.g., the vertex). Studies were excluded if they used a non-TMS stimulation technique, for example transcranial alternating current stimulation (tACS) or transcranial direct current stimulation (tDCS), or did not involve any stimulation.

We only considered studies using inhibitory/disruptive TMS protocols. The inhibitory/disruptive TMS protocols included offline repetitive TMS (rTMS) at a low frequency (less than 5Hz), online event-related TMS(ER), single/paired pulse TMS (SP/PP) and continuous Theta Burst Stimulation (cTBS).

2.2.3 Data Extraction and Management

One researcher used a standardized data extraction form specifically designed for this review to collect data from the included studies. Extracted data included the following: author, publication year, description of participant sample (age, sex, handedness), task used, TMS related parameters (frequency, offline/online, duration, stimulation site, stimulation type, and baseline condition). Results were extracted in terms of statistical values reporting for the

following categories: left stimulation and ipsilateral bias; left stimulation and contralateral bias; right stimulation and ipsilateral bias; right stimulation and contralateral bias. For articles only reporting data in figures, numerical results were extracted from the figures using GetData Graph Digitizer 2.24. All of these extraction steps were double-checked by other researchers.

2.2.4 Statistical Analysis

Statistical analyses were performed with SPSS (IBM), Stata, and RStudio (Metafor and Meta package). Changes in detection performance in participants were analyzed using paired or one sample T -tests. For studies that reported the F value, the formula $T=\sqrt{F}$ was used to estimate the T -test statistic from the one-way analysis of variance (Lipsey & Wilson, 2001). For studies reported mean value and standard error of baseline and TMS conditions, rather than T -statistic, we used the paired sample T -statistic and formulas outlined in Morris and DeShon (Morris & DeShon, 2002) to derive the correlation between outcome measures.

$$\frac{\underline{X}_1 - \underline{X}_2}{\sqrt{\frac{S_1^2 (n_1 - 1) + S_2^2 (n_2 - 1)}{n_1 + n_2 - 2}}} = \frac{\underline{X}_1 - \underline{X}_2}{S_{pooled}} \quad (1)$$

$$S_{pooled} = \frac{S_{gain}}{\sqrt{2(1-r)}} \quad (2)$$

\underline{X} = mean value from baseline (X_1) and experimental (X_2) conditions;

s^2 = variance for the baseline (s_1) and experimental (s_2) conditions;

n = total sample size;

s_{gain} = standard deviation squared (experimental condition);

r = correlation between baseline and experimental conditions.

The effect sizes in the form of Cohen's d were then calculated in these studies to characterize the difference in performance between the baseline (control) condition and each TMS condition, including studies using rTMS, single/paired pulse, cTBS and event-related triggered

stimulation. The current Cohen's d was coded as the ipsilateral shift effect, independently of whether TMS stimulated left or right hemisphere. For studies that reported T or F value, `effectsize::t_to_d` function in 'Meta' package was used to get the Cohen's d . For studies that reported data as mean value and standard error, the `escalc` function was used to obtain the (bias-corrected) standardized mean differences and corresponding sampling variances and transformed it to Cohen's d according to the 'Metafor' package. Since few of these studies reported the change of detection performance (compared with baseline, baseline as 0 or 1), then Stata Software was used to get the corresponding T value.

The cumulative effect size was determined by weighting the effect sizes of each study by the inverse of their variance (i.e., precision). The weights were then summed and divided by the sum of the weights to obtain the overall effect size (fixed effects model) or also take into account the between-study heterogeneity (random effects model). In order to support the choice between fixed or random effects models, heterogeneity was quantified with a Q test. A forest plot was generated to visualize Cohen's d by study. Next, a funnel plot was generated to visualize publication bias, further supported using an Egger test. This full process was repeated in a subgroup analysis of stimulation hemisphere (RPPC vs. LPPC). Finally, a meta-regression was performed to ensure other factors like publication year, and methodological factors (including control conditions, online/offline protocol, targeting by 10-20 system or MRI, comparison based on pre-post or post only; note all these factors were transferred to dummy variables) did not affect results, along with a sensitivity analysis to confirm that no single study exerted too much influence over the conclusion of the meta-analysis.

2.2.5 Multilevel Meta-Analysis

For studies include multiple interventions in one sample, dependence might be introduced. Given statistical independence was one of the core assumptions of meta-analytic pooling (Harrer, 2021). A dependency between effect sizes (i.e., the effect sizes are correlated) might artificially reduce heterogeneity and then lead to false-positive results. These dependencies that may exist in these nested designs can be handled using a multilevel meta-analysis. In multilevel meta-analysis, the variance in observed effect sizes is decomposed into sampling variance (level 1), between-study variance (level 2) and variance between groups of studies (level 3), and the

moderating effect of characteristics of studies (at level 2) and groups of studies (at level 3) can be explored. This analysis was conducted using the ‘Metafor’ package in R.

2.2.6 Bayesian Meta-Analysis

In addition to the conventional meta-analysis outlined above, we also performed a Bayesian meta-analysis. Within the R statistical computing environment, we used the “brms” package (Burkner, 2017), based on Stan software (Carpenter, 2015), to fit Bayesian multilevel models. The first step of Bayesian analysis was defining a prior distribution of standardized mean difference (SMD) as $SMD \sim N(0,1)$ and heterogeneity (τ) as $\tau \sim HC(0,0.5)$, then set up the formula for the model and the MCMC algorithm run 4000 iterations to fit the model. Before evaluating model fit, convergence was assessed by posterior predictive checks and R-hat values of the parameter estimates. Based on the obtained Bayesian model, we calculated the exact probabilities that the meta-analytic effect will be smaller/larger than a given effect size value by looking at the empirical cumulative distribution function (ECDF) of the posterior distribution for the pooled effect size.

2.3 Results

2.3.1 Overview

The initial literature search resulted in 2048 articles (duplicates removed) of which 325 were included in the related full-text review (details in Fig. 1). A total of 24 datasets from 18 different studies met the including criteria. Stimulation parameters and participants’ information are shown in Table.1.

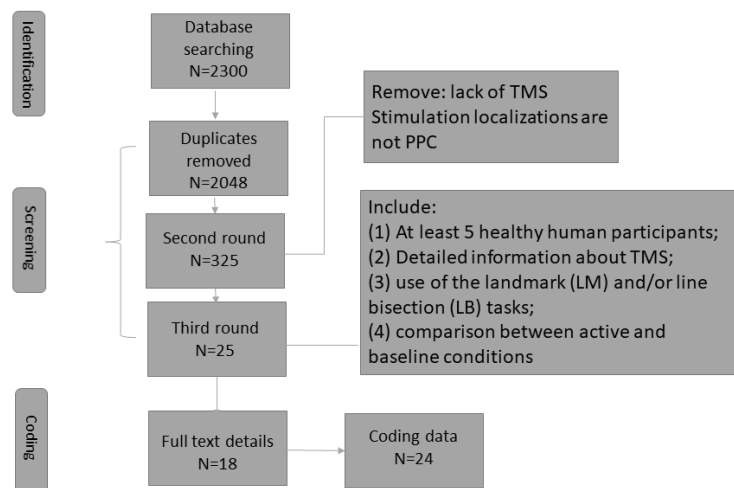


Fig.1. Flowchart of data extraction including database searches, the screening of study abstracts and full-texts, and the reasons for excluding studies.

Table.1 Summary of all included studies

study	Particip- ants	age	Handed- ness	task	TMS protocol	type of TMS	localization	baseline	Pre- post
(Bagattini, Mele, Brignani, & Savazzi, 2015)	20 (13 females)	19-34	Right	LB	offline, 90% of RMT, last for 30min at 1 Hz	rTMS	10-20 system coordinates P4-P8	no TMS	Pre-post
(Bjoertomt, Cowey, & Walsh, 2002)	6(4 females)	21-26	Right	LB	online, 65% of MSO, at stimulus onset, last for 500ms each trial	SP	rPPC by TMS(behaviorally hunting procedure) and structural MRI co-register check	sham	Post only
(Brighina et al., 2002)	11	28-68	Right	LM	online, 115% RMT, at stimulus onset, 10 pulses per trial at 25Hz .	ER	10-20 system coordinates P6	sham	Post only
(Cazzoli & Chechlac, 2017)	24(12 females)	26.5 ± 5.1	17 right and 7 left	LB	offline, 80% RMT, 801 pulses, 3-pulses bursts at 30 Hz	cTBS	MRI localizer on rIPS and lIPS	sham	Pre-post
(Ellison, Schindler, Pattison, & Milner, 2004)	5(2 females)	21-36	Right	LM	online, 65% of MSO, at stimulus onset, 5 pluses per trial at 10Hz	ER	3 *3 cm grid hunting rPPC	sham	Post only

(Fierro et al., 2000)	11	25-67	Right	LM	online, 115% RMT, at stimulus onset 10 pulse per trial at 25Hz	ER	10-20 system coordinates P5,P6	sham	Pre-post
(Fierro, Brighina, Piazza, Oliveri, & Bisiach, 2001)	10	20-68	Right	LM	online, 115% RMT,(150ms,225ms, 300ms) after stimulus onset, 10 pulses per trial at 25Hz	SP	10-20 system coordinates P6	no TMS	Post only
(Fierro et al., 2006)	13	24-30	Right	LM	online, single pulse,120% RMT, 150ms after stimulus; paired-pulse,150ms after stimulus	SP&PP	10-20 system coordinates P6	no TMS	Post only
(Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007)	10(5 females)	21.8 ±5.2	Right	LB	online,15% of MSO above the RMT, at "go" instruction onset, last for 5s trains at 5 Hz	ER	10-20 system coordinates P6	no TMS	Pre-post
(Giglia et al., 2015)	15(8 females)	28.2 ±6.3	Right	LM	online, 110% RMT, 100 ms before visual task, 5 pulses per trial at 10 Hz	ER	10-20 system coordinates P6	no TMS	Post-only
(Mahayana, Tcheang, Chen, Juan, & Muggleton, 2014)	15(5 females)	23	NA	LM	online, 60% of MSO, at stimulus onset, 5 pluses per trial at 10Hz	ER	individual MRI scans on rPPC	No-TMS	Post-only
(Oliveri et al., 2009)	7(3 females)	20-36	NA	LB	offline, 90% RMT, last for 10 min at 1 Hz	rTMS	P4 (RH); EEG 10-20	No-TMS	Post-only
(Oliveri & Vallar, 2009)	10(9 females)	21-34	Right	LB	online, 100% RMT, at stimulus onset, 10 pulses per trial at 25Hz	ER	P4 and 1.5cm anterior to P4 -- EEG 10-20	sham	Post-only
(Salatino et al., 2019)	13(9 females)	26.7 7	Right	LM	online, 115% of RMT, at stimulus onset,	ER	3 *3 cm grid hunting rPPC	sham	Pre-post
(Salatino, Poncini, George, & Ricci, 2014)	8(5 females)	21-28	Right	LM	online,115% of RMT,150ms after stimulus onset,	SP TMS	3*3cm grid stimulation P5 and P6 as the stimulation center; EEG 10-20)	No-TMS	Pre-post
(Szczepanski & Kastner, 2013)	6(2 females)	26-38	Right	LM	online, 60% of MSO, 200ms after stimulus onset, 10 pulses per trial hz	SP	Topographic ROIs overlaid on individualised MRI (right and left IPS1/2 MRI-guided, Brainsight frameless stereotaxic system	No-TMS	Pre-post
(Schintu et al., 2021)	17(11 females)	25.9 4 ± 1.01	Right	LB	offline, 80% RMT, 600 pulses , 3-pulse bursts at 50 Hz	cTBS		No-TMS	Pre-post

(Mariner, Loetscher, & Hordacre, 2021)	14(9 females)	18- 30	Right	LB	offline,70% RMT, 600 pulses, 3-pulses bursts at 50 Hz	cTBS	10-20 system coordinate s P4	No-TMS	Pre- post
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RMT: resting motor threshold; MSO: maximum stimulator output; rTMS: repetitive TMS; SP: single pulse, PP: paired-pulse; ER: event-related; cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging; EEG: electroencephalogram.

As illustrated in Fig. 1, from the third round screening to the coding stage, 7 studies were excluded because they did not report the actual TMS effect on the attention shift but an interaction effect with other variables (such as Cattaneo, Silvanto, Pascual-Leone, & Battelli, 2009) or they used excitatory TMS (Kim et al., 2005) rather than inhibitory protocols. Within the final 18 studies, some conducted both right and left hemisphere stimulation and are thus represented as two data points (such as Cazzoli & Chechlacz, 2017; Szczepanski & Kastner, 2013). Two studies (Bjoertomt, Cowey, & Walsh, 2002; Ellison, Schindler, Pattison, & Milner, 2004) used the landmark task but reported the attention shift by condition, such as right elongated line/ bisected line/ left elongated line and left side shorter/ right side longer. For these two studies, conditions were combined by formula (3) (4) (5) to obtain average sample size, mean value and standard deviation so that found average effect as previous studies (Higgins, 2019). For the Fierro studies (Fierro et al., 2006; Fierro et al., 2000; Fierro, Brighina, Piazza, Oliveri, & Bisiach, 2001), the single or paired pulse time intervals were excluded. Some studies included additional experimental manipulations of task-related factors such as distance to the monitor, the eccentricity of the stimuli, or additional TMS targets other than P3/P4. In these cases, we opted to include those conditions that were most similar to the other studies included here. Specifically, in the studies of (Bjoertomt, Cowey, & Walsh, 2002; Giglia et al., 2015; Mahayana, Tcheang, Chen, Juan, & Muggleton, 2014), where several viewing distances from the display (near vs far /vs. far with stick) were reported, only near stimuli were included here since 60 cm distance was common in other studies. In the studies of Salatino and her colleagues (Salatino et al., 2019; Salatino, Poncini, George, & Ricci, 2014), a 3 cm × 3 cm target grid was centered over P3 or P4 according to the 10-20 EEG system. Although the P5 and P6, as they reported, showed the highest effect in those 3×3 targets, P3 and P4 were included instead to ensure optimal comparison of TMS localization across studies.

$$\underline{N} = N_1 + N_2 \quad (3)$$

$$\underline{M} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2} \quad (4)$$

$$\underline{SD} = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2} (M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}} \quad (5)$$

\underline{N} = combined sample size from conditions (N_1 , N_2);

\underline{M} = combined mean value from conditions (M_1 , M_2);

SD^2 = variance for the conditions (SD_1^2 , SD_2^2);

\underline{SD} = combined standard deviation.

2.3.2 Meta-analysis of TMS-induced attention shifts (TMS vs. baseline)

To assess the TMS induced attention shifts in general, 24 datasets were merged to yield a pooled effect size regarding left or right PPC stimulation. The test for heterogeneity was marginally significant ($I^2 = 33\%$; $\tau^2 = 0.0361$, $p = .06$) and we opted for the more conservative approach of proceeding with a random effects model, showing a significant ($z = 7.14$, $p < .0001$) positive Cohen's d 0.58, 95% CI ranged from 0.42 to 0.74.

The Egger test showed a significant ($p = .05$) publication bias, visualized in the funnel plot (see Fig. 2). To ensure that publication year and methodological factors did not affect results and no single study exerted too much influence over the conclusion of the meta-analysis, meta-regression and sensitivity analysis were conducted. Results showed that the publication year did not impact the effect ($p = .19$), control condition ($p = .92$), online or offline protocol ($p = .35$), TMS targeting by 10-20 system or MRI ($p = .86$) and the effect remained after omitting any single study. In sum, the overall TMS effect was convincing and robust.

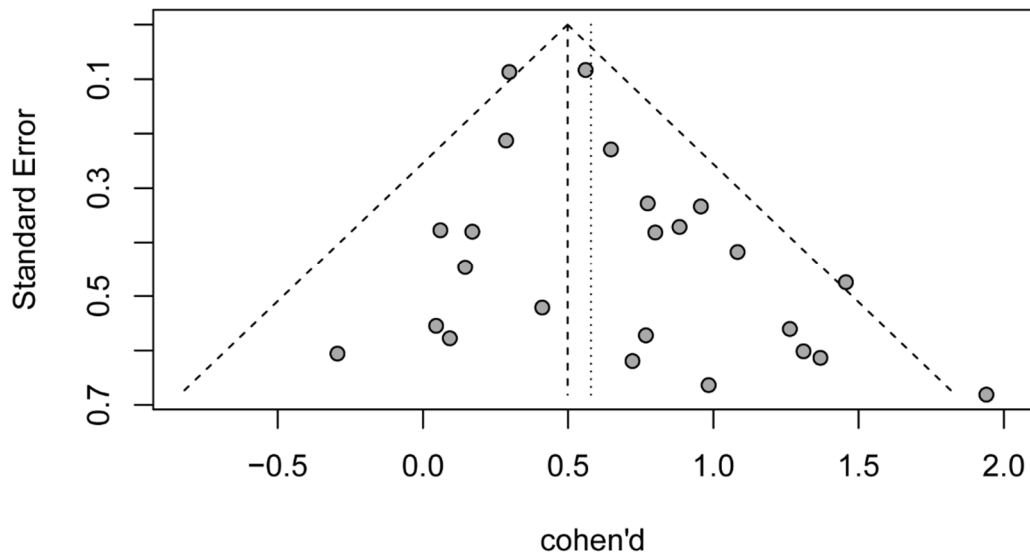


Fig.2. Funnel plot standard errors by standard difference in means.

As mentioned above, given the potential dependencies caused by multiple datasets stemming from single studies, we took such dependencies into account by integrating a third layer into the structure (we used a 3-level model including the sampling variation for each ES (level 1), variation across ESs within a study (level 2), and variation across studies (level 3)). Here, multiple separate datasets from two studies (Bjoertomt, Cowey, & Walsh, 2002; Ellison, Schindler, Pattison, & Milner, 2004), which collected data from multiple sites, were added. The full model showed that the pooled effect size was 0.68, 95% CI ranged from 0.43 to 0.99. After checking the variance distribution of the full model, it was clear that layers 1, 2, and 3 accounted for 47%, 36% and 17% of the variance respectively. The comparison between the full model and the leave-level 2-out and leave-level 3 -out model suggested the full model as winning model (lower AIC and BIC level 2: $p = .2$; level 3: $p = .55$).

2.3.3 Subgroup comparison (LPPC vs. RPPC stimulation)

First, we assessed a potential ‘subgroup effect’ of the LM and LB tasks. No significant difference between these two tasks was found ($Q = 0.25$, $df = 1$, $p = .62$). Then, given that most studies did not assess hemispheric asymmetries directly, we used subgroup analysis to test potential differences for results stemming from left PPC or right PPC TMS. The results showed that right PPC and left PPC stimulation did not cause significant different attention shift effects ($Q = 3.5$, $df = 1$, $p = .06$). To provide a more comprehensive understanding of the current data and explore potential patterns or trends, further analyses were conducted. The specific RPPC

and LPPC effects are shown in Fig.3. For the RPPC stimulation, the fixed effect model showed a significant positive Cohen's *d* 0.52, 95% *CI* ranging from 0.42 to 0.62. For LPPC stimulation, the random effects model showed an insignificant positive Cohen's *d* 0.26, 95% *CI* ranging from -0.06 to 0.58. Because of the imbalance between LPPC and RPPC studies, a subgroup analysis containing 5 studies with both stimulation sites was conducted. Results showed the same pattern as the analysis of the entire dataset (The test for heterogeneity was not significant ($I^2 = 12.4\%$; $\tau^2 = 0.001$, $p = .33$), overall attention shift effect size: 0.4; 95% *CI*: 0.03 to 0.76; RPPC attention shift effect size: 0.64; 95% *CI*: 0.34 to 0.95; LPPC attention shift effect size: 0.08; 95% *CI*: -0.42 to 0.58; significant difference between LPPC and RPPC with $p = .05$). The subgroup analyses of the multilevel model were considered as well, the specific RPPC and LPPC effects were again different from each other. (For RPPC shift effect size is 0.76, 95% *CI* is 0.32 to 1.19, for LPPC shift effect size is 0.05, 95% *CI* is -0.38 to 0.49)

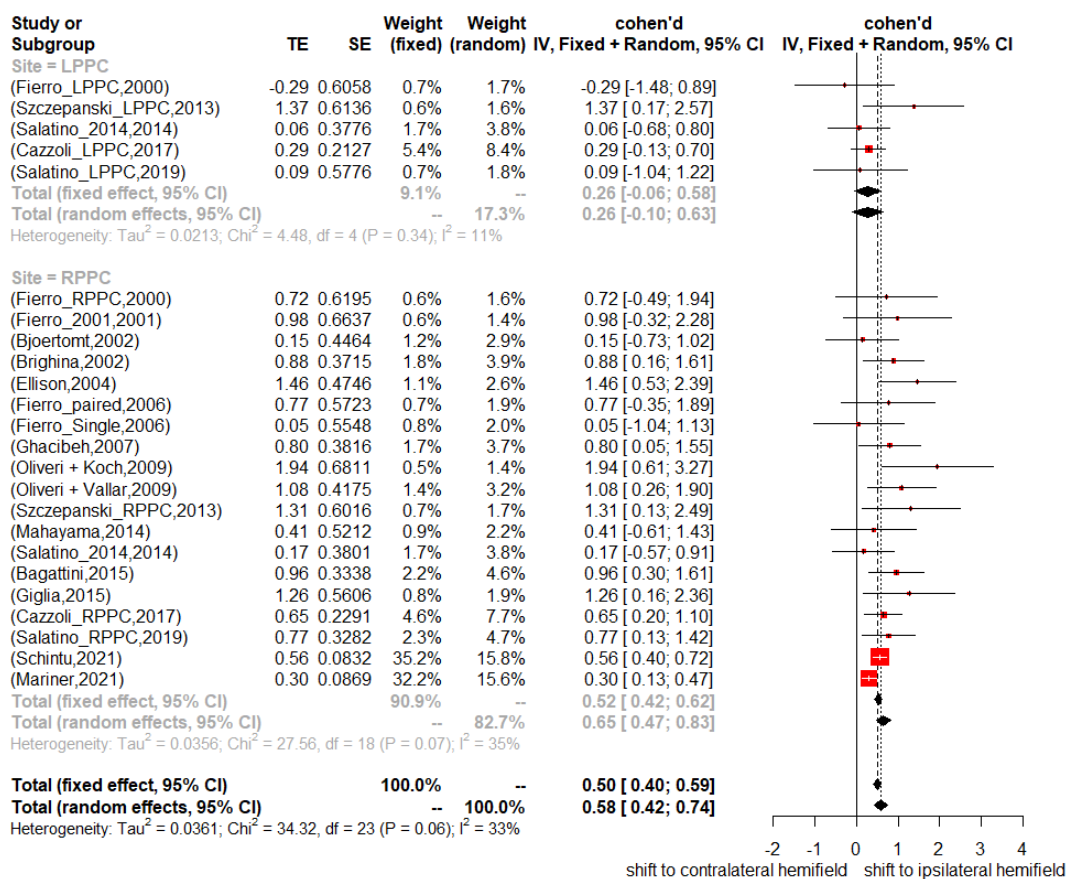


Fig.3. Subgroup comparison of the Mean effect size (Cohen's *d*) and 95% confidence intervals for the 24 datasets for line bisection/ landmark performance change after left vs. right PPC stimulation.

To ensure that the publication year and methodological factors did not affect results and no

single study exerted too much influence over the conclusion of the meta-analysis, meta-regression and sensitivity analyses were conducted on RPPC datasets only because of the limited number of LPPC dataset. Results showed that the publication year ($p = .07$), control condition ($p = .25$), online or offline protocol ($p = .26$), TMS targeting by 10-20 system or MRI ($p = .90$) did not impact the effect, and the effect remained after omitting any single study. In sum, the RPPC TMS effect was convincing and robust.

2.3.4 Bayesian meta-analysis of RPPC and LPPC stimulation (TMS vs. baseline)

Bayesian meta-analyses have a similar aim as frequentist meta-analytic techniques but use a different statistical approach that is particularly suitable if the number of included studies is small (Harrer, 2021) or like in our case if the unbalanced number of studies investigating left PPC and right PPC may affect the robustness of the analyses. Bayesian meta-analysis is well-equipped to deal with this problem since it allows to directly make predictions in the estimation of between-study heterogeneity (Harrer, 2021). The Bayesian meta-analysis was separately applied to the RPPC and LPPC stimulation sample. After confirming convergence ($\hat{R} = 1$), results showed nearly the same pooled effects for both hemispheres as compared to the results presented above (RPPC: a significant positive Cohen's d 0.65, 95% CI ranged from 0.44 to 0.94; LPPC: an insignificant positive Cohen's d 0.22, 95% CI ranged from -0.27 to 0.69). The ECDF function showed that the probability of the pooled effect being greater than 0.4 is very high (96.2%) after RPPC disruption. Therefore, the attention shift effect after the RPPC stimulation is very likely to be meaningful. However, the probability of the pooled effect being greater than 0.4 after LPPC stimulation is very low (21%), which means the attention shift effect after the LPPC stimulation is not very likely to be obviously significant.

2.4 Discussion

This meta-analysis study aimed to examine the hemisphere-specific effects of inhibitory TMS targeted at either right and/or left posterior parietal cortices on attention bias as measured by line bisection and landmark tasks. The main aim of this meta-analysis was to reveal whether TMS is capable of reliably producing significant spatial attention effects in healthy volunteers and whether such effects are more pronounced after left or right hemispheric TMS suppression. Based on the here presented data, we report quantitative evidence supporting the concept of

functional lateralization with specifically right hemispheric TMS-induced spatial attention deficits in healthy participants.

The results across 18 high-quality studies highlight that inhibitory TMS on posterior parietal cortex can indeed induce attention biases as measured by line bisection and landmark tasks, which provide strong support for the functional role of PPC in the here assessed attention processes. Critically, there was only a significant attention shift effect induced by right, but not left, parietal TMS although the direct statistical comparison between the left and right hemisphere failed to reach significance. This pattern of results suggests a hemispheric asymmetry in the functional relevance of left versus right posterior parietal cortex that mimics and reproduces the hemispheric asymmetry seen in neglect patients after left versus right hemispheric lesions (Beis et al., 2004; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Suchan, Rorden, & Karnath, 2012). The results of the Bayesian meta-analysis consistently support the significant attention shift effect induced only by right parietal TMS. Given the results of both traditional inferential and Bayesian statistical analyses, we provide strong evidence for the functional relevance of PPC in line bisection and landmark tasks. Regarding hemispheric asymmetries, the pattern of results suggests a difference in effect size between left versus right parietal TMS on spatial attention bias but statistical results were not unambiguous and a few considerations regarding sample size and methodology have to be kept in mind. Given the importance of hemispherical asymmetry, some methodological remarks need to be considered. Not surprisingly, since most of the previous studies (such as, Bjoertomt, Cowey, & Walsh, 2002; Ellison, Schindler, Pattison, & Milner, 2004) aimed to confirm the relevance of the right, but not left posterior parietal cortex for attention, the number of studies included in the left PPC subgroup is smaller than in the right PPC subgroup. This implies that our analyses regarding hemispheric asymmetry have less statistical power and might be influenced by methodological differences between left PPC and right PPC studies. For that reason, we conducted a subgroup analysis with the five studies that investigated both hemispheres. Importantly, these five studies had consistent results for right PPC but mixed results for the left PPC. To be specific, four (Cazzoli & Chechlacz, 2017; Fierro et al., 2000; Salatino et al., 2019; Szczepanski & Kastner, 2013) of the five studies reported an effect for right PPC stimulation whereas only one study (Szczepanski & Kastner, 2013) reported an effect for left PPC stimulation. For this subset of studies, it is very unlikely that methodological factors have

contributed to the observed hemispheric asymmetry because each pair of left and right PPC effect sizes originates from the same experiment. Moreover, in addition to the results of the here reported traditional meta-analyses, also the separately conducted Bayesian meta-analysis came to the same conclusion of a much more likely significant effect following right as compared to left parietal TMS.

The current findings can be interpreted in different ways. First, on a very general level, the results can be seen as support for right hemispheric dominance in attention. However, regarding the opposing theories of attention, such stronger contralateral attentional effects after right hemisphere suppression do not necessarily imply right hemisphere dominance in the sense of a generally stronger contribution to attention per se as proposed by Heilman's model (Heilman & Van Den Abell, 1980) of spatial attention. The here reported hemisphere-specific functional deficits after right parietal TMS are just as much in accordance with predictions based on Kinsbourne's model (Kinsbourne, 1977) according to which suppressive TMS over right parietal cortex leads to disinhibition of the (dominant) left parietal cortex resulting in increased bias towards the ipsilateral (right) side, and thus to left attention deficits. Moreover, instead of right or left hemisphere dominance, our findings may also simply imply that the right hemisphere is more susceptible to interference to some extent. In this sense, whereas the current meta-analysis provides support for asymmetric TMS attention effects after right as compared to left parietal TMS, thereby also mimicking the lateralization reported in hemineglect patients, this experimental data is nonetheless still limited in informing us about which of the two proposed theories is more likely to be correct. This is due mainly to a fundamental problem of both the line bisection and landmark task used in these studies. Both paradigms don't allow to segregate the exact differential contributions of each hemisphere for each hemifield specifically, which is indispensable when referring to the separate functional role of each hemisphere for hemisphere-specific attention biases, gains, and costs towards the ipsilateral versus contralateral side of space (Duecker & Sack, 2015).

There are a few general considerations and potential limitations to consider. First, the meta-analytic results presented here are discussed in the context of spatial attention theories, but we only included studies using the line bisection task and landmark task. While this allowed us to have a very homogenous dataset, it does pose a problem regarding the generalizability of our findings. At present, we cannot conclude that the pattern of results revealed in this meta-analysis

holds across the entire range of spatial attention tasks. Second, we could identify a small publication bias that may have led to an overestimation of effect size. However, the distribution of effect sizes clearly shows that the overall effect size is not the result of publication bias alone. Third, we performed a meta-regression analysis in order to identify additional potential confounders or factors of interest but none of them explained any variance across studies. Lastly, our meta-analysis clearly reveals a lack of direct comparisons between left and right PPC stimulation. Future research should aim to reveal these dominance of the right or left hemisphere for attention by other study paradigms such as visual detection tasks or spatial cueing tasks, or we could focus on TMS combined with neuroimaging studies and set more comprehensive range of studies, employing standardized protocols, and minimizing heterogeneity. This would enhance the reliability and applicability of the findings in the field.

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Chapter 3

The myth of TMS-induced ipsilateral enhancements in visual detection paradigms: a Systematic review and Meta-Analysis

Based on: Wang, T., de Graaf, T., Williams, J., Wang, Z., Schuhmann, T., Duecker, F., & Sack, A. T. (2023). The myth of TMS-induced ipsilateral enhancement in visual detection paradigms: a Systematic review and Meta-Analysis of inhibitory parietal TMS studies in healthy participants. *Neuroscience & Biobehavioral Reviews*, 105437. <https://doi.org/10.1016/j.neubiorev.2023.105437>

Abstract

Spatial attention control involves specialized functions in both hemispheres of the brain, leading to hemispheric asymmetries. Neuropsychological models explain this lateralization mainly based on patient studies of hemineglect. Studies in healthy volunteers can mimic hemineglect using transcranial magnetic stimulation (TMS) by disrupting the left/right posterior parietal cortex (PPC) during visual detection tasks, enabling a comparison of hemispheric contributions to stimulus detection in the contra- versus ipsilateral hemifields. Kinsbourne's opponent processor model and Heilman's hemispacial model present contrasting hypotheses regarding the behavioral consequences of unilateral PPC disruption. A pivotal prediction in distinguishing between these models is the occurrence of ipsilateral enhancement. Our meta-analysis assessed inhibitory TMS effects on PPC during visual detection tasks across ten studies (1994 – 2022). PPC disruption caused contralateral impairment for bilateral stimuli, but no ipsilateral enhancement for unilateral or bilateral stimuli. These results are at odds with influential reports of ipsilateral enhancement after PPC disruption in healthy volunteers that have shaped the field of spatial attention research and should prompt a re-evaluation of current theoretical models of attention and their application to novel brain stimulation-based therapeutic interventions.

Keywords: transcranial magnetic stimulation; spatial attention; visual detection; meta-analysis; hemispatial theory; opponent processor theory

3.1 Introduction

Among the most common consequences of brain damage is a neuropsychological syndrome called spatial hemineglect that can be observed after lesions to frontal, parietal, or sub-cortical structures (Corbetta et al., 2005). Spatial neglect is characterized by impaired attentional processing within the space contralateral to the lesion's location. As a consequence, patients typically fail to attend, explore, and act upon one side of space which also leads to peculiar effects in the perceptual domain. The phenomenon of spatial neglect is more common and severe after right hemisphere damage than after left hemisphere damage, suggesting a functional asymmetry of the mechanisms underlying spatial attention (Mesulam, 1981). Based on this observation, two competing theories regarding the neural dynamics underlying spatial attention have emerged, namely Heilman's "hemispacial" theory (Heilman and Abell, 1980) and Kinsbourne's "opponent processor" theory (Kinsbourne, 1977), both accounting for this asymmetry but proposing very different mechanisms. See Fig.1

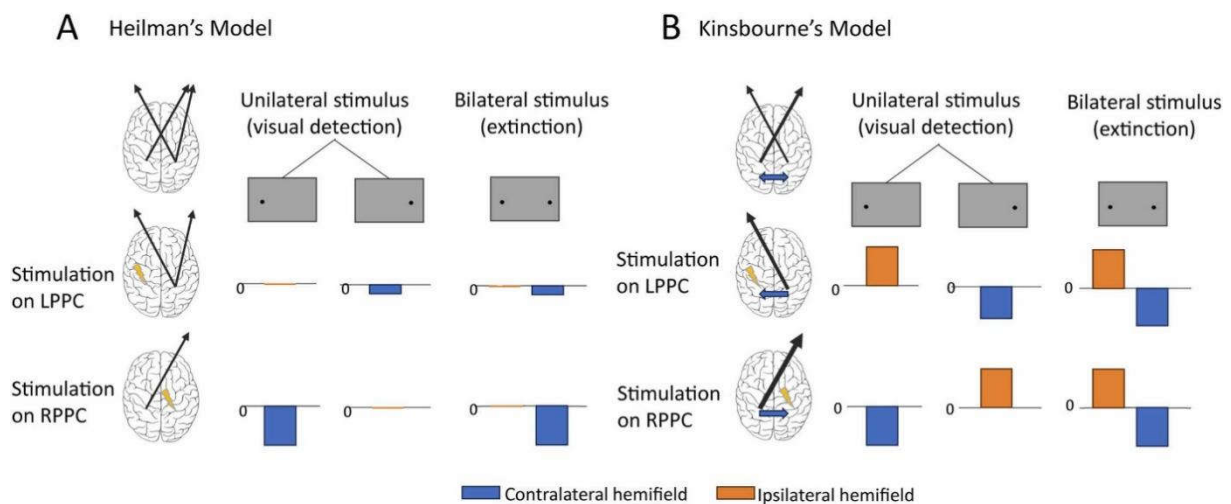


Fig.1. Schematic representation of competing models of attention and their behavioral predictions. Please note that 'stimulation' always refers to the applications of TMS, whereas 'stimulus' always refers to the visual target presented in one or both hemifields. *A. Heilman's hemispacial model* predicts that only right PPC disruption causes a contralateral impairment. *B. Kinsbourne's opponent processor model* predicts that left and right PPC disruption both cause an imbalance between hemispheres causing contralateral impairment and ipsilateral enhancement.

According to Heilman's "hemispacial" model, the right hemisphere contributes to attention allocation to both left and right hemifield, whereas the left hemisphere only contributes to attention allocation to the right hemifield. In this model, left parietal lesions can be compensated for by the right hemisphere but not vice versa. According to Kinsbourne's "opponent processor"

model, both hemispheres induce attentional biases toward their respective contralateral visual hemifield, while at the same time actively inhibiting each other via inter-hemispheric suppression in order to maintain a system balance. In this model, the left hemisphere-induced bias towards the right hemifield is somewhat stronger and once disinhibited after right hemispheric lesion (loss of interhemispheric balance), this stronger functional spatial attention bias towards the right side causes left hemineglect. Taken together, the explanatory approaches of both theories are very different but the predicted behavioral consequences of left and right hemisphere damage are very similar making it difficult to dissociate them empirically on behavioral level alone. Taken together, the explanatory approaches of both theories are very different but the predicted behavioral consequences of left and right hemisphere damage are very similar making it difficult to dissociate them empirically on behavioral level alone.

In addition to neuropsychological evidence based on brain lesion studies that indicate hemispheric asymmetries in the behavioral functional relevance of left versus right parietal cortex for spatial attention, a more rigorous and controlled experimental investigation of these asymmetries in healthy volunteers using neuroscientific research tools is paramount. Although extensive neuroimaging work on human visual attention has addressed the role of the right and left hemisphere (e.g., (Corbetta and Shulman, 2002; Driver, J., Vuilleumier, P., & Husain, 2004; Serences and Yantis, 2006)), standard neuroimaging studies struggle to assess differential hemispheric functional contributions to attention.

Transcranial magnetic stimulation (TMS), as a functional intervention, allows the temporary disruption of local neural activity in healthy individuals (Bien et al., 2012b; Cohen Kadosh et al., 2007; Duecker et al., 2013; Gurel et al., 2018; Jeurissen et al., 2014; Pascual-Leone, 2000; Sack et al., 2007). Several such TMS experiments have been conducted to investigate the behavioral consequences of disrupting either the left or right hemisphere in the context of visual detection and spatial attention paradigms. Many of these studies reported results seen as evidence in favor of Kinsbourne's "opponent processor" model (Dambeck et al., 2006; Hilgetag et al., 2001; Silvanto et al., 2009). As a prime and highly cited example, Hilgetag et al. (2001) found contralateral impairments and ipsilateral enhancements of target detection after inhibitory TMS over left and right parietal cortex. Especially the reported ipsilateral enhancement effects in visual detection following unilateral inhibitory TMS seem to be in accordance with predictions made on the basis of Kinsbourne's opponent processor model. According to this

model, the inhibitory TMS protocol applied over, e.g., left parietal cortex, not only suppresses the left hemisphere causing contralateral, i.e. right hemifield, impairments in visual detection tasks, but at the same time also dis-inhibits the right hemisphere (because it is now released from inhibition from the suppressed left hemisphere) causing left hemifield enhancement in visual detection. This combination of contralateral impairment and ipsilateral enhancement after unilateral suppressive TMS is exactly what was found and reported in this study. Also in accordance with this interpretation, Dambeck et al. (2006) revealed that target detection is unaffected when suppressive TMS is applied simultaneously over left and right parietal cortex because a second contralateral lesion should restore interhemispheric balance with consequent recovery of the attention deficit.

Importantly, based on these findings, a consensus seems to have emerged in the scientific community that most TMS studies largely confirm the specific predictions made by the opponent processor model with unilateral TMS causing both, contralateral impairment but also ipsilateral enhancement of visual detection. Consequently, current clinical TMS protocols to treat hemineglect in stroke patients are based on this notion, using suppressive TMS protocols applied over the unaffected healthy hemisphere in stroke patients to enhance their ipsilateral, i.e. contralesional detection / attention deficits and thus to alleviate their hemineglect symptoms. This is in fact the now common and recommended clinical practice of using TMS in stroke rehabilitation (Lefaucheur et al., 2020). And while this clinical application of TMS in stroke rehabilitation is very promising (Valero-Cabré et al., 2020), the underlying mechanisms are by no means established and generalization across intact and lesioned brains do not necessarily hold.

Here, we present findings of a systematic classical and Bayesian meta-analysis where we aggregated all parietal inhibitory TMS studies in healthy volunteers targeting either the left hemisphere, right hemisphere, or both, to systematically assess to what extent this notion of TMS-induced ipsilateral enhancements in visual detection paradigms is really supported by the existing empirical evidence. We focus on TMS studies in the context of visual detection paradigms which allow to analyze the separate functional role of each hemisphere for hemisphere-specific attention biases, gains, and costs towards the ipsilateral versus contralateral side of space, and thus to allow for a systematic assessment of detection performance in each hemifield in isolation (Duecker and Sack, 2015). Based on the here

aggregated data, we aim to objectify the current empirical evidence base for a reliable TMS-induced i) contralateral impairment, ii) ipsilateral enhancement and iii) attentional selection in visual detection paradigms.

3.2 Methods

The current review was not registered but followed the PRISMA guidelines.

3.2.1 Literature search and study selection

The literature search was conducted on PubMed, Elsevier, and Web of Science using the search codes (TMS OR "transcranial magnetic stimulation") AND (PPC OR "parietal") AND ("extinction" OR "visual detection" OR "visuospatial attention" OR "spatial attention" OR "spatial neglect"). The search was restricted to journal articles written in English, between 1994 and February 2022. Two researchers searched articles fully independently according to the PRISMA guideline and inconsistencies in the search results were resolved in team discussions.

3.2.2 Inclusion and exclusion criteria

Search results were imported into Endnote and duplicates removed in the first round of screening. Then two researchers conducted the abstract and full-text review respectively. Inclusion criteria were: (1) healthy human participants (at least 5); (2) TMS targeting any region of the PPC (labeled as intraparietal sulcus or close to the MNI coordinates reported by (Fox et al., 2006)); (3) using the visual detection/extinction task; (4) comparison of active stimulation to baseline condition (no TMS or sham stimulation or control site stimulation (e.g., the vertex)); (5) inclusion of at least one detection performance measure (e.g. detection rate, error rate).

3.2.3 Data extraction and management

One researcher used a standardized data extraction form specifically designed for this review to collect data from the included studies. Extracted data included the following information: author; published year; a detailed description of the participants, their age, sex, handedness; TMS related parameters, frequency, offline or online TMS application, duration, TMS localization; detection performance change compared with baseline. For articles only reporting data in figures, numerical results were extracted from the figures using GetData Graph Digitizer 2.24. All of these extraction steps were double-checked by the senior researchers.

3.2.4 Statistical methods

Statistical analyses were done with SPSS (IBM), Stata, and R software (Metafor and Meta package). Changes in detection performance in participants were analyzed using paired or one-sample T -tests. For studies that reported the F value, the formula $T = \sqrt{F}$ was used to estimate the T -test statistic from the one-way analysis of variance. For studies that reported the mean value and standard error of baseline and TMS conditions, but not the T -test statistic, we used the paired sample T -statistic and formulas (see below (1) and (2)) outlined in Morris and DeShon (Morris and DeShon, 2002) to derive the correlation between outcome measures.

$$ES = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}}} = \frac{\bar{X}_1 - \bar{X}_2}{S_{pooled}} \quad (1)$$

$$S_{pooled} = \frac{s_{gain}}{\sqrt{2(1-r)}} \quad (2)$$

The former part of formula 1 is suitable for independent t-test, and the latter part is also suitable for paired t-test but should combine formula 2 to get the pooled standard deviation

ES= effect size Cohen's d

\bar{X} = mean value from baseline (X_1) and experimental (X_2) conditions;

s^2 = variance for the baseline (s_1) and experimental (s_2) conditions;

n = total sample size;

s_{gain} = standard deviation squared (experimental condition);

r = correlation between baseline and experimental conditions

The effect sizes (Cohen's d) were then calculated in these studies, including studies using repetitive TMS (rTMS), continuous theta burst stimulation (cTBS) and event-related TMS stimulation. For studies that reported T or F value, `effectsize::t_to_d` function was used to get the Cohen's d . For studies that reported data as mean value and standard error, the `escalc` function was used to obtain the (bias-corrected) standardized mean differences and corresponding sampling variances and transformed it to Cohen's d according to the 'Metafor

'package. Since few of these studies reported the change of detection performance (compared with baseline, baseline as 0 or 1), then Stata Software was used to get the corresponding t value.

After calculating the merged effect sizes, we evaluated their significance by checking whether the 95% confidence interval included 0 or not. Besides a homogeneity analysis was carried out, followed by Q Test measures for heterogeneity, and the Egger test and funnel plot to determine publication bias. In case of a significant publication bias, trim and fill methods were used. Lastly, we generated forest plots to visually display results and conducted a sensitivity analysis and subgroup analyses by 'Meta' package in R.

3.2.5 Multilevel meta-analysis

For studies that include multiple nested interventions in a single sample, dependence might be introduced. Statistical independence is one of the core assumptions of meta-analytic pooling (Harrer et al., 2021), and dependency between effect sizes (i.e., the effect sizes are correlated) could artificially reduce heterogeneity and lead to false-positive results. These dependencies that may exist in these nested designs can be handled using a multilevel meta-analysis. In multilevel meta-analysis, the variance in observed effect sizes is decomposed into sampling variance (level 1), between-study variance (level 2) and variance between groups of studies (level 3), and the moderating effect of characteristics of studies (at level 2) and groups of studies (at level 3) can be explored. This analysis was conducted using the metafor package in R.

3.2.6 Bayesian meta-analysis

In addition to the conventional meta-analysis outlined above, we also performed a Bayesian meta-analysis. Within the R statistical computing environment, we used the "brms" package (Bürkner, 2017) based on Stan software (Carpenter et al., 2017), to fit Bayesian multilevel models. The first step of Bayesian analysis was defining a prior distribution of standardized mean difference (SMD) as $SMD \sim \mathcal{N}(0,1)$ and heterogeneity(τ) as $\tau \sim HC(0,0.5)$, then set up the formula for the model and the MCMC algorithm run 4000 iterations to fit the model. Before evaluating the model fitting, convergence was assessed by posterior predictive checks and the R-hat values of the parameter estimates. Based on the obtained Bayesian model, we calculated the exact probabilities that the meta-analytic effect will be smaller/larger than a given effect size value by looking at the empirical cumulative distribution function (ECDF) of the posterior distribution for the pooled effect size.

3.3 Results

3.3.1 Overview

The initial literature search resulted in 813 articles (duplicates removed) of which 144 were included in the full-text review (details in Fig.2). Ultimately, a total of 10 different studies met the inclusion criteria. Stimulation parameters and participants' information are shown in Table 1.

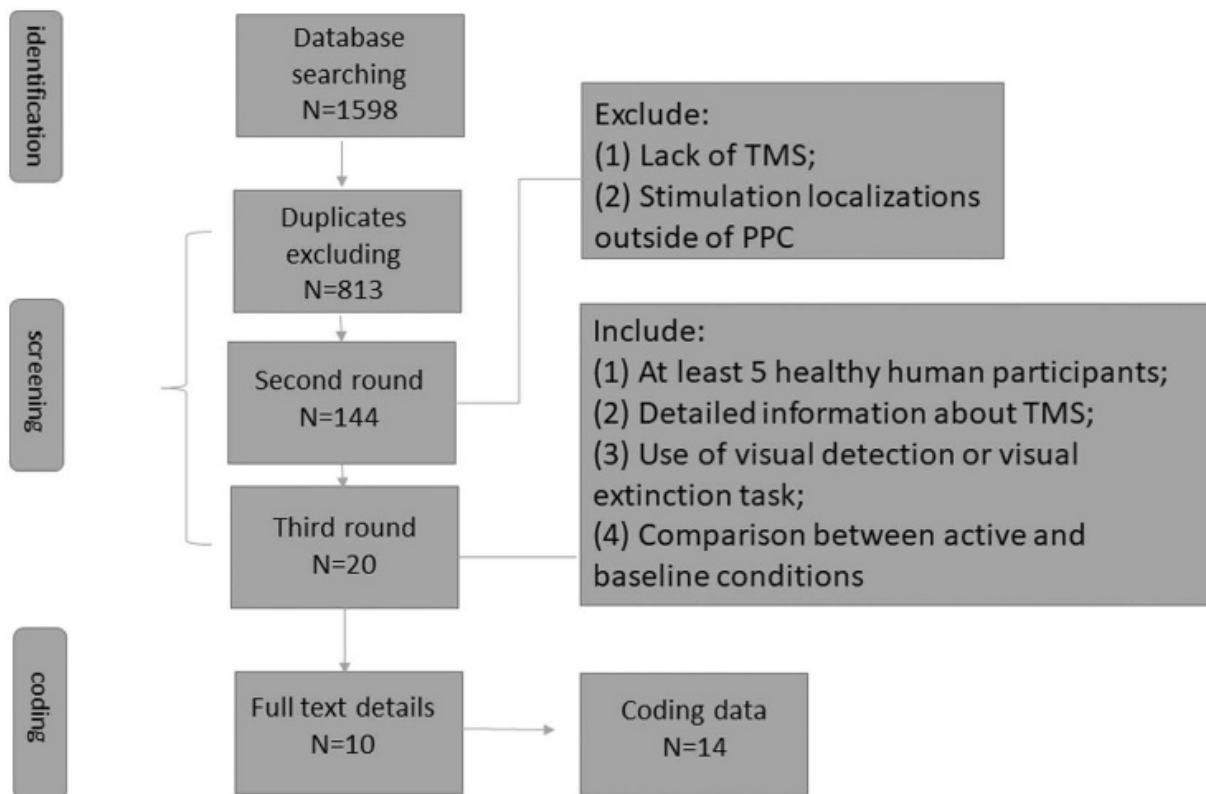


Fig.2. Flowchart of data extraction. The flowchart includes database searches, the screening of study abstracts and full-texts, and the reasons for excluding studies.

Table.1. Summary of all included studies

Study	Participants	Age	Handedness	TMS protocol	Type of TMS	Localization	Baseline condition
Cazzoli et al.,2009	30 (3 groups, no TBS, TBS, and vertex)	22-49	26 Right & 4 Left	offline, 80% RMT, 801 pulses, 3-pulses bursts at 30 Hz, repeated at intervals of 100ms	cTBS	Electrode position P4 in 10-20 system	No TMS
Dambeck et al.,2006)	10	23.9±3.3	Right	online,60% MSO, ISI after	single pulse	Electrode position P3, P4,	No TMS

Hilgetag et al.,2001	7 females	27-37	Right	stimulus 150ms/250ms offline, 90% RMT, last for 10min at 1Hz	rTMS	and P3 + P4 in 10-20 system Electrode position P3 or P4 in 10- 20 system	No TMS
Koch et al.,2005,sTMS	9(5 females)	20-33	Right	online, 130% RMT, 150ms after stimulus	SP	Electrode position P4 in 10-20 system	Sham at P4
Koivisto et al.,2017	12(5 males)	19-28	Right	online, 75% MSO, 50ms after stimulus onset	SP	MRI localizer to MNI coordinates of left and right IPS and vertex	Controls site (vertex)
Müri et al.,2002	10(6 males)	22-40	9 right & 1 left	online, 80% MSO, 270ms after stimulus with 100ms ISI	DP	Electrode position P3 or P4 in 10- 20 system	No TMS
Petit et al.,2015	5(4 males)	23.8±4.7	NA	offline, 90% RMT, last for 15min at 1Hz	rTMS	fMRI localizer on rANG/IPS	No TMS
Schauer et al.,2016	12(4 females)	26.42±5.7	9 right & 3 left	offline, 40% MSO, 3- pulses bursts at 50 Hz, lasting for 40 s	rTMS	MRI localizer on right anterior and posterior SPL	No TMS
Vesia et al.,2015	11(5 females)	19-45	Right	offline, 80%MT, 3- pulse burst at 50 Hz repeated every 200 ms	cTBS	Electrode position P3 or P4 in 10- 20 system	No TMS
Gießing et al., 2020	20(16 females)	18-31	NA	offline, 40% MSO, last for 10 min at 1Hz	rTMS	Electrode position P4 in 10-20 system	Sham at P4

RMT: resting motor threshold; MSO: maximum stimulator output; rTMS: repetitive TMS; SP: single pulse, DP: double-pulse; cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging; EEG: electroencephalogram.

As illustrated in Fig. 2, from the third-round screening to the coding stage, several studies were excluded. Five studies did not use a simple detection task (Battelli et al., 2009; Hung et al., 2005; Leitão et al., 2017; Mahayana et al., 2014; Muggleton et al., 2006). One study (Bien et al., 2012a) was excluded because the control condition in the study was considered inadequate because trials without TMS were interleaved with TMS trials (Duecker & Sack, 2013). Two

studies did not report the required data and there was no way to retrieve them (Hilgetag et al., 2003; Pascual-Leone et al., 1994). Two high frequency offline TMS studies (i.e., excitatory instead of inhibitory TMS effects) were excluded, namely Dombrowe et al. (2015) and Jin et al. (2008). Eventually, ten studies with almost identical stimulation sites, experimental tasks, and conceptually matching TMS protocols remained that were included in the final meta-analysis.

Among the final 10 studies (Cazzoli et al., 2009; Dambeck et al., 2006; Gießing et al., 2020; Hilgetag et al., 2001; Koch et al., 2005; Koivisto et al., 2017; Müri et al., 2002; Petit et al., 2015; Schauer et al., 2016; Vesia et al., 2015), some conducted right hemisphere stimulation as well as left hemisphere stimulation, so there were two datasets within one study (Dambeck et al., 2006; Hilgetag et al., 2001; Koivisto et al., 2017; Vesia et al., 2015). The authors of two studies (Schauer et al., 2016; Vesia et al., 2015) supplied raw data and additional details on request to enable inclusion in our analyses. For the study by Dambeck et al. (2006), the bilateral TMS stimulation was excluded as well as a longer ISI conditions because no other studies explored these parameters. For Koch et al. (2005), two control conditions and the paired-pulse TMS condition with different ISI were excluded. To keep some parameters as consistent as possible across all included studies, for the study of Schauer et al. (2016), only the stimulation site in posterior SPL was included as this was most similar to the other PPC targets in this meta-analysis. For the study by Vesia et al. (2015), the cTBS effect peaked after 20 – 25 minutes, so only blocks three to six were combined and included.

3.3.2 Meta-analysis of a contralateral TMS effect on a unilateral stimulus

To check the contralateral TMS effect on a unilateral stimulus, 11 datasets from previous studies were merged to yield a pooled effect size for left and right PPC stimulation. The test for heterogeneity was not significant ($I^2 = 14\%$; $\tau^2 = 0.0233$, $p = 0.31$), supporting the rationale for computing a fixed effect model. The fixed effect model showed a non-significant negative Cohen's d -0.13, 95% CI ranged from -0.35 to 0.1 (See Fig.3A). The Egger test showed that there was no significant publication bias ($p = 0.23$). After omitting any single study, the effect was essentially the same. Thus, the current result was robust and not impacted by other variables.

The subgroup analysis showed that there was no significant difference between right PPC and left PPC stimulation ($Q = 0.14$, $df = 1$, $p = 0.7$). For right PPC stimulation, the fixed effect model showed a non-significant effect size (Cohen's $d = -0.09$; 95% CI ranged from -0.37 to

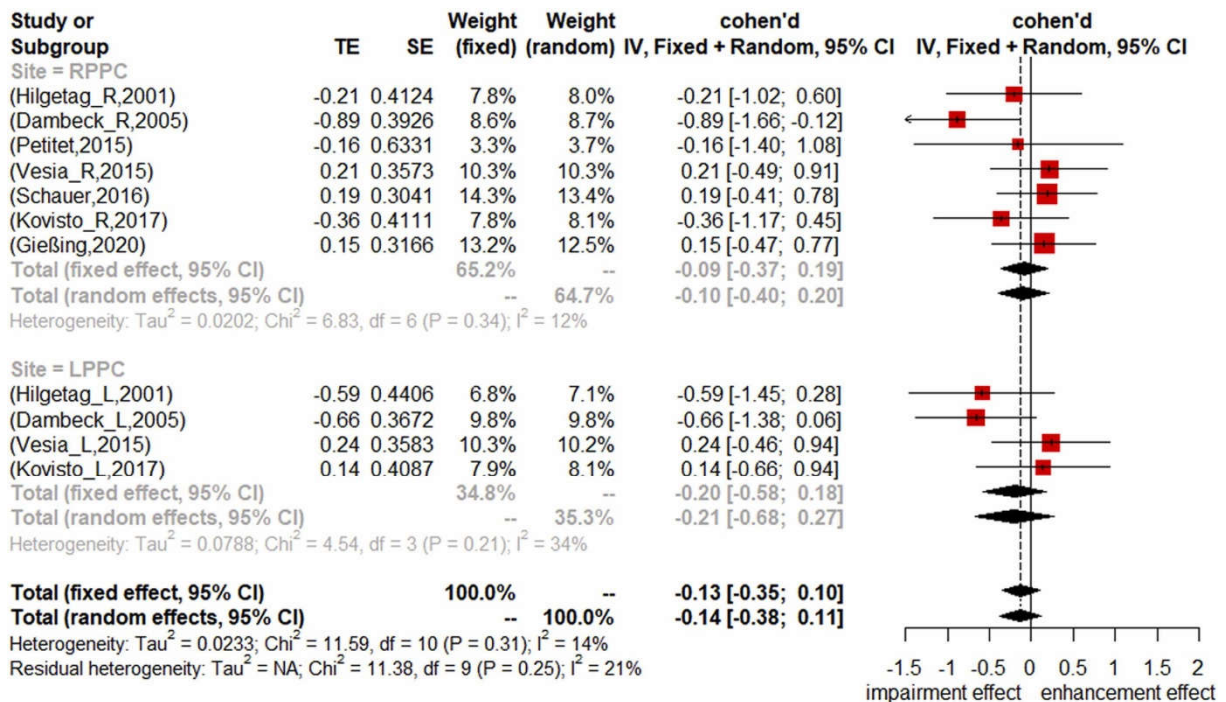
0.19), and the same was true for left PPC stimulation (Cohen's $d = -0.2$; 95% CI ranged from -0.58 to 0.18). Therefore, the result suggested TMS over RPPC/LPPC does not impaired detection performance in the contralateral hemifield when a unilateral stimulus was presented.

As mentioned above, given the potential dependencies caused by multiple datasets stemming from single studies, we considered such dependencies by integrating a third layer into the structure. We used a 3-level model including the sampling variation for each ES (level 1), variation across ESs within a study (level 2), and variation across studies (level 3). Here, several datasets from four studies (Dambeck et al., 2006; Hilgetag et al., 2001; Koivisto et al., 2017; Vesia et al., 2015), which collected data from multiple sites, were added. The full model showed that the pooled effect size was -0.21, 95% CI ranged from -0.52 to 0.11. After checking the variance distribution of the full model, it was observed that layer 1 to layer 3 accounted for 79 %, 0%, and 21% variance, respectively. From the comparison between the full model and the leave-level 3-out model, no significant model fitting difference were found (lower AIC and BIC; $p = 0.48$).

3.3.3 Meta-analysis of an ipsilateral TMS effect on a unilateral stimulus

To check the ipsilateral TMS effect on a unilateral stimulus, 10 datasets were merged to yield a pooled effect size for left and right PPC stimulation. The test for heterogeneity was not significant ($I^2 = 43\%$; $\tau^2 = 0.1141$, $p = 0.06$), supporting the rationale for computing a fixed effect model. The fixed effect model showed a non-significant positive Cohen's d 0.14, 95% CI ranged from -0.09 to 0.37 (See Fig.3B). The Egger test showed there was no significant ($p = 0.1$) publication bias, but the funnel plot (see Fig.4A) suggested that there was some degree of publication bias. Using the trim and fill method, three virtual studies were added (Fig.4B), the effect was non-significant (Cohen's d -0.01, 95% CI ranged from -0.36 to 0.33). After omitting any single study, the effect was still essentially the same. Thus, the current result revealed was robust and not impacted by other variables.

A. Unilateral stimulus: contralateral impairment effect



B. Unilateral stimulus: ipsilateral enhancement effect

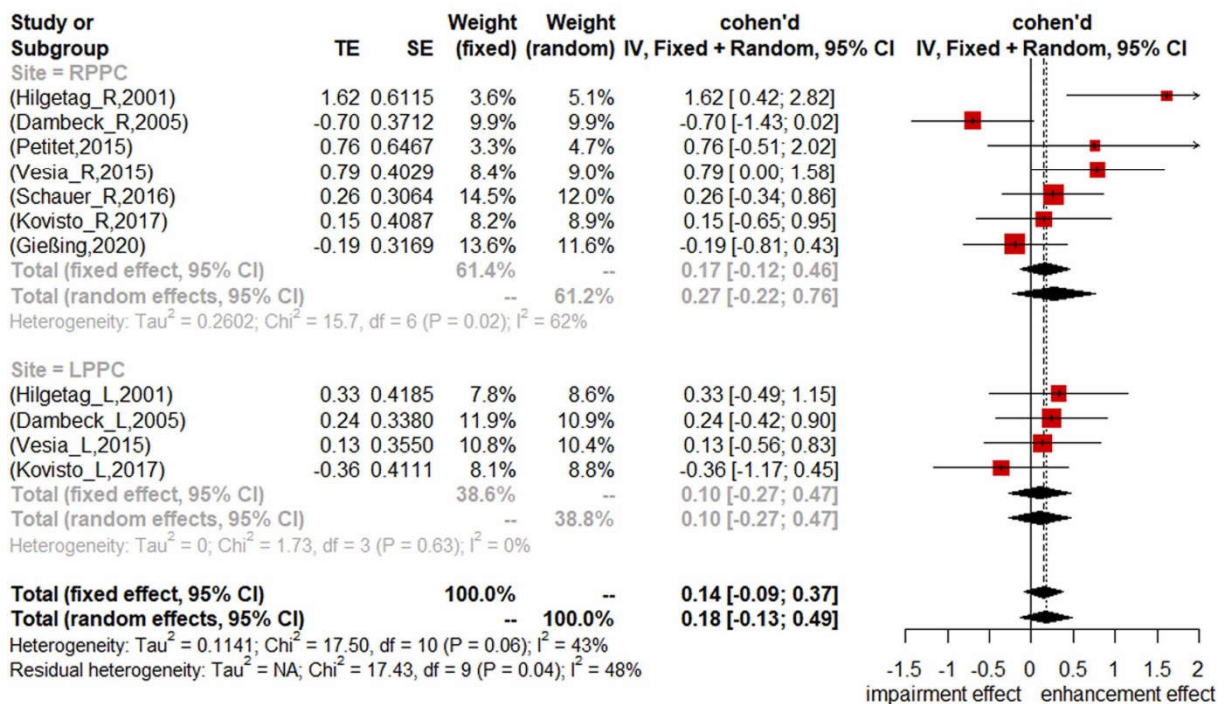


Fig.3. Unilateral stimulus contralateral impairment and ipsilateral enhancement effects. Subgroup comparison of the Mean effect size (Cohen’s *d*) and 95% confidence intervals for the 11 datasets for visual detection performance changes a unilateral stimulus presented in the contralateral hemifield (Fig. 3A, which correspond to the expectation Fig.1, unilateral stimulus blue bar) and ipsilateral hemifield (Fig. 3B, which

correspond to the expectation Fig.1, unilateral stimulus orange bar) after left vs. right PPC stimulation. The red color squares represent the mean effect of each single study, and the black squares represent the pooled effects.

The subgroup analysis showed that there was no significant difference between the right PPC and left PPC stimulation ($Q = 0.18$, $df = 1$, $p = 0.67$). For the left PPC stimulation, the fixed effect model showed a non-significant positive effect size (Cohen's $d = 0.17$, 95% CI ranged from -0.12 to 0.46), and the same was true for right PPC stimulation (Cohen's $d = 0.1$, 95% CI ranged from -0.27 to 0.47, See Fig.3B). Therefore, the result suggested TMS over RPPC/LPPC did not enhance detection performance in the ipsilateral hemifield when a unilateral stimulus was presented.

The multiple meta-analysis full model showed that the pooled effect size was 0.08, 95% CI ranged from -0.22 to 0.38. After checking the variance distribution of the full model, it was observed that layer 1 to layer 3 accounted for 75 %, 25% and 0% variance respectively. From the comparison between the full model and the leave-level 2-out, no significant model fitting difference were found (lower AIC and BIC) ($p = 0.59$).

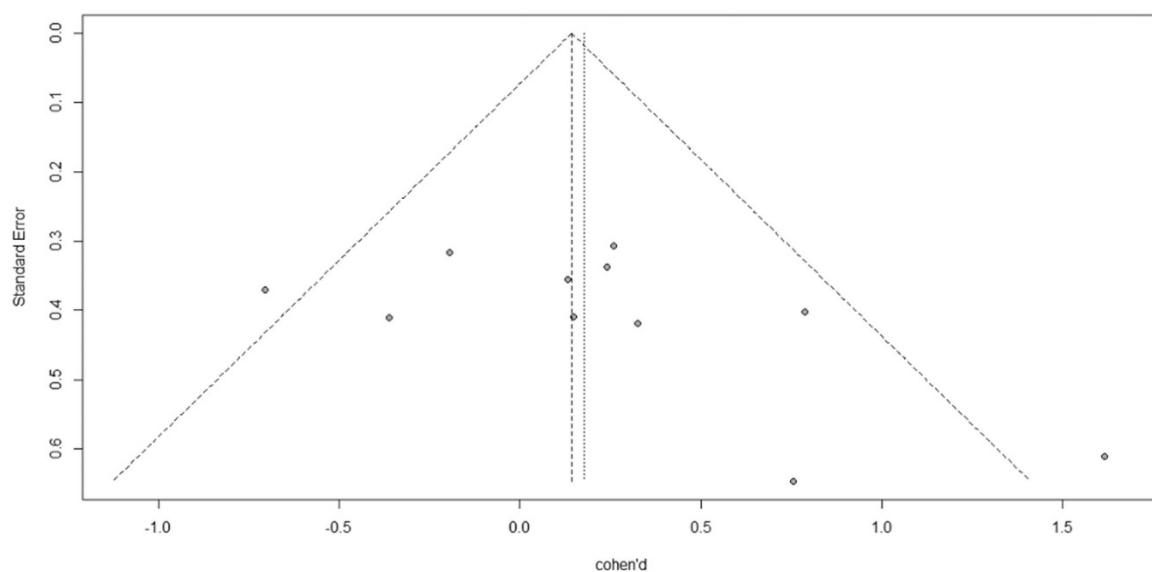


Fig.4. The funnel plot of TMS unilateral stimulus ipsilateral enhancement effect. A. The original funeral plot. Every dot represents a single study. B. The funeral plot after trim virtual studies. Black dots represent real studies and white dots represent virtual studies.

3.3.4 Meta-analysis of TMS induced impairment effect on a bilateral stimulus

In order to assess whether TMS induced an impairment effect on a bilateral stimulus, 11 datasets were merged to yield a pooled effect size for left and right PPC stimulation. The test for heterogeneity was not significant ($I^2 = 42\%$; $\tau^2 = 0.1114$, $p = 0.07$), supporting the rationale for computing a fixed effect model. The fixed effect model showed a non-significant Cohen's d -0.24, 95% CI ranged from -0.47 to -0.01 (see Fig. 5A). The Egger test showed that there was no significant publication bias ($p = 0.47$). After omitting any single study, the effect was still essentially the same.

For the right PPC stimulation, the fixed effect model showed a significant negative Cohen's d -0.39, 95% CI ranged from -0.68 to -0.1. For the left PPC stimulation, the fixed effect model showed a non-significant negative Cohen's d -0.03, 95% CI ranged from -0.36 to 0.41. In other words, only right PPC TMS impaired detection of a bilateral stimulus. In order to further investigate the hemifield-specific contributions to this effect (i.e., potential contralateral impairment and ipsilateral enhancement effects), follow-up analyses focused exclusively on the right PPC.

3.3.5 Meta-analysis of a contralateral TMS effect on bilateral stimulus (right PPC only)

As shown in Fig.5B, 7 datasets were merged into a pooled effect size. The test for heterogeneity was not significant ($I^2 = 51\%$; $\tau^2 = 0.1779$, $p = 0.06$), supporting the rationale for computing a fixed effect model. The fixed effect model showed a significant negative Cohen's d -0.87, 95% CI ranged from -1.17 to -0.58. The Egger test showed that there was no significant publication bias ($p = 0.09$). After omitting any single study, the effect was still essentially the same, i.e., TMS over right PPC impaired detection performance in the contralateral hemifield when a bilateral stimulus was presented.

3.3.6 Meta-analysis of an ipsilateral TMS effect on bilateral stimulus (right PPC only)

As shown in Fig.5C, 6 datasets were merged into a pooled effect size. The test for heterogeneity was not significant ($I^2 = 33\%$; $\tau^2 = 0.0848$, $p = 0.21$). The fixed effect model showed a non-significant Cohen's d 0.05, 95% CI ranged from -0.33 to 0.44. The Egger test showed there was no significant ($p = 0.1$) publication bias. After omitting any single study, the effect was still

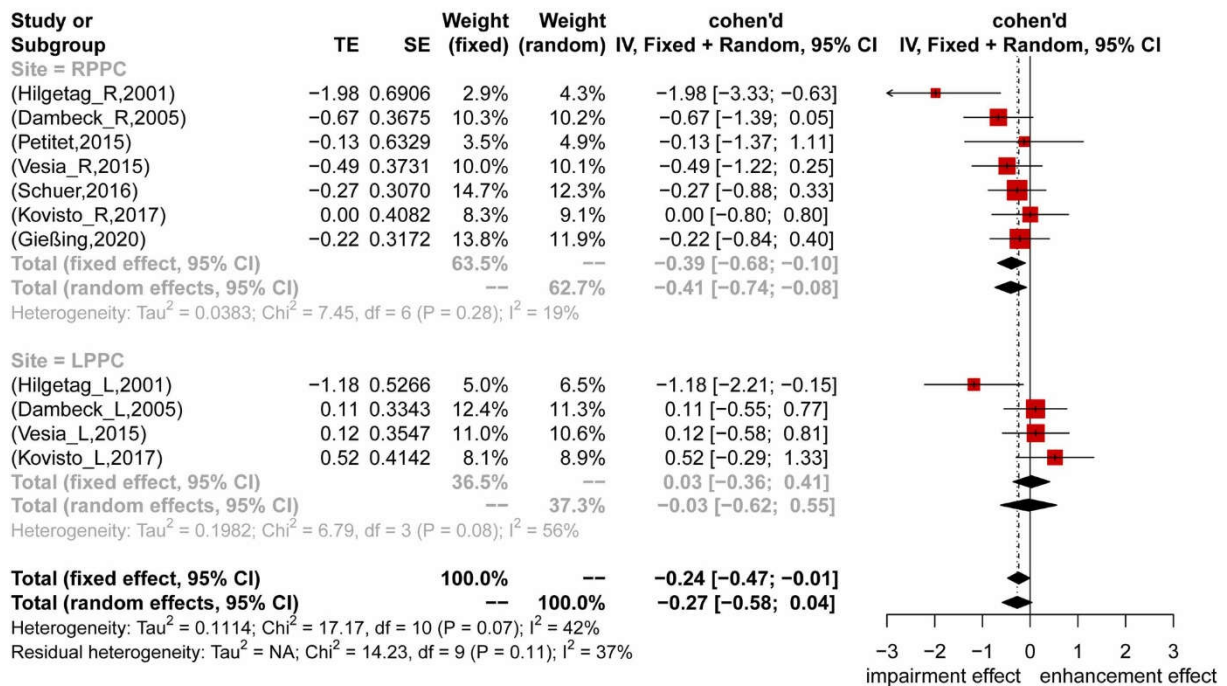
essentially the same, i.e., TMS over right PPC did not enhance detection performance in the ipsilateral hemifield when a bilateral stimulus was presented.

3.3.7 Bayesian meta-analysis of ipsilateral enhancement effects

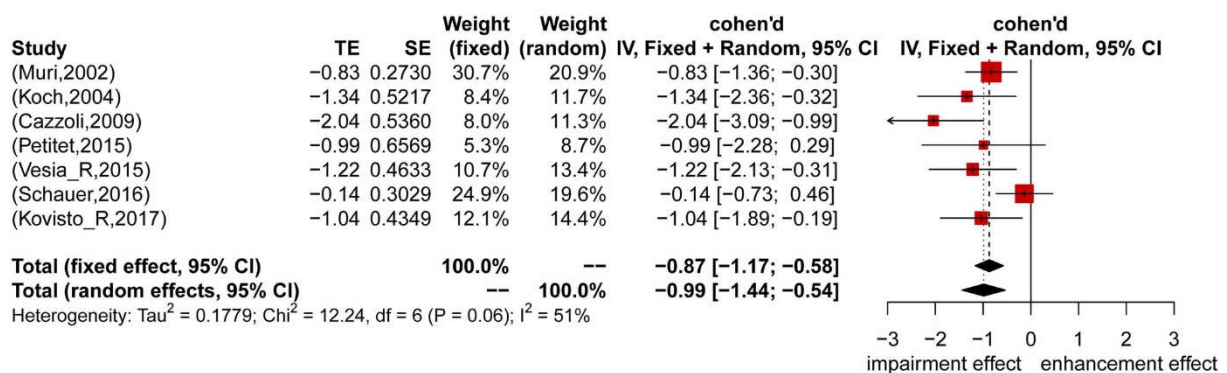
A critical aspect of the results reported above is the absence of an enhancement effect in the ipsilateral hemifield. We also performed Bayesian meta-analyses to obtain additional support for the null hypothesis. In addition to conventional confidence intervals of effect sizes, a Bayesian meta-analysis can also provide a distribution of effect sizes and thus estimate the probability that the true effect is larger than x , given the data. Lastly, this analysis is particularly suited when the number of included studies is relatively small, as is the case here (Harrer et al., 2021).

For a unilateral stimulus presented in the ipsilateral hemifield, we combined the data of left and right PPC stimulation, whereas only right PPC stimulation conditions were considered for the performance in the ipsilateral hemifield for a bilateral stimulus, thus intended as direct follow-up analyses of the results outlined above. After confirming convergence ($\hat{R} = 1$), results showed essentially the same pooled effects for both analyses (unilateral stimulus: a non-significant positive Cohen's d 0.17, 95% CI ranged from -0.13 to 0.49; bilateral stimulus: a non-significant positive Cohen's d -0.11, 95% CI ranged from -0.42 to 0.75). The ECDF function was then used to obtain the probability of the pooled effect being greater than a fixed effect size of 0.4 (medium effect size). Critically, there is only a 6% probability of an ipsilateral enhancement effect size of that magnitude for the unilateral condition, and a 13% probability for the bilateral condition. Taken together, this provides additional support for the absence of an ipsilateral enhancement effect, mirroring the outcome of the conventional meta-analysis.

A. Bilateral stimulus : total impairment effect



B. Bilateral stimulus : contralateral impairment effect



C. Bilateral stimulus : ipsilateral enhancement effect

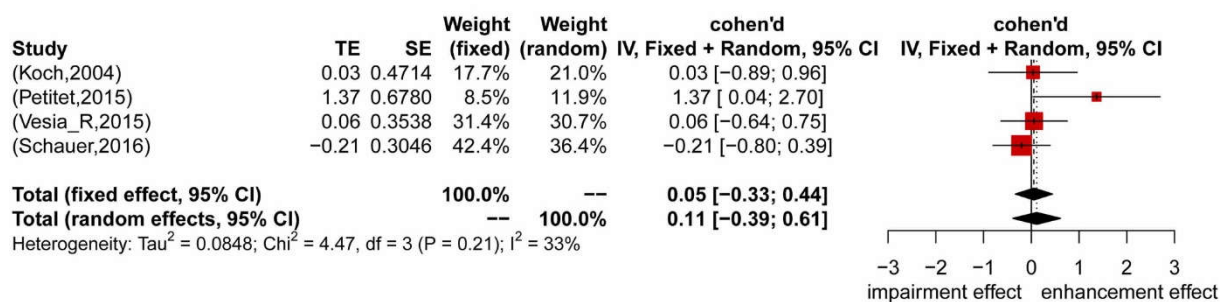


Fig.5. Bilateral stimulus TMS-induced effect. A. Subgroup comparison of the Mean effect size (Cohen’s *d*) and 95% confidence intervals for the 11 datasets for visual detection performance change on bilateral trials after left vs. right PPC stimulation; B. the Mean effect size (Cohen’s *d*) and 95% confidence intervals for the 7 datasets for visual detection contralateral hemifield performance change on bilateral trials (which correspond to the expectation Fig. 1, bilateral stimulus blue bar) after right PPC stimulation; C. the Mean effect size (Cohen’s *d*) and 95% confidence intervals for the 4 datasets for visual detection ipsilateral hemifield performance change on bilateral

trials (which correspond to the expectation Fig. 1, bilateral stimulus orange bar) after right PPC stimulation. The red color squares represent the mean effect of each single study, and the black squares represent the pooled effects.

3.4 Discussion

The objectives of this meta-analysis were to quantify the current empirical evidence base for a reliable TMS-induced i) contralateral impairment, ii) ipsilateral enhancement and iii) attentional selection bias in visual detection paradigms. We focused on studies using visual detection paradigms that allowed to assess the specific functional contributions of parietal cortex in both hemispheres to attentional processing in each hemifield separately, and thereby to evaluate diverging predictions of two influential theories of spatial attention control: the Heilman hemispatial theory and Kinsbourne's opponent processor theory. This is not only important for basic research on the cognitive neuroscience of spatial attention control, but also has direct clinical relevance as the currently common and officially recommended clinical TMS protocols in stroke rehabilitation are largely based on an assumed notion that most TMS studies are in agreement with the opponent processor model by revealing not only an inhibitory TMS-induced contralateral impairment in visual detection, but also ipsilateral enhancement.

We here included 10 studies using inhibitory/disruptive TMS applied over left or right parietal cortex in the context of visual detection/extinction paradigms. Our meta-analysis of these studies globally revealed that inhibitory/disruptive TMS applied over posterior parietal cortex does functionally impact visual detection performance, confirming previous studies regarding the functional role of parietal cortex for visual detection performance (Bien et al., 2012a; Dambeck et al., 2006; Gießing et al., 2020; Hilgetag et al., 2001). More specifically, we found a significant contralateral impairment effect after TMS over right PPC in bilateral visual stimulus conditions, i.e. when two simultaneously presented visual stimuli are competing for attention. In the unilateral visual stimulus conditions, however, no significant contralateral impairment effect was observed. Importantly, we also could not find any significant ipsilateral enhancement effects in both, bilateral and unilateral visual stimulus condition. In addition, our findings revealed a hemisphere asymmetry in the bilateral stimulus conditions, where only stimulation of the right parietal cortex resulted in a significant impairment effect.

These findings nicely support and complement our previous meta-analysis (Wang et al., 2023) on left versus right parietal TMS effects on line-bisection and landmark tasks, which measured the attention bias. In this previous meta-analysis, we could confirm that studies using

inhibitory/disruptive TMS over the right parietal cortex provided evidence for the functional relevance of the posterior parietal cortex in successfully executing these attentional tasks, but not the left parietal cortex. Similar to the previous meta-analysis, the current meta-analysis also clearly demonstrates that TMS applied over the right parietal cortex results in a significant contralateral impairment in bilateral stimulus conditions, while no such effect was observed in the left parietal cortex. Both findings are nicely replicating the hemispheric functional asymmetry also reported in neglect patients.

In comparison to the previous meta-analysis (Wang et al., 2023), the current meta-analysis addressed several limitations. The line bisection task may engage not only attentional mechanisms but also magnitude processing/comparison, which were predominantly a right parietal process (Cantlon et al., 2006; Failenot et al., 1999; Piazza et al., 2006; Pinel et al., 2004; Sack et al., 2009; Seydell-Greenwald et al., 2019) and had a mixed attentional effect. More importantly, however, only the current meta-analysis allowed us to segregate the exact differential contributions of each hemisphere for each hemifield specifically, which is indispensable when referring to the separate functional role of each hemisphere for hemisphere-specific attention biases, gains, and costs towards the ipsilateral versus contralateral side of space (Duecker and Sack, 2015). As concluded in our previous meta-analysis, this can only be achieved by using a visual detection task. These tasks not only allow the calculation of attention bias (i.e. difference in detection performance left versus right for unilateral stimuli, or proportion of left versus right responses in case of bilateral stimuli) but furthermore allow assessment of detection performance in each hemifield in isolation (i.e. detection rates of left stimuli or right stimuli considered in isolation). Focusing on those studies employing such visual detection paradigms in the context of parietal TMS, our current meta-analysis indeed again also revealed TMS-induced contralateral impairment effects, but only for bilateral visual stimuli and not for unilateral visual stimulus conditions. This difference between TMS effects on bilateral versus unilateral conditions could be due to differences in task difficulty, with bilateral trials being more demanding for perceptual and attentional processes thus making them more susceptible to disruption by TMS. Alternatively, this result could also hint at a dissociation of unilateral and bilateral detection performance potentially related to a specific involvement of the targeted parietal regions in visual extinction. Vossel et al. (2011) have argued that

unilateral spatial neglect and visual extinction can be linked to distinct lesion profiles and our results may also reflect this dissociability of the two phenomena.

Regarding the assumed and often referred to TMS-induced ipsilateral enhancement effect, we here could not find any supporting evidence for the existence of such an enhancement effect, neither during unilateral nor bilateral visual stimulus conditions. The conventional and Bayesian meta-analytical results statistically challenge the ipsilateral enhancement effect after parietal TMS. The pooled effect size in our meta-analysis, twenty years after the first highly influential reports of ipsilateral enhancement (Hilgetag et al., 2001), is simply not in support of such an enhancement effect when considering all available data. We conclude that the TMS-induced attentional shift consistently reported in line bisection or landmark tasks is probably exclusively caused by a contralateral impairment effect without any contribution of the ipsilateral hemifield. Accordingly, these meta-analytic findings of TMS-induced visual extinction in healthy volunteers are also not in support of Kinsbourne's opponent processor theory according to which the inhibition of one hemisphere by suppressive TMS should not only lead to contralateral impairments, but also cause a disinhibition of the contralateral hemisphere (which is released from its inhibition in the context of inter-hemispheric competition), causing ipsilateral enhancement. But this is not what the current evidence from these TMS studies suggests. These results clearly invite further discussion, not only on scientific grounds but also because Kinsbourne's model (Kinsbourne, 1977), including the notion of interhemispheric balance/competition, seems core to the rationale of clinical TMS treatment in stroke rehabilitation. Some clinical studies on neglect patients report ipsilateral enhancement after parietal stimulation targeting the healthy, unaffected hemisphere (Nyffeler et al., 2009; Yi et al., 2016), but in many clinical studies, the evaluation of improvement is based on paradigms that are not suited to separate ipsilateral and contralateral effects and/or the hemisphere-specific contribution in isolation (Lim et al., 2010; Oliveri et al., 2001; Song et al., 2009; Sparing et al., 2009) also see in the review (Mylus et al., 2012). While it remains difficult to compare healthy brains to those of lesion patients, the current meta-analysis raises concerns regarding the assumed TMS-induced enhancement in visual detection paradigms. We at this point and based on the currently available literature in fact need to acknowledge that there is no strong evidence base for claiming such a specific TMS-induced ipsilateral enhancement of attention after parietal stimulation in healthy volunteers. This often referred to and repeatedly communicated

notion is based on an early and highly influential study that could not be replicated ever since. However, it continues to fuel the narrative for using inhibitory/disruptive TMS interventions targeted at the unaffected healthy hemisphere in neglect patients. While the verdict regarding the clinical efficacy of this specific TMS approach is still out (as an injured brain may respond very differently to TMS as compared to a healthy brain), the assumed empirical support for TMS-induced ipsilateral enhancements in visual detection paradigms in healthy volunteers seems to be a myth.

The predictions from Heilman's hemispatial theory (Heilman and Abell, 1980) are more in line with the current results. Heilman's model predicts contralateral deficits, which we found here, and makes no prediction of ipsilateral enhancement. However, our results do not explicitly support the 'soft supposition' of a larger contralateral impairment effect induced by right, as compared to left, parietal cortex disruption. Again, it is difficult to compare healthy brains to those of lesion patients, and TMS insults are fundamentally weaker and different by nature. There might be a difference between both hemispheres in their ability to compensate for an insult to the contralateral side, which remains hidden because TMS insults are not severe enough.

In sum, the current meta-analysis study challenges the Kinsbourne's opponent processor model and supports Heilman's hemispatial theory. The findings contribute to a better understanding of the visual attention system, hemispheric asymmetries, and highlights the importance of building strong empirical and theoretical foundations when translating fundamental research to clinical application.

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Chapter 4

Group-based TMS coil positioning sometimes outperforms individualized approaches: evidence from resting-state-, diffusion-, and functional-MRI

Based on: Ting Wang*, Michael Capalbo*, Felix Duecker, Alexander T. Sack. (2023). Group-based TMS coil positioning sometimes outperforms individualized approaches: evidence from resting-state-, diffusion-, and functional-MRI. *In preparation*.

Chapter 5

Dissecting alerting and orienting effects in
exogenous visuospatial attention with drift
diffusion model analysis

EMBARGOED

Based on: Ting Wang, Felix Duecker*, Alexander T Sack*. (2023). Dissecting alerting and orienting in visuospatial attention based on an online exogenous cueing task and drift diffusion models. *Submitted*.

Chapter 6

Dissecting alerting and orienting effects in endogenous visuospatial attention with drift diffusion model analysis

EMBARGOED

Based on: Ting Wang, Felix Duecker*, Alexander T Sack*. (2023). Dissecting alerting and orienting in visuospatial attention based on an endogenous cueing task and drift diffusion models. *In preparation*.

Chapter 7

Electrophysiological correlates of cognitive processes based on drift diffusion models for the alerting and orienting effects in an endogenous cueing task

Based on: Ting Wang, Felix Duecker*, Alexander T Sack*. (2023). Electrophysiological correlates of cognitive processes based on drift diffusion models for the alerting and orienting effects in an endogenous cueing task. *In preparation.*

Chapter 8

General discussion

8.0 Discussion

The present thesis aimed to investigate spatial attentional bias and the visuospatial attention effects of alerting and orienting. This work was divided into three main parts (see Fig. 1). In the first part, we performed meta-analyses of research on the effects of TMS on attentional bias tasks to assess the presence of hemispheric asymmetries and then discussed the implications for competing theories of the functional organization of attention networks. In the second part, we focused on TMS localization methods based on MRI data and compared the differences between individual task-based fMRI and individual resting-state fMRI, as well as group-based approaches, trying to evaluate the performance of each method and find the differences between them. In the third part, we used Posner cueing tasks, combined with DDM analyses of behavioral data, to explore the cognitive processes of alerting and orienting effects and also linked these to their neural dynamic signals using EEG data. In the following, we summarize the main findings of the thesis and discuss its implications.

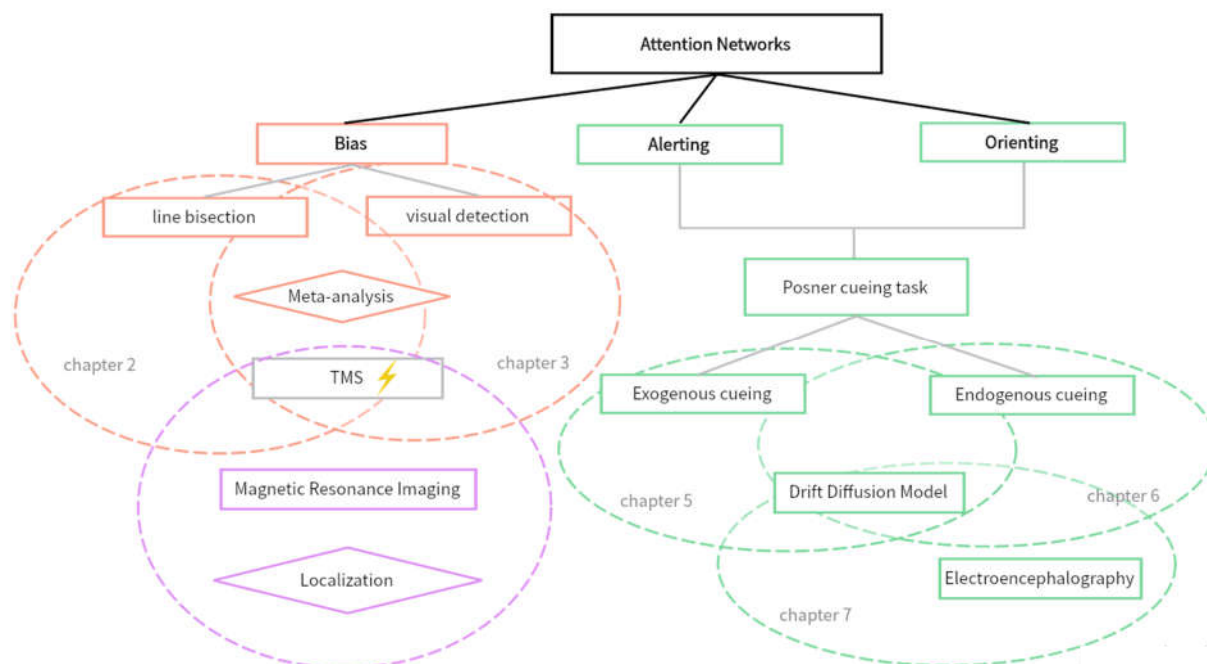


Fig. 1. General overview of this thesis; the squares represent key concepts and methods. When a circle includes several squares, it implies a combination of these concepts and methods for a particular study (or chapter). Red refers to Part I, which focused on attentional bias. Purple refers to Part II, which focused on TMS localization. Green refers to Part III, which covered alerting and orienting effects. **Part I:** *Chapter 2* consisted of a meta-analysis of research on the inhibitory TMS effect on the left and right parietal cortex based on line bisection task performance. This was done to determine whether TMS could mimic the case of neglect patients and to compare the left and right hemisphere effects in attentional bias shifting. *Chapter 3* contained a meta-analysis of the findings pertaining to the inhibitory effect of TMS on the left and right parietal cortex based on visual detection

performance, which separated attentional bias into the left and right hemifields to evaluate the left and right hemisphere asymmetry mechanism and further assess the related visuospatial attention theories. **Part II: Chapter 4** explored and compared various MRI-guided TMS target localization approaches for the core nodes of the DAN and the VAN. **Part III: Chapter 5** described the performance of an exogenous cueing task using a DDM to examine the cognitive mechanisms associated with alerting and orienting effects on visual spatial attention. Along similar lines, *Chapter 6* described an endogenous cueing task but also evaluated the alerting and orienting hemifield lateralization that might be caused by hemispheric asymmetries. *Chapter 7* used the same endogenous cueing task, but with EEG recordings, to find the link between neural dynamics and cognitive processes in alerting and orienting.

8.1 Part I: Attentional bias and hemispheric asymmetries in attention networks

Hemisphere asymmetry plays a significant role in attentional networks, as it influences the attentional biases observed in a variety of tasks, such as line bisection and landmark tasks. The prevalent notion of right hemispheric dominance in attention has led to a long debate in cognitive neuroscience regarding the mechanisms underlying attentional control (Corbetta & Shulman, 2011; Heilman & Abell, 1980; Kinsbourne, 1977; Mesulam, 1981). These theories diverge in their explanations due to differing interpretations of each hemisphere's role in attentional control, which emphasizes the necessity of comprehending their distinctive contributions. While neuroimaging studies have explored the involvement of both hemispheres during attention tasks (e.g., Corbetta & Shulman, 2002; Gazzaniga, M. S., & Mangun, 2014; Serences & Yantis, 2006), distinguishing their specific contributions has proven challenging (Corbetta & Shulman, 2011). Several studies have shown how TMS allows for the temporary disruption of local neural activity in healthy individuals (Bien et al., 2012; Cohen Kadosh et al., 2007; Duecker et al., 2013; Gurel et al., 2018; Jeurissen et al., 2014; Pascual-Leone, 2000; Sack et al., 2007) and can induce “virtual lesions” to mimic spatial neglect (Babiloni et al., 2007; Chambers et al., 2004; Esterman et al., 2007; Fuggetta et al., 2006; Harris et al., 2008; Koch et al., 2005; Rounis et al., 2007; Rushworth et al., 2001; Sack, 2010). A number of TMS experiments have investigated the behavioral consequences of disrupting either the left or right hemisphere in the context of visual spatial attention paradigms based on attentional bias. Unfortunately, qualitative summaries of this literature have thus far failed to discover a consistent pattern of results, making it difficult to draw strong conclusions based on these studies. In this vein, it was believed that a meta-analysis may prove helpful, as it offers a systematic, objective method for summarizing the effects of left and right hemispheric stimulation from various research groups. It can also generate an overall effect size and

subgroup analyses to compare both hemispheric effects directly. Such an approach was expected to provide quantitative evidence for the exact role of each hemisphere in attention from an integrated perspective.

In *Chapter 2*, we conducted a meta-analysis of studies applying inhibitory TMS to suppress activity in the left and/or right posterior parietal cortices (PPC), which allowed us to assess the effects on attention biases via the classic landmark and line bisection tasks. This study revealed a hemispheric asymmetry in the functional relevance of the left versus right posterior parietal cortex that mimicked and reproduced the hemispheric asymmetry seen in neglect patients after left versus right hemispheric lesions (Beis et al., 2004; Corbetta et al., 2005; Suchan et al., 2012). However, with regard to theories of attention, a stronger ipsilateral attentional effect after right hemisphere suppression does not necessarily imply right hemisphere dominance in the sense of a generally stronger contribution to attention per se, as proposed by Heilman's model of spatial attention. The reported hemisphere-specific functional deficits after right parietal TMS are just as much in accordance with predictions based on Kinsbourne's model (Kinsbourne, 1977), according to which suppressive TMS over the right parietal cortex leads to the disinhibition of the (dominant) left parietal cortex, resulting in increased bias toward the ipsilateral (right) side. Moreover, instead of right or left hemisphere dominance, the findings may also imply that the right hemisphere is more susceptible to interference. In this sense, whereas the current meta-analysis provides support for asymmetric TMS attention effects after right as compared to left parietal TMS, thereby mimicking the lateralization reported in hemineglect patients, these experimental data alone are incapable of informing us about which of the two proposed theories is more likely to be correct. This is mainly due to the fundamental problem of both the line bisection and landmark tasks used in these studies. Neither paradigm allows for a look into the exact differential contributions of each hemisphere for each hemifield separately, which is essential when referring to the separate functional role of each hemisphere for hemisphere-specific attention biases, gains, and costs toward the ipsilateral versus the contralateral side of space (Duecker & Sack, 2015).

In *Chapter 3*, we overcame the drawbacks of the line bisection and landmark tasks and conducted a meta-analysis of inhibitory parietal TMS on visual detection tasks, which allowed for the isolated assessment of the left versus right hemispheric contribution to stimulus detection in the contra- versus ipsilateral hemifield. The results showed no significant

differences between hemispheres, as well as the additional important finding of a significant contralateral impairment effect, but no significant ipsilateral enhancement effect. Specifically, the pooled effect sizes were found to support contralateral impairment but doubt ipsilateral enhancement. Accordingly, a reasonable hypothesis is that ipsilateral bias, in terms of bias measures, is wholly attributable to contralateral impairment. This finding thus contradicted the theory proposed by Kinsbourne (1977), while the predictions from Heilman's hemispacial theory (Heilman & Abell, 1980) were found to be more in line with it. These results are interesting and invite further discussion, not only on scientific grounds, but also because Kinsbourne's model (Kinsbourne, 1977), including the notion of interhemispheric balance/competition, seems core to the rationale of clinical TMS treatment of stroke. While it remains difficult to compare healthy brains to those of lesion patients, and visual detection tasks are only one class of tasks in their own right. Accordingly, this approach and body of literature might merit further review and investigation.

Both *Chapters 2* and *3* shared a fundamental objective centered on the investigation of attentional bias and its modulation through inhibitory TMS targeting the left and right posterior parietal cortex. *Chapter 2* focused on the line bisection and landmark tasks, while *Chapter 3* delved into the visual detection/extinction tasks. Despite the divergence in paradigms, the core theme remained consistent, which was the examination of attentional biases driven by TMS-induced disruption in the left and right PPC. Together, these chapters contribute to a comprehensive exploration of how TMS manipulation of specific brain regions can uncover the intricacies of attentional control and its lateralized neural basis. However, taken together, it is worth noting that these effects of left and right parietal stimulation on attention appeared inconsistent. Specifically, we found significant differences between hemispheres in the line bisection task, but no differences in the visual detection task. The absence of this discrepancy in visual detection tasks provided an intriguing insight into the symmetry of attentional bias across both the left and right hemispheres. To make this very explicit, the detection task was intended to provide hemifield-specific effects. It was thus expected that this would allow us to determine whether TMS-induced changes in line bisection performance after right parietal cortex disruption are due to ipsilateral enhancement, contralateral impairment, or a combination of both. When considering only the right hemisphere TMS results, one might conclude that there is no ipsilateral enhancement, and only contralateral impairment. Consequently, the

contralateral segment of the line is prone to underestimation or even outright disregard, which precipitates a phenomenon in which the entire line appears shorter on the contralateral side. This apparent shortening imparts a perceptual shift toward the ipsilateral side, causing the midpoint to relocate accordingly and manifesting as a characteristic ipsilateral bias. However, the presence of a TMS effect after left hemisphere TMS casts doubt on this interpretation because there was no effect of left TMS on the line bisection task, whereas visual detection was impaired. This mismatch thus requires consideration of alternative explanations.

One alternative explanation for this phenomenon might be that line bisection and detection performance are not pure measures of attentional bias, but rather involve differential cognitive processes. The most obvious differences between these tasks are the stimulus material and instructions, namely, a line spanning both hemifields requiring a length judgment versus the simple detection of the presence of a stimulus. In this vein, the line bisection/landmark tasks have been argued to involve magnitude processing (Vogel et al., 2013), whereas the visual detection task does not. This suggests that the difference may be linked to magnitude processing. This connection resonates with the findings from related neuroimaging and TMS studies, which consistently demonstrate right hemispheric dominance in magnitude processing (Cantlon et al., 2006; Cohen Kadosh et al., 2007; Faillenot et al., 1999; Piazza et al., 2006; Pinel et al., 2004; Sack et al., 2009; Seydell-Greenwald et al., 2019). This phenomenon holds true even in scenarios involving numerical bisection tasks, as evidenced by studies conducted by Seydell-Greenwald et al (2019).

Another pivotal finding is that, strikingly, our exploration reveals that the emergence of ipsilateral bias cannot be attributed to an ipsilateral enhancement effect when it comes to either unilateral or bilateral stimuli. These findings cast a critical shadow over the foundational notion of ipsilateral enhancement, which is central to Kinsbourne's model and forms the theoretical underpinning of clinical interventions for spatial neglect (Cazzoli et al., 2012; Sack, 2010). Some clinical studies on neglect patients have reported some measure of ipsilateral enhancement after parietal TMS (Nyffeler et al., 2009; Yi et al., 2016), but in many clinical studies, the evaluation of improvement actually comes from line bisection tasks (Lim et al., 2010; Mylius et al., 2012; Oliveri et al., 2001; Song et al., 2009; Sparing et al., 2009). These clinical effects may arise based on a different principle that we have yet to fully comprehend. Importantly, it remains difficult to compare healthy brains to those of lesion patients, and visual

detection tasks are only one class of tasks in their own right. These revelations wield substantial implications, not just within the realms of theoretical exploration, but in the practical application of research findings to clinical contexts.

While a TMS “virtual lesion” enables the use of fundamental methods on healthy participants to mimic clinical symptoms, translating findings from fundamental studies directly into clinical applications remains complex. As we stand at the precipice of translating research insights into tangible clinical strategies, it is imperative to meticulously elucidate the underlying mechanisms at play. Further studies could benefit from being combined with clinical samples to understand the real mechanism of TMS rehabilitation. Moreover, research dedicated to TMS localization may also provide valuable insights. Many TMS studies in our meta-analyses and other clinical studies rely on the 10-20 system for brain region localization. Although some have reported effects caused by TMS, not all showed the same pattern. This reminds us of the importance of precise coil positioning, as its improved accuracy could guarantee precise targeting of the intended brain regions, thereby enhancing the effectiveness of TMS in both healthy groups and stroke patients.

8.2 Part II: TMS localization

The meta-analyses in Part I were grounded in TMS studies with the objective of disrupting a core node of the DAN in the posterior parietal cortex, namely the intraparietal sulcus (IPS). In the majority of these studies, localization of the target region was achieved through a scalp-based approach. The TMS coil was simply positioned over electrode position P3/P4. While this method generally approximates the IPS reasonably well, it is admittedly a somewhat crude procedure and does not guarantee precise stimulation of the intended brain region in all participants. It stands to reason that this less-than-ideal TMS localization approach has had some influence on the consistency and magnitude of the results. It has been agreed that functional localization based on individual task-based fMRI data provides the best localizer (Swallow et al., 2003); however, this cannot always be achieved for all brain regions and/or participants. Another common localizing method is a map-based approach, which is based on resting-state MRI (rs-MRI) of functional connectivity. This resting-state functional connectivity requires an anatomical underpinning, whether direct or indirect, in the form of structural connectivity, which can be measured with diffusion weighted imaging (DWI).

Indeed, studies have shown that structural connectivity and rs-MRI overlap considerably and suggest combining rs-MRI and DWI. Finally, the Talairach coordinate system has also been used in some studies. All of these MRI-based localization approaches can be applied to the attention systems of the DAN and VAN.

In *Chapter 4*, we aimed to explore and compare various MRI-guided TMS target localization approaches for the core nodes, which included FEF, aIPS, pIPS, TPJ, MFG, and IFG (Corbetta et al., 2008). We looked into (1) whether the map-based approach can profit from the combination of rs-MRI and DWI; (2) the success rate of different localization approaches (task-based functional MR localizer, rs-MRI localizer, combined rs-MR and DWI localizer, and static Talairach coordinate localizer) on an individual subject basis; (3) the difference in the localization yield of these various approaches; and (4) whether alternative map-based approaches could provide a valid localization target when localization fails in an individual subject. We found that (1) resting-state MRI and the overlap between rs-MRI and DWI were roughly equally successful in localizing individual brain areas. However, by using both structural and functional means, localization was more certain, as underpinned by both structure and function. With respect to (2), except the ROI of aIPS, not all individual methods consistently performed well in localization. For (3), taking the task-based localizer as the golden standard, we assessed the performance of each method by considering both the proportion of successfully localized areas and the distance in millimeters of localization from this standard. It was revealed that when disregarding the bad performance of the Talairach coordinates, all other localization results were in close proximity to each other (i.e., in almost all cases being within 1 cm). Finally, (4) in cases where localization failed in an individual subject, using a group-task localizer, which incorporates data from the remaining subjects, was often effective. This approach essentially interpolates the location of the area based on group data. Additionally, if localization accuracy within one centimeter is acceptable, then all methods examined here, except using Talairach coordinates, are equally suitable. This flexibility should allow researchers or practitioners to choose the localization method that best fits their specific situation. It is worth noting that our study was based on a sample of 20 subjects, and we acknowledge that a larger sample size would enhance the validity and generalizability of the results. Future research could also expand on these questions with larger groups, potentially by leveraging databases such as the Human Connectome Project. Additionally, applying these

MRI localizer approaches in real TMS experiments and comparing the resulting effects would be a valuable next step. Finally, current TMS localization efforts have primarily centered on the DAN and VAN. This focus contributes not only to the advancement of research on attentional bias but also to the functions of other attention effects, such as alerting and orienting.

8.3 Part III: Alerting and orienting effects

Attentional networks play a central role in our cognitive processes, as they direct our focus onto relevant stimuli in our environment while filtering out distractions. Among the key components of attention are the alerting and orienting networks (see Fig. 2), which contribute to our ability to stay vigilant and to efficiently shift our attention toward specific stimuli, respectively (Petersen & Posner, 2012; Posner & Rothbart, 2007). It is well known that both alerting and orienting increase the speed of response to target stimuli. However, relying solely on RTs or accuracy as outcome measures has its limitations (Voss et al., 2013), because it is typically difficult to isolate and pinpoint the specific cognitive (sub)processes that have contributed to the changes in RT. These RT measures are thus unable to provide a more specific understanding of the cognitive processes involved and are also limited in their ability to explain the origin of alerting and orienting effects. At the cognitive level, a DDM (Ratcliff, 1978; Ratcliff & Tuerlinckx, 2002; Voss et al., 2004) can estimate cognitive processes through the distribution of response time and is described by the average slope of the diffusion process (drift rate: v , which represents the evidence accumulation speed), threshold separation (a , which represents the information needed for design making), and duration of non-decisional processes (t_0 , which represents the entire non-decisional time) (Ratcliff, 1978). In the last part of this thesis, we investigated how alerting cues lead to faster response times, and how spatial cues lead to faster response times than non-spatial cues in visuospatial cueing tasks. We conducted DDM analyses on Posner cueing tasks to uncover the sub-processes of alerting and orienting effects.

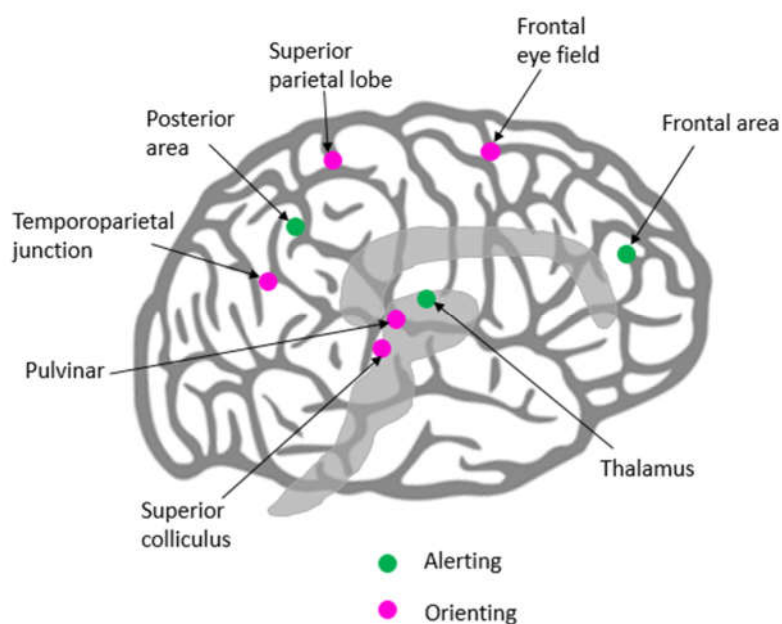


Fig. 2. Illustration of the cortical areas involved in three attention networks. The alerting network (green) includes the thalamic and cortical sites related to the brain's norepinephrine system. The orienting network (pink) is centered on parietal sites. This figure is based on the work of Posner, Sheese, Odludas, & Tang (2006).

In *Chapters 5 and 6*, we utilized exogenous and endogenous spatial orienting tasks in combination with DDM analysis. The DDM analyses allowed us to disentangle the entire behavioral response into its decisional and non-decisional components. The decisional part is characterized by a separation threshold (a) and drift rate (v), which encompass the entire decision-making stage. Conversely, the non-decisional part is solely defined by non-decisional time (t_0) and represents the stages of early visual processing and the phase occurring after decision making in the response output stage. Our objective was to employ the differences in DDM parameters under different conditions (alerting: no cue vs. neutral cue; orienting: neutral cue vs. spatial cue) to dissect the RT distinctions associated with alerting and orienting. This approach aimed to enhance our comprehension of alerting and orienting effects at a cognitive level beyond mere response time measurements. The results suggest that behavioral models can establish a link between behavioral performance and cognition. We will delve into the specifics of the alerting and orienting effects in later sections.

In *Chapter 7*, we merged the DDM and behavioral results from *Chapter 6* with EEG to establish a comprehensive connection between neural and cognitive information pertaining to alerting and orienting effects. Combining EEG signals offers several advantages in this regard. For one

thing, they furnish us with more detailed temporal information, thereby aiding in the differentiation of non-decisional time into two distinct temporal phases. More importantly, this approach provides us with a fresh perspective on how to integrate mathematical behavioral models with observations of brain activity. This integration enables us to elucidate and forecast perceptual performance as it is rooted in visual attention (Zandbelt et al., 2014). We will delve into the specifics of the model-based neural mechanisms underlying alerting and orienting effects in subsequent sections of our discussion.

8.3.1 Alerting

Alerting is the function of generating and maintaining a vigilant state (Coull et al., 1999; Posner & Petersen, 1990). It handles the spread of attention over a broad area of space, and a higher alert state allows for faster information processing, independently of its spatial location.

As mentioned in previous paragraphs, in *Chapter 5*, we found the non-decisional time and drift rate when comparing trials with neutral cues to those with no cues. The simultaneous decrease in non-decision time during the neutral cue condition indicated that the time required to prepare the response was reduced. This non-decision time difference clearly supports the notion that the revealed alerting effect (reduced RT) was due to a cue-related increase in arousal and/or vigilance that helped prepare for the upcoming stimulus (Mather & Sutherland, 2011). However, the decrease in drift rate observed during the neutral cue condition implied a reduction in evidence accumulation, indicating that the quality of information extracted from the target was inhibited by the cue. Therefore, the decrease in drift rate, although related to the distraction of evidence accumulation, could not be attributed to alerting itself. One possible explanation for this cue-related inhibition could be the circular shape of the cue, which might create a surface effect (the enclosed shape resembles a surface rather than specific lines), leading to forward masking (Lowe, 2003; Schmidt & Schmidt, 2010) due to the short stimulus onset asynchrony. This inhibition could also be linked to an excessive amount of attention being captured by cues that interfere with the processing of other stimuli. Interestingly, it should be noted that a decrease in the drift rate could also increase the reaction time at a constant separation threshold (a). In other words, the decrease in drift rate resulted in a longer reaction time, while the change in non-decision time led to a shorter reaction time. The latter not only compensated for the drift rate deficits, but also resulted in a significantly faster overall reaction

time in response to cues. In general, the alerting effect primarily occurred during the non-decisional processes of preparing and executing motor responses after the decision had been made.

For the endogenous cueing task in *Chapter 6*, we also observed non-decisional time and drift rate variations. The difference here was the drift rate, which decreased for the exogenous cueing task but increased for the endogenous cueing task. As for the decrease in non-decisional time, we believed it was due to the reduced preparation time for the response prompted by a neutral cue. The reason for the faster decision time caused by the alerting cue could be related to the fact that alerting information heightened perceptual sensitivity and reduced uncertainty (see Kusnir et al., 2011). In comparing this drift rate change to the exogenous cueing task, it was interesting to observe that both exhibited changes, but in different directions. This difference could be attributed to the time for exogenous cues being too short to release attention. In contrast, for the endogenous cue, participants voluntarily initiated attentional arousal, prepared for a response (non-decision time), and adjusted the rate at which they gathered and evaluated evidence based on their expectations and goals. It needs to be added here that both exogenous and endogenous cueing tasks demonstrated the reliability of the DDM because of the fully repeatable findings in a retest session.

These two chapters were nicely repeated under separate sessions but also showed some consistency across exogenous and endogenous cueing tasks, especially in terms of non-decisional time. The distinction between involuntary attention (exogenous cues) in *Chapter 5* and voluntary attention (endogenous cues) in *Chapter 6* sheds light on the differential impact of these attentional mechanisms on cognitive processing. Involuntary attention primarily affected the preparation process, with minimal influence on the cognitive evaluation process. In contrast, voluntary attention influenced both the preparation and accumulation stages, demonstrating a more intricate interplay between attentional control and cognitive processing. This supports the idea that voluntary attention enhances perceptual representation, whereas involuntary attention plays a more selective role in behavioral performance dynamics (Prinzmetal et al., 2009). However, we need to be cautious in making this conclusion because the exogenous and endogenous cueing tasks were in different design frames, and the effects could not be directly compared.

In *Chapter 7*, the investigation was extended by conducting an EEG analysis to explore the correlation between EEG signals and DDM parameters across different levels of attentional processing, including alerting and orienting effects. This stage revealed significant correlations between specific EEG signals and DDM parameters, indicating a connection between neural dynamics and cognitive processes. Importantly, regarding the non-decisional time of the before-and-after decision-making stage, these stages could not be distinguished solely based on the DDM parameters. The interpretations in the behavioral DDM chapters were grounded in DDM and theoretical knowledge, but as a high temporal resolution neural technique, EEG, especially post-stimuli ERPs, could provide us with more precise information about the timing of processes. For example, in line with a previous study (Hillyard & Anllo-Vento, 1998; S J Luck & Hillyard, 1994; Steven J. Luck et al., 1994), while early visual processing is likely to be linked to the latency of early ERP components, such as P1, N1, the post decision-making stage can be related to the latency of late ERP components. Among the EEG signals observed, only the posterior P2 amplitude and pre-stimulus alpha and low beta power were found to reflect the alerting effect. This suggests that the neural dynamics captured by this EEG marker are associated with aspects of preparation and motor control, given that the posterior P2 is a relatively late component that aligns with the preparatory phase of alerting cues. In fact, this preparation could already start before the target presentation. Of these EEG signals, only the posterior P2 amplitude reflects non-decisional time. Still, this connection underscores the intricate relationship between neural activation and attentional processes in alerting situations.

8.3.2 Orienting

Orienting enables directional shifts of attention to a relevant spatial location (Fan et al., 2002). In *Chapter 5*, we observed variations only in the non-decisional time when comparing trials with spatial cues to those with non-spatial cues. The simultaneous decrease in non-decision time during the spatial cue condition, which differed from the neutral cue condition, indicated that the time required to process early visual information was reduced. Although both alerting and orienting effects were associated with a decrease in non-decisional time, the non-decisional stage might differ between them. For spatial cues, not only do they provide information on where the target will present, but also when it will present. In other words, participants are engaged in the same response preparation here as in the case of neutral cues, with the difference coming from spatial information. This suggests that participants should rapidly shift their

attention toward the cue's location and manage to initiate the visual attention process more swiftly, as indicated by the shorter early visual preprocessing time. This orienting effect is classically held to be caused by spatial attention being automatically directed toward the source of sensory signals (i.e., the cue), thereby enhancing the response to the subsequent target being presented in the same location (decreased RT to target). Therefore, it has been assumed that this orienting effect mainly increases the attention resource on the target location (Pearson et al., 2022; Talcott et al., 2022) and facilitates the accumulation of evidence (Loughnane et al., 2016).

In our DDM analysis, however, we revealed that this expedited response did not result in an accelerated speed of evidence accumulation. This discrepancy could indicate that orienting effects might predominantly affect the preparatory phases of attention, such as the initial allocation of attentional resources to the cued location. The stimuli were presented in a rapid sequence, and the timing between the cue and target stimuli was brief; accordingly, the potential impact on evidence accumulation time might have been less pronounced. The orienting effect might have mainly influenced the early stages of processing, as the relatively short time interval might not have allowed for substantial adjustments in the rate of evidence accumulation. In the case of orienting effects, the emphasis might be on the rapid allocation of resources to the location of interest, which enhances the efficiency of early visual processing. However, this allocation might not necessarily lead to a corresponding change in the allocation of resources for evidence accumulation. This dissociation between resource allocation for early processing and subsequent evidence evaluation could explain why the evidence accumulation time remained relatively constant.

Interestingly, the orienting effect in the DDM parameters was perfectly repeated in *Chapter 6*. For one thing, we believe that the orienting effect benefits from the early visual preprocessing time. Participants rapidly shifted their attention toward the cue's location and managed to initiate the visual attention process more swiftly after the spatial cue was presented. Similarly, the relatively short time interval might not have allowed for substantial adjustments in the rate of evidence accumulation and only facilitated non-decision time.

In the case of the orienting effects and EEG signals in *Chapter 7*, as we believe the orienting effect arises from early visual processing, it is likely to be reflected in early ERP components, such as P1, N1, or even pre-stimuli alpha and low beta power. However, we found only the anterior P2 amplitude and reflected the orienting effect, and the analysis did not reveal a significant relationship between the EEG markers and non-decision processes. It should be noted that the reliability of the DDM and EEG signals was all demonstrated because of the fully repeatable findings in a retest session. This could indicate that the neural dynamics captured by the anterior P2 amplitude might not play a substantial role in the preparatory aspects of orienting attention, which further suggests a potential dissociation between the neural processes underlying orienting effects and certain non-decisional components. Such a result would reveal the intricate and multifaceted nature of attentional processes.

Overall, Part III of the study provided insights into the nuanced effects of attentional cues on specific cognitive processes and validated the utility of DDM methods in the context of visual attention. The repeated effects observed underscore the power of DDM analyses in dissecting alerting and orienting effects in behavioral response time into different cognitive processes. From a cognitive perspective, the alerting effect appears to result from both decisional and non-decisional time, while the orienting effect primarily stems from non-decisional time. However, it is worth noting that the DDM tends to combine early visual processing and response output stages into a single parameter of non-decisional time. Therefore, when deeper insights into alerting and orienting effects are needed, theoretical knowledge remains crucial. At the same time, EEG signals, to some extent, enhance our understanding of cognitive processing stages in the alerting effect because they provide additional temporal information. Although EEG signals did not reveal non-decisional time in the orienting effect, there is hope that this could be achieved with a larger sample size. The link between neural processes and cognitive processes thus represents a promising but early step for future exploration.

While the research conducted in Chapters 5, 6, and 7 shed light on the intricate relationship between attentional processes and neural dynamics using the DDM and EEG analysis, several limitations should be acknowledged. First, regarding exogenous and endogenous task differences, while observing different results between the exogenous cueing task and endogenous cueing task is noteworthy, it is important to exercise caution in drawing direct conclusions about differences in cognitive processes based solely on separate experiments.

Without a direct comparison between the two tasks within a single experimental design, the observed differences could stem from various factors beyond just cognitive processes. Second, we worked with limited stimuli and variables, which limits the generalizability of our conclusion. For example, the stimuli were limited to moving dots, the cue-target interval was limited to 100/1500ms, and the validity of the cue was limited to 100%. Third, the experiments mainly focused on overall findings, which might not capture the full extent of cognitive variability and trial-level differences. Finally, the neural connectivity of attentional effects remains an area for further exploration.

There are several ways in which future studies could address these limitations. First, studies may focus on the alerting and orienting effect differences between exogenous and endogenous cueing tasks in one experimental design to make them comparable. Future research could also incorporate a broader range of variables into these Posner cueing tasks, such as different stimulus types. Third, visuospatial attention processes and neural dynamics based on trial-by-trial descriptions could be combined, as could advanced techniques, such as dynamic causal modeling or network analyses, which would provide further insights into the dynamic interplay between the brain regions involved in attention.

8.4 Concluding remarks

This thesis systematically explored attentional networks by conducting several studies on attentional bias and visuospatial attention. Through meta-analyses of inhibitory TMS, we probed the fascinating realm of attentional shifts and hemisphere effects. These chapters illuminated the complexities of attentional bias, showing that the brain's hemispheres play a pivotal role in shaping our attention. The work presented here thus serves as a foundation upon which we can build our understanding of attentional networks. Looking into TMS localization has equipped us with the tools needed to navigate the intricate networks that guide our attention, and by refining our understanding of this process, we have paved the way for a deeper dive into attentional mechanisms. In the grand finale of our exploration, we ventured into the intricate realm of attention, peeling back its layers to reveal the complex interplay between cognitive processes and neural dynamics. In doing so, we have illuminated the key facets of alerting and orienting effects, which has provided valuable insights into the world of visual attention.

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Appendix

Impact paragraph

The present thesis aims to unravel the intricate mechanisms underlying visual attention bias and the effects of alerting and orienting. The impact of this thesis is multi-faceted, extending across the realms of scientific, and clinical impact.

This research significantly contributes to the scientific understanding of visual attention bias and the effects of alerting and orienting. By employing a multifaceted approach that integrates meta-analyses, neuroimaging techniques, computational models, and electrophysiological measures, this work unravels the intricate mechanisms underlying these attentional phenomena. Specifically, the findings in Part I provide insights into the hemispheric asymmetries of attentional control and have implications for a long-standing debate between competing theories of attentional control. The aggregation of TMS studies in two meta-analyses reveals that not all effects reported in the literature are robust and replicable. It demonstrates how conclusions based on small studies can shape a research field even when the evidence at large does not support the same view. The meta-analytic perspective also serves as a strong foundation for further research, expanding our understanding of how hemispheric specialization influences attentional biases and revealing interpretative challenges and knowledge gaps. The impact of Part II has clear implications for the application of brain stimulation in research setting where neuroimaging-guided localization of target areas is the gold standard. By evaluating various TMS target localization methods guided by MRI, our research provides valuable guidance to researchers aiming to precisely target brain regions for intervention. The validation of group-based maps as a reliable approximation of individual task-based targets offers an efficient alternative when individual data is lacking or inconsistent. The Part III uncovers novel insights into attentional mechanisms of cognitive processes. The application of drift diffusion models and EEG signal analysis unveils the mechanisms driving alerting and orienting effects, leading to a more nuanced comprehension of attention dynamics. This comprehensive exploration enriches the existing knowledge base, enhancing our grasp of how attention operates in the human brain.

From a clinical standpoint, the significance of this work lies in its potential to improve the treatment of neglect and attentional diseases. Firstly, the work in Part I challenges an influential theoretical model by Kinsbourne. The model predicts a particular enhancement effect of

attention following unilateral disruption of the attention system and has become the basis for brain stimulation-based rehabilitation strategies of spatial neglect. We clearly show that fundamental research in healthy volunteers contradicts this model and this casts doubt on the principles that have guided clinical procedures in stroke patients. A reevaluation of the mechanisms underlying current effect treatment approaches might be called for and our work can serve as a reminder that translational research requires a cautious approach based on strong evidence. Secondly, precise TMS localization is crucial for effective interventions in neurological and psychiatric disorders. The insight of Part II enhances the accuracy of TMS-based interventions, facilitating more effective treatments for individuals with neurological and cognitive disorders. Finally, understanding the cognitive mechanisms underlying alerting and orienting effects is relevant to clinical assessments of attention deficits, potentially informing the design of diagnostic tools and interventions for conditions involving attentional impairments.

In summary, this research leaves a lasting impact across multiple dimensions. It not only advances scientific knowledge, but also informs clinical practices. Through its multifaceted contributions, this work enriches various facets of human life and knowledge.

Appendix

Summary

The primary purpose of this thesis was to obtain a deeper understanding of visual attention bias and attention effects of alerting and orienting. Using a multimodal approach including meta-analysis, magnetic resonance imaging (MRI), drift diffusion model (DDM), and electroencephalography (EEG), we addressed specific aspects of these attentional phenomena in three parts.

Part I: Attentional Bias

Attentional bias was explored through meta-analyses of Transcranial Magnetic Stimulation (TMS) effects. In Chapter 2, we focused on the inhibitory/disruptive effects of TMS on the left and right parietal cortex, specifically examining performance on line bisection and landmark tasks revealing attentional bias shifts and evaluating potential hemisphere asymmetries. The results provided strong support for hemispheric asymmetry of TMS effects on attentional bias with TMS effects only being present after right parietal TMS but not left parietal TMS. This pattern of results mimics the lateralization reported in hemineglect patients. However, this work is limited in informing us about why the right hemisphere plays a more important role than left hemisphere. Chapter 3 tried to tackle this problem by assessing the inhibitory/disruptive effects of TMS on the left and right parietal cortex, this time examining performance on a visual detection task that separates the role of the left and right hemifield. This allows for the isolated experimental assessment of the left versus right hemispheric contribution to stimulus detection in the contra- versus ipsilateral hemifield. These analyses aimed to elucidate mechanisms of hemisphere asymmetry and inform visuospatial attention theories. This study rejected the critical prediction of ipsilateral enhancement that is a cornerstone of Kinsbourne's opponent processor model (1977). Moreover, the presence of contralateral impairment effects was in general agreement with Heilman's hemispacial theory (Heilman & Abell, 1980).

Part II: TMS Localization Methods

Next, we focused on TMS target localization methods guided by MRI. Chapter 4 explored and compared various MRI-guided approaches for localizing TMS targets in the Dorsal Attention Network (DAN) and Ventral Attention Network (VAN). We found that individual task-based

localization generally works well but not consistently for all individuals or brain regions. Aggregating task data across participants yields the best approximation of individual targets when individual localization failed and is thus a good alternative approach in such situations. Additionally, the other alternatives like resting state and the overlap of resting-state and tractography had mixed success across brain regions, with individual data sometimes deviating more from individual task-based targets than group average data.

Part III: Alerting and Orienting Effects

Lastly, we delved into the cognitive mechanisms underlying alerting and orienting effects in visuospatial attention. Chapter 5 employed an online exogenous cueing task combined with a DDM to investigate these cognitive mechanisms. This study revealed that DDM could be a useful tool to understand cognitive processes of alerting and orienting effect. The alerting effect could be attributed to the rapid capture of attention by the exogenous cues, initiating a faster motor response preparation. And the orienting effect can be attributed to rapidly shift attention towards the cues location and managed to initiate the visual attention process more swiftly, as indicated by the shorter early visual preprocessing time. In Chapter 6, an endogenous cueing task was employed to explore similar mechanisms while also assessing alerting and orienting hemifield lateralization potentially influenced by hemispheric asymmetry. We not only found motor response preparation but also drift rate varies in alerting effect, indicating the adjustment of the rate of gathering evidence based on expectations and goals. The orienting effect also had a shorter early visual preprocessing time. Surprisingly, the lateralization of alerting and orienting was not found, neither on the behavioral level nor in model parameter (or cognitive processes) level. Chapter 7 extended this by utilizing EEG signals during the same endogenous cueing task to establish links between neural dynamics and cognitive processes associated with alerting and orienting effects. It revealed that only posterior P2 amplitude reflects motor response preparation processes in alerting effect but nothing was found for the orienting effect. This connection highlights the intricate relationship between neural activation and attentional processes in alerting situations. It also demonstrates that combining modeling with electrophysiological signals is a promising approach to help understand cognitive and neural processing mechanisms.

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Appendix

Nederlandse samenvatting

Het primaire doel van dit proefschrift was om een beter begrip te krijgen van de vertekening van visuele aandacht en aandachtseffecten van alertheid en oriëntatie. Met behulp van een multimodale benadering, waaronder meta-analyse, magnetische resonantie beeldvorming (MRI), drift diffusiemodel (DDM) en elektro-encefalografie (EEG), hebben we specifieke aspecten van deze aandachtsverschijnselen in drie delen behandeld.

Deel I: Aandachtsvertekening

Aandachtsvooringenomenheid werd onderzocht door middel van meta-analyses van effecten van Transcraniële Magnetische Stimulatie (TMS). In hoofdstuk 2 richtten we ons op de remmende/versturende effecten van TMS op de linker en rechter pariëtale cortex, waarbij we specifiek de prestaties op lijnbisectie en landmark taken onderzochten, waarbij we verschuivingen in de aandachtsbias ontdekten en potentiële hemisfeer asymmetrieën evalueerden. De resultaten gaven sterke ondersteuning voor hemisferische asymmetrie van TMS effecten op aandachtsvooringenomenheid, waarbij TMS effecten alleen aanwezig waren na rechter pariëtale TMS maar niet na linker pariëtale TMS. Dit patroon van resultaten bootst de lateralisatie na die werd gerapporteerd bij hemineglect patiënten. Dit werk is echter beperkt in het informeren over waarom de rechter hersenhelft een belangrijkere rol speelt dan de linker hersenhelft. Hoofdstuk 3 probeerde dit probleem aan te pakken door de remmende/versturende effecten van TMS op de linker en rechter pariëtale cortex te beoordelen, dit keer door de prestaties te onderzoeken op een visuele detectietaak die de rol van het linker en rechter hemiveld scheidt. Dit maakt de geïsoleerde experimentele beoordeling mogelijk van de linker versus rechter hemisferische bijdrage aan stimulusdetectie in het contra- versus ipsilaterale hemiveld. Deze analyses hadden tot doel mechanismen van hemisfeerasymmetrie op te helderen en visuospatiale aandachtstheorieën te onderbouwen. Deze studie verwierp de

kritische voorspelling van ipsilaterale versterking die een hoeksteen is van Kinsbourne's opponent processor model (1977). Bovendien was de aanwezigheid van contralaterale verzwakkingseffecten in algemene overeenstemming met de hemispatale theorie van Heilman (Heilman & Abell, 1980).

Deel II: TMS lokalisatiemethoden

Vervolgens hebben we ons gericht op TMS doel lokalisatie methoden gestuurd door MRI. Hoofdstuk 4 onderzocht en vergeleek verschillende MRI-geleide benaderingen voor het lokaliseren van TMS targets in het Dorsal Attention Network (DAN) en Ventral Attention Network (VAN). We ontdekten dat lokalisatie op basis van individuele taken over het algemeen goed werkt, maar niet consistent voor alle individuen of hersengebieden. Het aggregeren van taakgegevens over deelnemers levert de beste benadering op van individuele doelen wanneer individuele lokalisatie mislukt en is dus een goed alternatief in dergelijke situaties. Daarnaast hadden de andere alternatieven zoals rusttoestand en de overlap van rusttoestand en tractografie gemengd succes in hersengebieden, waarbij individuele gegevens soms meer afweken van individuele taakgebaseerde doelen dan groepsgemiddelde gegevens.

Deel III: Waarschuwendende en oriënterende effecten

Tenslotte onderzochten we de cognitieve mechanismen die ten grondslag liggen aan alertheid en oriëntatie effecten in visuospatiale aandacht. Hoofdstuk 5 gebruikte een online exogene cueing taak gecombineerd met een DDM om deze cognitieve mechanismen te onderzoeken. Uit dit onderzoek bleek dat DDM een nuttig instrument zou kunnen zijn om de cognitieve processen van het alertheidseffect en het oriëntatie-effect te begrijpen. Het waarschuwingseffect kan worden toegeschreven aan het snel vangen van de aandacht door de exogene cue's, waardoor een snellere voorbereiding van de motorische respons op gang komt.

En het oriënterende effect kan worden toegeschreven aan het snel verplaatsen van de aandacht naar de locatie van de signalen en slaagde erin het visuele aandachtsproces sneller op gang te brengen, zoals blijkt uit de kortere vroege visuele voorbewerkingstijd. In hoofdstuk 6 werd een endogene cueing taak gebruikt om vergelijkbare mechanismen te onderzoeken, terwijl ook de lateralisatie van het waarschuwend en oriënterend hemiveld beoordeeld werd, mogelijk beïnvloed door hemisferische asymmetrie. We vonden niet alleen motorische voorbereiding van de respons, maar ook variatie in de driftsnelheid in het alerting effect, wat wijst op de aanpassing van de snelheid van het verzamelen van bewijs op basis van verwachtingen en doelen. Het oriënterende effect had ook een kortere vroege visuele voorbewerkingstijd. Verrassend genoeg werd de lateralisatie van alertheid en oriëntatie niet gevonden, noch op gedragsniveau, noch op het niveau van modelparameters (of cognitieve processen). Hoofdstuk 7 breidde dit uit door gebruik te maken van EEG signalen tijdens dezelfde endogene cueing taak om verbanden te leggen tussen neurale dynamiek en cognitieve processen geassocieerd met alertheid en oriëntatie effecten. Hieruit bleek dat alleen de posterior P2 amplitude motorische respons voorbereidingsprocessen weerspiegelt in het alertheidseffect, maar niets werd gevonden voor het oriëntatie-effect. Dit verband benadrukt de ingewikkelde relatie tussen neurale activatie en aandachtsprocessen in alerte situaties. Het laat ook zien dat het combineren van modellering met elektrofysiologische signalen een veelbelovende aanpak is om cognitieve en neurale verwerkingsmechanismen te helpen begrijpen.

Appendix

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When I start to write this acknowledgement, I realize that my time in Maastricht is drawing to a close. In the past four years, I had a lot fun and hard time. I love people here and enjoy cooking by myself. At the same time, I hate the weather and transportation systems. But this is Maastricht, this is the Netherland. It gives me a totally different experience and provides me a new perspective to look the whole world.

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写在人生的第 30 岁（于巴黎）

Appendix

About the author

Ting Wang(汪婷) was born in Hubei, China, on 5 December 1993. She completed her secondary education at Wuhan No.23 senior high school in 2011. After that, she enrolled at the faculty of psychology, Yangtze University, where she obtained a bachelor's degree in applied psychology in 2015. Given her interest in psychology, she decided to continue with psychology study and started master research at Shenzhen University under the supervision of Prof. Can Jiao. After obtaining master's degree (Outstanding Graduate) in 2018, she got a research assistant position in the applied psychology team headed by Prof. Tianyou Guo. After few months, she gained the support of Chinese Scholarship Council (CSC No. 201908440406) for studying as PhD student under the supervision of Prof. Alexander T. Sack and Dr. Felix Duecker. Her research focused on dissecting visual attention on the basis of attention bias, alerting and orienting effects. In March 2024, Ting will work as a postdoctoral fellow at South China Normal University, where she will focus her research on cognition and emotion in children and adolescents.

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Wang, T., de Graaf, T., Williams, J., Wang, Z., Schuhmann, T., Duecker, F., & Sack, A. T. (2023). The myth of TMS-induced ipsilateral enhancement in visual detection paradigms: a Systematic review and Meta-Analysis of inhibitory parietal TMS studies in healthy participants. *Neuroscience & Biobehavioral Reviews*, 105437. <https://doi.org/10.1016/j.neubiorev.2023.105437>

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*contribute equally, cor-last author

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