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Automatic visuospatial attention shifts: Perceptual correlates, interventions and oscillatory signatures

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Abstract

Our visual perception is shaped by both external and internal factors, which continuously compete for limited neural resources. Salient external (exogenous) events capture our attention automatically, whereas internal (endogenous) attention can be directed towards sensory events according to our current behavioural goals. Advances in neuroimaging and brain stimulation have allowed us to begin to map the underlying functional neural architecture mediating both exogenously driven and endogenously controlled visual attention, including electrophysiological techniques such as electroencephalography and magnetoencephalography (EEG/MEG). However, while the neural EEG/MEG correlates of endogenously controlled attention have been investigated in much detail, the neural EEG/MEG correlates of exogenously driven attention are substantially less well understood. One reason for this is that exogenously driven effects are difficult to isolate from the influence of endogenous control processes.

In a series of three experiments, I sought to: 1) Study how the perceptual outcomes of both endogenously and exogenously driven attention can be effectively dissociated and investigated. 2) Provide a better understanding of the functional architecture of attention control in regards to its underlying neural substrates and oscillatory signatures, particularly when exogenously driven. To this end, I employed a visuospatial attention paradigm which, by design, behaviourally dissociates exogenous from endogenously driven effects (experiment 1). Furthermore, by utilizing the same behavioural paradigm in combination with neuronavigated MRI-based transcranial magnetic stimulation (TMS) over two key attentional network nodes (i.e., the right intraprarietal sulcus and right temporo-parietal junction), I probed the extent to which the neural substrates of endogenous vs. exogenous orienting are overlapping or can be dissociated (experiment 2). Lastly, I used electroencephalography (EEG) to investigate the oscillatory signatures underlying attention in a task which is

typically employed to study exogenous orienting and which putatively triggers exogenous attention in isolation (experiment 3).

The results revealed that while exogenous attentional processes can be behaviourally dissociated from endogenous attention (experiment 1), the neural substrates of exogenous attention appear to cover a wide network of attention areas. This includes nodes in both the right ventral attention network (i.e., right temporo-parietal junction) but also the right dorsal network (i.e., the right intraparietal sulcus), which has predominantly been associated with endogenous attention control (experiment 2). Interestingly, even in tasks that have been utilized to test exogenous attentional effects in isolation, endogenous control processes, as indexed by increased mid-frontal theta-band activity, can heavily influence the behavioural outcome (experiment 3). Based on these results, I conclude that there appears to be strong interplay between endogenous control and exogenously driven attention processes. These findings highlight that in order to better understand the functional architecture of (purely) exogenously driven effects, we need to effectively account for the potential influence of endogenous control. One approach to achieve this is by manipulating both types of attention simultaneously instead of in separation, as illustrated in the present work.

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Abbreviations

ANOVA	Analysis of Variance
AG	Angular gyrus
BF	Bayes Factor
EEG	Electroencephalography
EOI	Electrodes of interest
FEF	Frontal eye fields
fMRI	function Magnetic Resonance Imaging
IFG	inferior frontal gyrus
IOR	Inhibition of return
IPS	Intraparietal sulcus
LH	Left hemisphere
LVF	Left visual field
MEG	Magnetoencephalography
MFG	middle frontal gyrus
RH	Right hemisphere
RT	Reaction time
RVF	Right visual field
SLF	superior longitudinal fasciculus
SMG	supramarginal gyrus
SPL	superior parietal lobule
TFR	Time-frequency representation
TMS	Transcranial Magnetic Stimulation
TPJ	Temporo-parietal junction
VF	Visual field
VFC	Ventral frontal cortex
Vs.	Versus

Author’s Declaration

I declare that this thesis represents my own work except unless indicated in the text and that it does not include work forming part of a thesis presented for another degree.

[redacted]

Merle-Marie Ahrens

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Previous dissemination of findings

Results of Chapter 2

- Published article: **Ahrens M-M**, Veniero D, Gross J, Harvey M, Thut G. (2015).Visual Benefits in Apparent Motion Displays: Automatically Driven Spatial and Temporal Anticipation are Partially Dissociated. *PLoS ONE* 10(12): e0144082. doi:10.1371/journal.pone.0144082
- Published abstract: **Ahrens M-M**, Veniero D, Harvey M & Thut G (2015). Spatial extrapolation vs. temporal anticipation of reflexive attention are governed by separate mechanisms. *Perception*, Vol. 44(S1)pp.136 doi:10.1177/0301006615598674

Results of Chapter 3

- Presented orally (Talk): 'Interfering with dorsal and ventral parietal network nodes during endogenous and exogenous visuospatial attention: A TMS study' at the *Society for Neuroscience* (SfN), 11th–16th of November 2017, Washington D.C., USA

Results of Chapter 4

- Published abstract: **Ahrens M-M**, Veniero D, Harvey M, Thut G. (2017). Investigating the Neural Correlates of Automatic Attention Shifts in Electroencephalography. *Journal of Vision*, Vol.17, Issue 10, 384. doi:10.1167/17.10.384
- Presented orally (Talk): 'Investigating the Neural Correlates of Automatic Attention Shifts in Electroencephalography' at *The Vision Science Society* (VSS), 19th-24th of May 2017, St. Pete Beach, Florida, USA

Chapter 1

General Introduction

1.1 Visuospatial attention shifts

Our senses are continuously exposed to a vast and complex amount of competing information from our environment. Due to limited cognitive processing capacities and resources, ***visual attention*** serves as the mechanism which allows us to resolve this competition, based on our behavioural goals in order to effectively and selectively filter relevant from irrelevant information in the visual domain. In principle, visual attention biases the competition between the underlying neuronal interactions by increasing the response of the early visual cortical representations such that they primarily respond to the attended event, object or location if in their receptive fields (Reynolds et al. 1999). In particular, ***visuospatial attention*** refers to our ability to shift the focus of attention towards (or away) from specific locations in our visual field (i.e., spatial orienting) (Posner 1980).

Visuospatial attention shifts have been divided into two main concepts with specific properties/characteristics. The first concept is referred to as ***endogenous attention*** which means that given a specific behavioural goal or instruction, we can direct and allocate our attention accordingly. This type of attentional deployment is also referred to as goal-driven, top-down or voluntary attention. The second concept is referred to as ***exogenous attention*** which means that unexpected, salient events that occur in our environment will automatically draw our attention towards them (Posner 1980; Petersen and Posner 2012). This type of attention is also referred to as stimulus-driven, bottom-up, involuntary, automatic or reflexive attention. Both types of attentional orienting are crucial in order to process information depending on current task demands and to act on our environment accordingly. While endogenous attention allows us to stay focused on a specific task or goal (e.g., driving), exogenous attention is triggered by sudden, behaviourally relevant events (e.g., a running child) that may require an immediate response or action (i.e., stopping the car).

In experiments on visuospatial attention, endogenous attention is typically manipulated with centrally presented spatial symbolic cues (e.g., arrows), that indicate the upcoming target location with high predictability (e.g., 80%) in the left or right visual field. This means that in 80% of the trials the target appears at the cued target location (validly cued) and on 20% of trials the target appears at the opposite location (invalidly cued). Participants are usually required to either perform a detection or discrimination task whilst maintaining central fixation (covert attention shifts). Results show that reaction time (RT) is faster and performance accuracy is higher at validly as compared to invalidly cued target locations. These behavioural benefits reflect voluntary allocation of attention according to the direction of the cue, enhancing visual processing at validly cued target locations, whilst invalidly cued locations are ignored. Exogenous attention shifts are typically manipulated by presenting peripheral cues (e.g., brief luminance changes) nearby or directly at a potential target location. Importantly, exogenous cues are always equally probable to appear in either the left or right visual field and are therefore uninformative as to upcoming target position (50%

predictability of target location). Results show that responses are faster and performance accuracy is higher at cued relative to uncued locations, despite the fact that these cues are non-predictive as to the upcoming target location. The behavioural benefits reflect exogenously triggered attention towards the cue, enhancing visual processing at this location (relative to the uncued location) (Posner 1980; Petersen and Posner 2012; Chica et al. 2013). Typically, these manipulations of endogenous and exogenous orienting are performed in isolation, for instance in separate experimental sessions, counterbalanced across separate blocks or trial-by-trial.

A variety of different parameters have been identified that can influence the behavioural outcome in these type of paradigms, such as the cue- and target-presentation times, the validity of the cues or whether participants are asked to perform overt (i.e., saccades) or covert shifts of attention (i.e., to maintain fixation) (see Chica et al. 2014 for a detailed review of the parameter space). A key variable is the cue-target interval (i.e., time interval between cue onset and target presentation) which allows for tracking of the temporal dynamics of visuospatial attention shifts. Endogenous attention gradually builds up (~300ms after the cue) and is associated with sustained perceptual benefits thereafter (Posner 1980). Compared to endogenous attention shifts, exogenously triggered shifts are more rapid and transient. Typically, this results in facilitatory behavioural effects at short cue-target intervals (<200ms), whilst as time progresses this facilitation turns into an inhibition of target perception at longer cue-target intervals (>300ms). This effect is known as inhibition of return (IOR), where RT and performance accuracy is impaired at the cued location (relative to the uncued location) (Posner et al. 1985; Klein 2000; Lupianez et al. 2006).

In addition to these well-established, “classic” spatial cueing paradigms described above, a particularly interesting protocol for the study of attention shifts, not just in space but also in the temporal domain, is to employ rhythmic visual stimulation (Rohenkohl et al. 2011; de Graaf et al. 2013; Breska and Deouell 2014). Rhythmic visual stimulation involves the presentation of rhythmic streams of stimuli, such as apparent motion or brief luminance changes (i.e., flicker) on the screen at specific frequencies. It has been suggested that the rhythmicity of events triggers exogenous attention processes which optimize perception of upcoming events in the event sequence. This results in enhanced visual performance at time points and positions that lie spatially and temporally in the event stream (Coull and Nobre 1998; Rohenkohl and Nobre 2011b; Rohenkohl et al. 2011).

Whilst such dynamic rhythmic stimuli drive exogenous attentional processes, it is difficult to dissociate exogenous effects from potential higher-level anticipatory processes that may engage endogenous control concurrently to the exogenous process. For instance, participants may (intentionally or unintentionally) engage with the event stream to predict upcoming events. Hence, this can result in attention-driven effects which may partially be contingent on endogenous control (i.e., exogenous cues may in part be processed endogenously) (Folk et al. 1992; Ansorge and Heumann 2003; Serences et al. 2005). In particular, to what extent the effect of rhythmic motion stimulation on visual perception at spatially and temporally expected locations is of exogenous nature, and whether exogenous processes can be dissociated from endogenous engagement will be the main focus of Chapter 2.

1.2 Neuroanatomical and functional basis of visuospatial attention

Previous research has shown that cortical visual areas are organized in hierarchical order, originating from primary visual cortex (V1) and projecting into two major cortical processing pathways. While the ***dorsal visual pathway*** projects into the posterior parietal cortex and has been shown to be primarily involved in “spatial” vision, the ***ventral visual pathway*** is directed into the inferior temporal cortex and is mainly specialized for “object” vision (Mishkin et al. 1983). The complexity and receptive field size of neurons increases progressively within each processing pathway towards higher visual areas (Felleman and Van Essen 1991). For example, intracranial recordings in behaving monkeys have shown that cells in higher visual areas, such as V4, show complex interconnections with other cortical regions and that their responses are highly dynamic, state-dependent and modulated by selective spatial attention (Haenny and Schiller 1988; Desimone and Duncan 1995; Luck et al. 1997). In tasks that require spatial or object selection, some incoming sensory input can be processed in parallel. However, resources decline as simultaneous sensory input increases (e.g., multiple objects) and eventually compete for neural representations and resources within the same receptive field. Under these conditions, the neural responses will be biased either by bottom-up signals in particular when stimuli are novel and salient, or by top-down signals that enhance the neural responses to the stimuli at the attended location/object in accordance with behavioural goals (biased competition model; Desimone & Duncan 1995; Luck et al. 1997; Desimone 1998; Reynolds et al. 1999).

This raises the question about the ***neural substrates*** that resolve such competition for neural representations. Early findings, primarily based on lesion studies in patients, have shown that spatial attention is impaired in particular when patients suffer from right hemisphere damage to the posterior parietal lobe and ventral parietal regions, causing abnormal spatial biases (i.e., unilateral spatial neglect) (e.g., review; Halligan et al. 2003). These observations have led to two early prominent, global models on visuospatial attention, the right ‘hemispheric dominance’ model and the ‘interhemispheric competition’ model. The right ‘hemispheric dominance’ model suggests that while the left hemisphere codes only for incoming information from the contralateral (i.e., right visual) field, the right hemisphere codes for both contra- and ipsilateral (left and right) visual fields, hence proposing a right hemispheric dominance for spatial attention (Heilman & Abell 1980). The ‘interhemispheric competition’ model suggests involvement of both hemispheres in the allocation of spatial attention, which, in the healthy brain, is governed by a mutual “inhibitory” balance of neural activity levels between the left and right hemisphere. Hence, an imbalance in activation in one hemisphere relative to the other causes an attentional bias towards the contralateral visual field (Kinsbourne 1970; Kinsbourne 1977; Kinsbourne 1994).

Developments in neuroimaging have advanced these early theories by identifying more specific neuroanatomical structures and neural circuits that can bias spatial attention. The most prominent functional neuroanatomical model has been proposed by Corbetta and Shulman (2002), who suggested that there are two large-scale, partially segregated fronto-parietal attention networks, the dorsal and ventral fronto-parietal network (**Figure** 1).

The ***dorsal fronto-parietal network*** comprises the intraparietal sulcus (IPS) and frontal eye fields (FEF) and is represented in both hemispheres. Neuroimaging findings have shown that when participants are informed (by a cue) about the forthcoming target location and covertly shift their attention towards that location, blood oxygenation level dependent (BOLD) responses increase significantly in the IPS and FEF, in particular contralateral to the attended visual field. Consequently, these regions have been associated with spatial orienting, mediating top-down control on visual processing (e.g., Corbetta et al. 1993; Nobre et al. 1997; Kincade 2005; Vossel et al. 2012; for a review see, Corbetta & Shulman 2002). In addition the IPS and FEF show strong connections via long-range fronto-parietal tracts, specifically the dorsal superior longitudinal fasciculus (SLF I) (Corbetta and Shulman 2002; Thiebaut De Schotten et al. 2011).

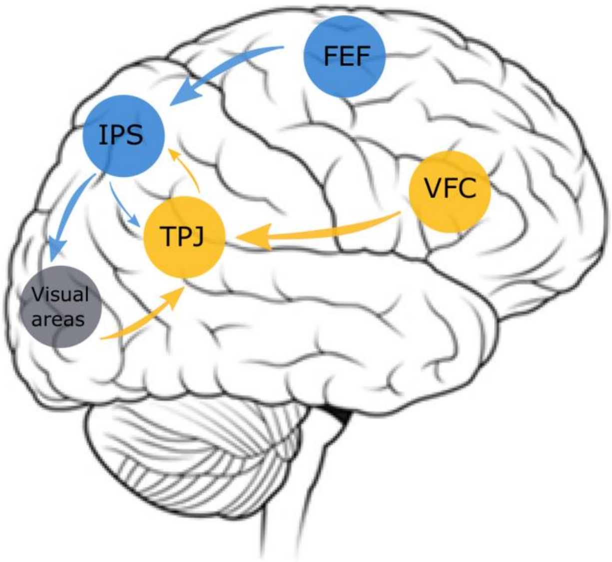

Figure 1: Schematic neuroanatomical illustration of the dorsal and ventral fronto-parietal attentional network nodes of the right hemisphere (based on the model proposed by Corbetta and Shulman 2002). The dorsal fronto-parietal network nodes are depicted in blue (IPS = intraparietal sulcus; FEF = frontal eye fields). The ventral fronto-parietal network nodes are depicted in yellow (TPJ = temporo-parietal junction; VFC = ventral frontal cortex). Arrows indicate the main pathways of top-down (blue) and bottom-up control (yellow) relevant for this model (i.e., arrows indicate direct and indirect connections and do not represent a true reflection of anatomical connections).

The ***ventral fronto-parietal network*** consists of the temporo-parietal junction (TPJ) and ventral frontal cortex (VFC), connected via the ventral superior longitudinal fasciculus (SLF III), and is strongly lateralized to the right hemisphere (Corbetta and Shulman 2002; Thiebaut De Schotten et al. 2011; Vossel et al. 2012). In contrast to the dorsal attention network, the TPJ and VFC show an increase in BOLD response during target detection, in particular when targets appear unexpectedly at unattended target locations (i.e., when invalidly cued). Thus the TPJ and VFC are primarily activated during exogenous shifts of attention to reorient the attentional focus and interrupt ongoing endogenous control (Corbetta and Shulman 2002; Kincade 2005). Additionally, it has been shown that the dorsal and ventral network are connected via a middle long-range pathway (SLF II), providing a direct anatomical link between ventral parietal- and dorsal frontal regions (Thiebaut De Schotten et al. 2011).

Taken together, converging evidence suggests that the dorsal and ventral fronto-parietal attention networks are possible neural substrates mediating attentional selection either via top-down signals to the visual cortex and/or bottom-up signals to interrupt the ongoing top-down control. Nevertheless, under which circumstances these two cortical networks interact and overlap still remains unclear. An effective method to study the implication of distinct cortical regions in cognitive processes is through transcranial magnetic stimulation (TMS). TMS can be employed to transiently interfere with ongoing cognitive functions, which facilitates insights into the underlying neural substrates (e.g., reviews; Hallett 2007; Dayan et al. 2013). Its high temporal resolution and spatially precise target engagement at the macroscopic level allows for investigation of if (and when) certain brain regions are causally involved in a given task. In support of the neuroanatomical model described above, TMS-studies have causally implicated dorsal and ventral network nodes in endogenous and exogenous visuospatial orienting, respectively (Chica et al. 2011; Capotosto, Babiloni, et al. 2012; Capotosto, Corbetta, et al. 2012; Bourgeois et al. 2013). For the scope of this thesis, the focus will lie on the most prominent model described by Corbetta and Shulman (2002). In particular the role of right IPS and right TPJ in endogenous and exogenous spatial attention shifts will be the main focus of Chapter 3.

1.3 Neural oscillations in visuospatial attention

Oscillatory activity in the brain reflects rhythmic fluctuation in the excitability of neuronal populations, generated primarily by excitatory and inhibitory postsynaptic potentials (Lopes da Silva 1991; Buzsáki 2006; Buzsáki et al. 2012). The resulting electrical and magnetic brain signals can be recorded with electroencephalography (EEG) and magnetoencephalography (MEG) respectively from the human scalp surface. Oscillatory activity can be described in three dimensions: frequency, amplitude (or power) and phase. Frequency reflects the speed of an oscillation, and has been (somewhat arbitrarily) grouped into different frequency bands typically defined as delta (< 4Hz), theta (4-8Hz), alpha (8-14Hz), beta (14-30Hz) and gamma (> 30Hz)[1]. Power reflects the energy in a given frequency band (i.e., indicating the number of neurons that fire simultaneously) and phase reflects the position of the oscillation at any given time point (measured in radians or degrees of a unitary circle) (Pfurtscheller and Aranibar 1977; Pfurtscheller and Lopes 1999; Buzsáki et al. 2012). A growing body of research has started to functionally and anatomically associate these highly dynamic oscillatory brain signals with large-scale brain networks and various perceptual and cognitive functions (Varela et al. 2001; Hipp et al. 2011; Fries 2015), such as decision making (Pesaran et al. 2008), working memory (Palva et al. 2010) and selective and sustained attention (Womelsdorf and Fries 2007; Siegel et al. 2008; Clayton et al. 2015).

One of the first described and most apparent brain rhythms is the ***alpha-rhythm*** (cycling at about 10Hz), which can be observed even in raw EEG recordings and is most pronounced over occipital and parietal sites (Berger 1929). Advances in recording techniques such as EEG, MEG and intracranial recordings, as well as lesion studies, have identified different subcortical and cortical sources that generate and shape the activity of alpha oscillations. While a strong subcortical generator is the thalamus (Goldman et al. 2002; Hughes and Crunelli 2005; Liu et al. 2012), laminar recordings and source reconstructions have shown that alpha generators are also located in cortical layers in the visual (occipital) and posterior cortex (e.g., Bollimunta et al. 2008; Salmelin & Hari 1994; Hindriks et al. 2015).

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[1] Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Physiology (EEG Suppl. 52) Editors: G. Deuschl and A. Eisen q 1999 International Federation of Clinical Neurophysiology. All rights reserved. Published by Elsevier Science B.V

Numerous studies have revealed that alpha plays a crucial role in visual perception and selective/spatial attention. In particular, endogenous (goal-directed) attention shifts have been linked to specific oscillatory alpha modulations that are most pronounced over occipito-parietal areas. For example, in a task that requires attention shifts in space (e.g., to the left visual field), the typically observed oscillatory activity shows a contralateral decrease (i.e., right hemisphere), and ipsilateral increase in the alpha-band power (relative to the attended visual field) (Worden et al. 2000; Rihs et al. 2007; Kelly et al. 2006; Gould et al. 2011; Händel et al. 2011; Samaha et al. 2016; for a review see, Foxe & Snyder 2011). These specific alpha-band changes occur in anticipation of upcoming events (i.e., prior to target presentation) (Worden et al. 2000; Sauseng et al. 2005; Kelly et al. 2006; Thut et al. 2006), as well as during target presentation (Fan et al. 2007; Bauer et al. 2014). In relation to behaviour, both alpha power and phase predict task performance, where decreases in alpha power and certain alpha phase angles are associated with high visual cortex excitability and enhanced detection of targets, whilst high alpha power and opposite alpha phases angles are linked to reduced visual cortex excitability and detection of targets (Ergenoglu et al. 2004; Kelly et al. 2006; Thut et al. 2006; Romei et al. 2008; Busch et al. 2009; Mathewson et al. 2009; Dugue et al. 2011; Gould et al. 2011; Händel et al. 2011; Benwell, Tagliabue, et al. 2017). Causal evidence of alpha being actively implicated in visual perception has been provided by employing rhythmic TMS at 10Hz over occipital and parietal regions, showing that visual detection was impaired in the visual field contralateral and enhanced ipsilateral to the stimulated hemisphere (as compared to TMS at 5Hz and 20Hz) (Romei et al. 2010). Additionally, in accordance with the neuroanatomical model described in the previous section, alpha might be an underlying neuronal substrate of top-down control on visual areas, as suggested by TMS interferences of right FEF and IPS (using rhythmic TMS) disrupting (anticipatory) alpha-band desynchronization in occipital cortex (Capotosto et al. 2009).

Based on these and previous findings, it has been proposed that increases in the alpha-band reflect a suppression mechanism to inhibit potentially irrelevant visual information (Jensen & Mazaheri 2010; Klimesch et al. 2007; Clayton et al. 2015; Jensen et al. 2012; Mathewson et al. 2011). Furthermore, it has been proposed that this suppression mechanism is not continuous (or tonic), but follows a periodic (alpha) rhythm, allowing for windows of high and low cortical excitability within an alpha cycle, referred to as ‘pulses of inhibition’ ("pulsed-inhibition" hypothesis; Mathewson et al. 2011). This is consistent with and complementary to similar proposals of alpha representing an inhibitory timing mechanism (“inhibition-timing” hypothesis; Klimesch et al. 2007) or at a more cellular-level, inhibitory “gating” of neural processing ("gating by inhibition" hypothesis; Jensen & Mazaheri 2010; Jensen at al. 2012), where in principle rhythmic fluctuations in alpha-power and phase regulate the information that is being communicated between neuronal populations.

While the majority of studies, as described above, focus on oscillatory correlates during endogenous attention shifts, to date only a few studies have investigated the EEG correlates of attention shifts that are exogenously triggered. Thus, the specific underlying oscillatory signatures of exogenous attention shifts still remain unclear. Only recently, a few studies have started to employ EEG to investigate whether (and to what extent) alpha-band activity is associated with exogenously triggered orienting. For instance, Feng et al. (2017) showed enhanced visual perception at validly (relative to invalidly) cued locations in response to non-predictive auditory cues which was linked to sound-induced lateralized alpha desynchronization over occipital areas (Feng et al. 2017). A similar pattern was observed by Harris et al. (2017) who showed a distinct lateralized alpha desynchronization when attention was captured exogenously by non-predictive but goal-relevant features of the cue (i.e., color) (Harris et al. 2017). Together these findings suggest that lateralised alpha changes over occipito-parietal regions are not exclusively modulated during endogenous control of attention, but likewise during exogenous attention.

Although there has been great interest in the study of oscillatory alpha-band activity in relation to visuospatial attention, when attending or selecting specific information in our environment, other attentional processes are likely to be co-activated in response to or in anticipation of a visual change, i.e. in parallel with and/or consecutively to visuospatial attention. This is likely since attentional processes involve not just selecting information (i.e., spatial orienting), but also general alerting processes, and processes for inhibiting/suppressing potentially upcoming distractors (i.e., attentional control/executive control) (Petersen and Posner 2012). Previous research has shown evidence that these different types of attentional processes are linked to more complex, distinct oscillatory responses covering not just alpha-, but also the theta-, beta- and gamma-frequency range (Fan et al. 2007; Bauer et al. 2014; for a review see Clayton et al. 2015). For example, Fan et al. (2007) investigated the oscillatory signatures of precisely these different types of attentional processes, namely alerting, spatial orienting and attentional control. The results revealed complex oscillatory activity patterns, where alerting effects were linked to decreases in theta-, alpha- and beta-band activity. Spatial orienting on the other hand was associated with increases in the gamma-band, whilst attentional control induced an early increase in the gamma-band followed by a decrease in the beta- and gamma-bands (Fan et al. 2007). Multi-band contributions are also in line with the finding of distinct oscillatory responses to spatially cued target discrimination tasks, where pre-stimulus alpha-band desynchronization reflected the anticipation/prediction of upcoming events (i.e., increasing certainty of target appearance increased cortical excitability/alpha-band desynchronization), whereas gamma-band activity reflected the degree of surprise during stimulus processing when events were less predictive (i.e., increasing certainty of target appearance decreased gamma-activity) (Bauer et al. 2014).

Together these findings emphasise that different attentional processes, whether endogenously or exogenously driven, are likely reflected in dynamic oscillatory signals across different frequency bands which shape our visual perception. Investigating the oscillatory correlates of visuospatial attention shifts in a widely used spatial cueing task, thought to isolate exogenous attentional processes in particular (introduced by Posner 1980), will be the focus of Chapter 4.

1.4 Motivation and significance of this thesis

Numerous studies have investigated endogenous and exogenous attention shifts in separation by using ‘classic’ attention paradigms in different blocks or trials and have identified (partially) distinct underlying neuroanatomical and functional substrates. However, to better understand exogenously driven attention, it is crucial to account for potential, concurrently occurring anticipatory effects that may engage endogenous processes. Hence, it is unclear to what extent endogenous attention may have influenced exogenous attention effects, both in terms of behaviour but also (co-)activated networks, in many previous studies (e.g., see reviews, Ruz and Lupiáñez 2002; Macaluso & Doricchi 2013). With respect to the underlying neural oscillatory signatures of both types of attention shifts, the majority of studies have only manipulated endogenous shifts of attention (e.g., see review, Foxe & Snyder 2011), while substantially less focus has been put on the neural characteristics of exogenous spatial orienting. The experiments presented in this thesis are intended to contribute an effective design to the study of exogenous attention shifts in healthy participants, and to thereby provide a more accurate understanding with regards to its perceptually relevant functional substrates and oscillatory signatures.

Strengthening the understanding of exogenous attention shifts and the precise underlying neural mechanisms in ‘normal’/healthy functioning brains is crucial in order to apply this knowledge to clinical populations. For instance, patients suffering from ‘hemispatial neglect’ after stroke can display a variety of symptoms including an inability to attend to locations or objects that are presented contralateral to the brain lesion (e.g., see review; Halligan et al. 2003). In particular and most commonly, the “ventral attention” system in the right hemisphere is disproportionally affected in these patients (as compared to the left hemisphere), resulting in an inability to exogenously (re-)orient attention to unexpected events that occur in the left hemispace (Corbetta and Shulman 2002; Corbetta et al. 2005; He et al. 2007; Rengachary et al. 2011). This has a disabling impact on the quality of life in daily situations, including colliding with obstacles and other problems in terms of independently navigating within their environment. To date, evidence for effective cognitive rehabilitation methods in neglect is limited (Bowen et al. 2013). Hence, it is important to understand attention allocation in the unaffected brain which may in the future facilitate the development of targeted rehabilitation protocols in order to reduce the visuospatial attention deficits for these patients.

In a series of three experiments, one per experimental chapter, I investigated the perceptual correlates, the implication of specific attentional network nodes and the oscillatory signatures of attention orienting with an emphasis on exogenous visuospatial attention shifts in healthy participants. To this end, I employed a combination of psychophysical approaches, transcranial magnetic stimulation (TMS) and electroencephalography (EEG).

1.5 Thesis at a glance (Abstracts)

1.5.1. Chapter 2: Studying the behavioural dissociation between endogenously controlled and exogenously driven spatial and temporal attention (Experiment 1)

Behaviourally relevant sensory events such as motion stimuli have an intrinsic spatio-temporal structure. This engages exogenous attention processes but most likely also concurrent endogenous attention control, enhancing the perception of upcoming stimuli that appear in the motion path. Here, I sought to probe to what extent these attentional anticipatory processes will influence perception at spatially and temporally expected locations and time-points respectively, with an emphasis on exogenously driven attention in response to rhythmic motion streams. At the same time, I intended to control (by experimental design) for endogenous engagement with the exogenous input stream.

To this end, participants performed an endogenously cued target discrimination task, in which symbolic cues prompted attention shifts to lateralized positons in anticipation of upcoming targets (presented with 75% at validly cued positions). Simultaneously, exogenous apparent motion cues moved either rhythmically or arrhythmically across the screen (valid vs. invalid *temporal* motion cueing) such that targets appeared either in or out of motion trajectory (valid vs. invalid *spatial* motion cueing). Crucially, the paradigm isolated exogenous from endogenous processes by rendering the exogenous motion stimuli non-predictive of upcoming target position (by design) and task-irrelevant (by instruction), and by using the symbolic cues to create instead endogenous (orthogonal) expectations. The data revealed that endogenous cueing benefitted performance at validly (as compared to invalidly) cued spatial target locations, as expected. Importantly, this effect did not interact with spatial and temporal apparent motion cueing. Hence, any perceptual benefits from spatial or temporal motion cueing can be considered to reflect exogenously driven processes independent from the endogenous processes. Interestingly, the apparent motion cues triggered both exogenous spatial and temporal anticipatory processes which were dissociated. I further found evidence for left-lateralisation of temporal but not spatial processes. This indicates that distinct mechanisms may drive exogenous spatial and temporal extrapolation of upcoming events from rhythmic event streams. The results of this chapter highlight how to isolate exogenous driven processes from endogenous control for a better understanding of the various anticipatory mechanisms engaged in processing behaviourally relevant stimuli with predictable spatio-temporal structure, such as motion.

1.5.2. Chapter 3: Interfering with dorsal and ventral attention network nodes during exogenous versus endogenous spatial orienting with transcranial magnetic stimulation (TMS) (Experiment 2)

Neuroimaging and TMS studies suggest that partially segregated large-scale dorsal and ventral fronto-parietal networks play a crucial role in endogenous and exogenous visuospatial attention (Corbetta & Shulman 2002; Chica et al. 2011). However, to what extent and under which circumstances these networks interact and/or overlap remains under debate (Vossel et al. 2014). In particular, the findings of previous studies may have been confounded by endogenous attentional engagement during exogenous orienting due to their experimental designs.

Here, I addressed this issue by combining a visuospatial attention paradigm, previously shown to behaviourally isolate exogenous from endogenous orienting (Experiment 1), with neuronavigated double-pulse TMS over right intraparietal-sulcus (rIPS), right temporo-parietal-junction (rTPJ) and sham-TMS. In a within-subject design, participants were asked to perform a visual discrimination task, preceded by predictive symbolic cues engaging endogenous orienting to target positions (left vs. right). Simultaneously non-predictive, task-irrelevant apparent motion cues were presented in the background to trigger exogenous shifts of attention (leftward vs. rightward) to the same positions (same paradigm as described above in 1.5.1 and in chapter 2). The results reveal that during sham-TMS, endogenous and exogenous cueing both facilitated performance accuracy at validly vs. invalidly cued target locations. Importantly, there was no interaction between endogenous and exogenous cueing, successfully replicating the results of the experiment reported in chapter 2. Thus, the design effectively avoided endogenous engagement during exogenous orienting. Interestingly, while endogenous cueing accuracy benefits were unaffected by TMS (relative to sham), both rIPS- and rTPJ-TMS abolished accuracy benefits from exogenous orienting. There were no effects of active-TMS on reaction times, neither for endogenous nor exogenous cueing effects.

In conclusion, the findings indicate dissociated effects of TMS on endogenous and exogenous processes (performance accuracy), and an involvement of both dorsal and ventral nodes (i.e. rIPS and rTPJ) in exogenous orienting.

1.5.3. Chapter 4: Investigating the neural correlates of exogenous attention shifts in electroencephalography (EEG) (Experiment 3)

Previous research has highlighted posterior oscillations in the alpha-band to play a key role in goal-directed (top-down driven) visuospatial attention (Foxe & Snyder 2011). However, the oscillatory signatures of exogenously driven (bottom-up) alerting and orienting of attention remain uncertain. Likewise, it is unclear to what extent these exogenous processes are influenced by top-down components, such as mid-frontal oscillatory activity in the theta-band. These theta oscillations have been associated with cognitive control processes which are activated when goal directed bias over habitual responses is needed (Cavanagh & Frank 2014).

Here, I employed EEG to investigate the neural correlates of exogenous attentional engagement in healthy participants. I utilized a classic spatial cueing task known to test exogenous processes (Posner 1980). Following a non-predictable spatial cue or no-cue, targets were presented at cued or non-cued positions at four different cue-target delays (ranging from 105.8-705.8ms), known to induce initial attentional benefits and later inhibition-of-return (IOR). This experimental manipulation allowed me to investigate both exogenous alerting (cue vs. no-cue independent of space) and (re)orienting (cued vs. uncued position) at early and later stages of spatial attention processing. Between-subject correlations of reaction times (RTs) and alpha-power revealed that individuals who showed an early alerting effect (faster RTs in cue vs. no-cue) exhibited stronger alpha-band desynchronization over occipital regions before target onset (independent of space and hemisphere). Notably, the same analysis also revealed a negative influence of mid-frontal theta activity on alerting, where individuals with higher central theta-power displayed slower RTs. Interestingly, central theta-increases also negatively affected later spatial components of exogenous attention (i.e. IOR), where IOR was abolished in individuals with higher theta power.

These results suggest an interplay between top-down processes and exogenous attention, in accordance with cognitive control overriding reflexive processes. They highlight the need to control for the engagement of higher-order computations in order to better understand the neural correlates of exogenous processes in isolation.

Chapter 2

Studying the behavioural dissociation between endogenously controlled and exogenously driven spatial and temporal attention

2.1 Introduction

Visual perception is influenced by attention and expectations. While attention is driven endogenously by motivational goals or can be attracted exogenously by unexpected events, perceptual expectations depend on the history of prior events (or prior knowledge) and consequently on what is most probable in terms of forthcoming sensory input (for review see Summerfield & Egner, 2009). A variety of behaviourally relevant stimuli can generate expectations about forthcoming events through e.g. their inherent temporal and/or spatiotemporal structure. Examples include visual motion (Adelson and Bergen 1985; Khoei et al. 2013), looming sounds (Rosenblum et al. 1993; Ghazanfar et al. 2002) and speech stimuli (Jones and Boltz 1989; Arnal and Giraud 2012; Zion Golumbic et al.

2012). This in turn benefits processing of the future events: For instance, motion stimuli allow predictions of future events in the motion stream both in the spatial and temporal dimensions. Motion stimuli are also effective in capturing attention due to their behavioural relevance (e.g., Al-Aidroos, Guo, & Pratt, 2010; Franconeri & Simons, 2003). Accordingly, it is conceivable that motion stimuli engage exogenous processes that implement an effective, sensory-driven prediction of forthcoming events. This may occur exogenously without the need for time-consuming, higher-order cognitive resources, or can involve (intentional or unintentional) endogenous processes to actively predict the past motion trajectory to future time points. Hence, it is likely that exogenous attentional processes can be enhanced or suppressed by endogenous modulation (for review see, Ruz and Lupiáñez 2002). This co-implication of potential endogenous processes may influence or confound the to-be studied exogenous processes of interest (see Breska & Deouell, 2014 for similar aruguments regarding stationary flicker). In order to account for the engagement of endogenous control during exogenous processes, the ***first aim*** of this experiment is to establish whether the endogenous vs. exogenous processes can be behaviourally dissociated by experimental design.

Moreover, while there have been many studies on the anticipatory processes linked to spatially and temporally predictive sensory events in the domain of spatial and/or temporal attention (Coull and Nobre 1998; Doherty et al. 2005; Rohenkohl et al. 2014) and apparent motion research (e.g., Shioiri et al. 2002; Schwiedrzik et al. 2007; Hogendoorn et al. 2008), also dissociating between exogenous (unintentional) vs. endogenous (intentional) mechanisms (e.g., Breska & Deouell, 2014; Olk, 2014), little is known about the interaction between temporal and spatial anticipatory processes, in particular when exogenously driven.

Apparent motion cues are discrete events and their inherent spatial and temporal information allows manipulation of both dimensions. Following the ***spatial structure*** of apparent motion cues, perception of targets can be probed in or out of the perceived motion path. Several previous studies have investigated the effects of apparent motion stimuli on the processing of such a visual probe (Yantis and Nakama 1998; Shioiri et al. 2002; Doherty et al. 2005; Schwiedrzik et al. 2007; Hogendoorn et al. 2008), with the rationale that due to their predictive structure, apparent motion stimuli may engage perceptually relevant, covert motion completion mechanisms (when eyes fixated). Indeed, such completion mechanisms have been made evident behaviourally (Shioiri et al. 2000, 2002; Hogendoorn et al. 2008). These completion mechanisms may serve extrapolation as well as interpolation of apparent motion (Hogendoorn et al. 2008) each with likely different perceptual outcomes, namely benefits vs. costs due to anticipation vs. masking effects (for benefits see Doherty et al., 2005; Hogendoorn et al., 2008; Shioiri et al., 2002); (for costs see Hogendoorn et al., 2008; Schwiedrzik et al., 2007; Yantis & Nakama, 1998). In the present study, we focus on the beneficial effects of motion cueing using a pre-target motion paradigm that, by design, draws on anticipatory (extrapolation) mechanisms (Doherty et al. 2005; de Graaf et al. 2013).

As mentioned above, in addition to their spatially predictive structure, apparent motion cues also provide predictive information as to the ***timing*** of forthcoming events (i.e., rhythmicity). This can be experimentally explored in isolation by manipulating the temporal structure of static visual flicker stimuli, when no motion is present. Many behavioural studies have shown that rhythmicity *per se* conveys a benefit for target detection at rhythmically cued vs. un-cued time points; for instance, when targets are preceded by rhythmic as compared to arrhythmic events (Rohenkohl et al. 2011, 2012; Cravo et al. 2013), or when targets are presented in-phase vs. out-of-phase in a rhythmic stream of events (Doherty et al. 2005; Mathewson et al. 2010; Breska and Deouell 2014; Jones 2015). Notably, the benefit from rhythmic temporal cueing has been found to be independent of endogenously deployed attention to symbolically cued time points (Breska and Deouell 2014). This suggests that rhythmic stimuli engage automatic anticipatory mechanisms in the temporal dimension (see also, Jones and Boltz 1989). Finally, research on perceptual benefits from rhythmic cueing has gained momentum from research on its neuronal substrates. Electrophysiological studies have revealed that periodic stimulation leads to phase alignment of ongoing oscillations to the rhythmic input, reflecting entrainment of intrinsic rhythms to the external event streams (Lakatos et al. 2008; Schroeder and Lakatos 2009; Mathewson et al. 2012; Spaak et al. 2014). This presumably aligns phases of high neuronal excitability to the expected forthcoming event, a process for which brain oscillations may be ideally placed, given their rhythmic structure (Lakatos et al. 2008; Schroeder and Lakatos 2009). Taken together the prior evidence on spatial and temporal anticipation, the ***second aim*** of this experiment is to investigate the beneficial effects of spatial extrapolation and the interaction with temporal anticipation, particularly when exogenously driven by apparent motion.

To address the first aim of the present behavioural experiment (i.e., avoiding higher-order cognitive endogenous control confounding exogenous processes), endogenous and exogenous processes were concurrently manipulated. Symbolic spatial cueing was employed to manipulate endogenous attention, whilst simultaneously presented apparent motion stimuli were presented in the background to drive exogenous shifts of attention. Importantly, the apparent motion cues were kept entirely non-predictive of the upcoming target position, instead endogenous (orthogonal) expectations were created by using predictive symbolic cueing. Exogenous (versus endogenous) processing of the motion cues were further emphasized by instruction, explicitly qualifying the motion stimuli as task-irrelevant. Additionally, to investigate how spatial and temporal anticipatory mechanisms are orchestrated when exogenously driven (i.e., the second aim), visual probes were presented in and out of apparent motion trajectories (valid vs. invalid spatial trajectory cueing) moving at either rhythmic or arrhythmic pace (valid vs. invalid temporal trajectory cueing).

I expected to effectively isolate exogenously motion-driven benefits on target discrimination from endogenous benefits by controlling for endogenous engagement of attention to the motion cues. Furthermore, I expected that the manipulation of spatial trajectory and rhythmicity enhances perceptual processing for probes appearing at validly motion-cued as compared to invalidly motion-cued time-points and positions, presumably reflecting exogenous anticipatory mechanisms.

2.2 Methods

Participants

A total of twenty-five healthy participants took part in this study (16 females, 9 males, age range: 19-34, average age ± SD = 23.12 ± 4.21). All participants were right handed and had normal or corrected-to normal vision. Before taking part in the experiment, all participants provided written informed consent. Ethics approval was given by the College of Science and Engineering ethics committee of the University of Glasgow.

Apparatus

The experiment was presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) on a CRT monitor (Samsung Sync Master 1100MB, 20inch in diameter, spatial resolution of 1280 x 1024 pixels and refresh rate of 85Hz). A chinrest maintained a constant viewing distance of 35cm to the screen. Eye movements were monitored online using a CCTV camera to ensure participants understood the concept of the task (covert attention shifts without eye movements following the cues).

Stimuli and Task

A visual pre-target motion paradigm was implemented (adapted from de Graaf et al. 2013; initially inspired by Doherty et al. 2005). A matrix of 5 x 9 circles (placeholders) and a central fixation cross were presented at all times on the screen (**Figure 2** A). The placeholders were presented in grey on a black background together with the white fixation cross. Symbolic cues presented on top of the fixation cross were all white (**Figure 2** B). The diameter of the placeholders was 1.2cm, with a vertical distance of 3cm and a horizontal distance of 3.4cm.

Exogenous attention shifts were modulated by apparent motion stimuli. The motion stimuli consisted of five placeholders in the row below the fixation cross successively flashing from grey to white (left- or rightward motion x rhythmic or arrhythmic flashes) (**Figure 2** C). The flashing of the circles either started with the rightmost circle and ended with the central circle directly underneath the fixation cross (leftward motion) or started with the leftmost circle and ended with the same central circle (rightward motion). This created an apparent motion effect of the circles and was followed by a target presented in one of the adjacent placeholders, left or right from the central circle. Thus, targets appeared either in- or out- of apparent motion direction *(for **spatial trajectory cueing**/ probing spatial extrapolation).* Importantly, left- and rightward apparent motion direction was equally probable and uninformative of upcoming target position (pointing in 50% of trials towards and in the other 50% away from the target). In addition, the temporal structure of the apparent motion trajectory was manipulated *(for **temporal trajectory cueing**/ probing temporal anticipation).* To this end, the apparent motion cues (flash=35.3ms) flickered either rhythmically at 3.9Hz (four fixed ISIs of 258.8 ms) or arrhythmically with four intervals of 117.6, 152.8, 329.4 and 435.2 ms (shuffled and presented in random order per arrhythmic trial). The 3.9Hz intervals were chosen because visual stimuli moving in discrete steps at this frequency are perceived as apparent motion (Shioiri et al. 2000). In order to prevent differential forward masking (see also Schwiedrzik et al., 2007) between rhythmic and arrhythmic conditions, the last interval between the fifth circle and the visual target was fixed at 258.8ms across all trials. In addition, time from motion cue onset to target presentation was fixed across all trials of both the rhythmic and arrhythmic conditions (1294ms). Hence, rhythmic and arrhythmic trials only differed in rhythmic or arrhythmic trial history, but were not differentially informative as to time of target onset, emphasizing differences in deployed unintentional processes (linked to the rhythmicity of motion) rather than endogenous mechanisms (e.g. linked to time-estimation). Rhythmic and arrhythmic trials were presented in random order. Participants were instructed that motion stimuli were uninformative as to both forthcoming target position and time of appearance and therefore irrelevant to the task.

Although the motion trajectory was non-predictive as to forthcoming target location and participants were not required to engage with the flicker, participants may still process the apparent motion cues intentionally to extrapolate upcoming events. Thus, to prevent endogenous orienting to the motion cues, participants were asked to engage in a concurrent, symbolically cued ***endogenous attention orienting task***, in anticipation of the upcoming, to-be-discriminated targets: Informative, symbolic arrow-cues were presented at the beginning of the trial, in the centre of the screen (**Figure 2**), indicating the location of the upcoming target (i.e., left- or rightward arrows, 75% cue-validity) or indicating a neutral trial (bi-directional arrow which was non-predictive (50:50) of target location). Participants were asked to covertly shift attention towards the indicated target position upon presentation of a left- or rightward pointing arrow, or to maintain attention at the fixation cross in neutral trials (and to keep their fixation at the central fixation cross in all cases), while the uninformative motion cues flickered either rhythmically or arrhythmically across the screen (in the background). Targets consisted of a ‘+’ or ‘x’ which needed to be discriminated as fast and accurate as possible by button press (keys ‘1’ and ‘2’ counterbalanced across participants).

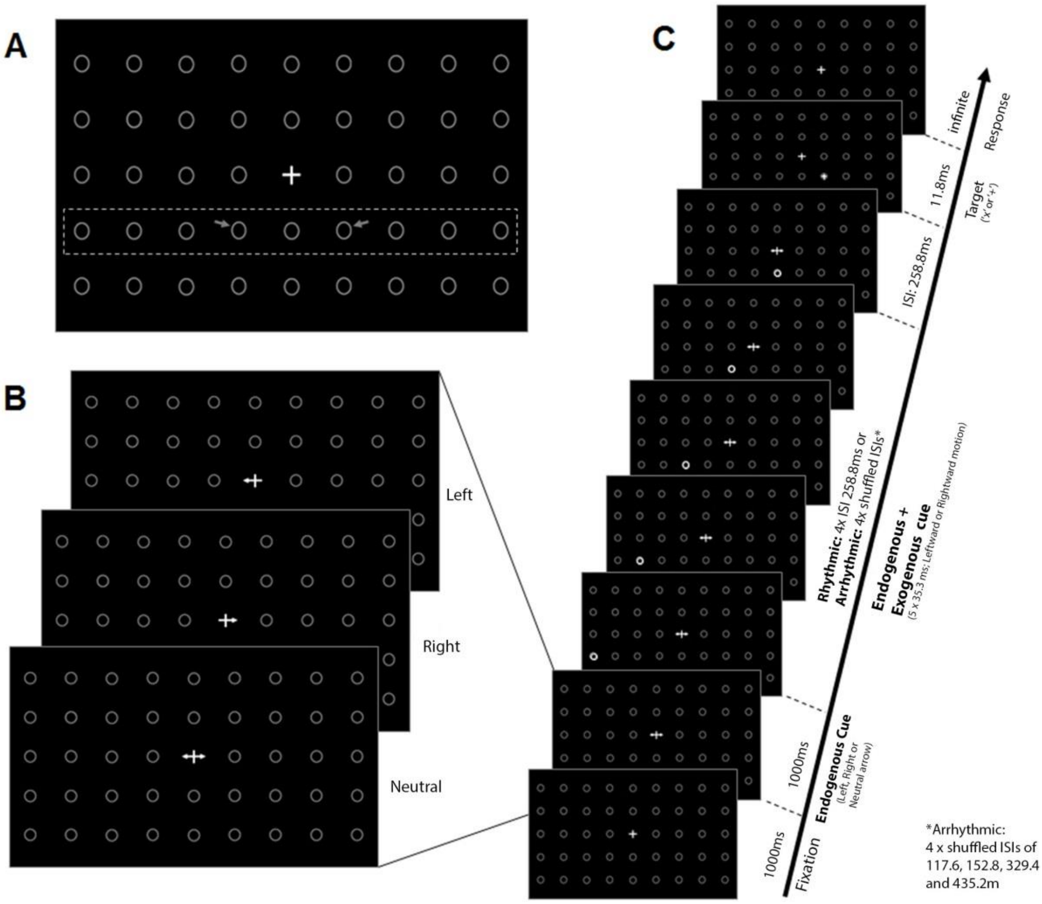


Figure 2: Schematic representation of the experimental design. (A) Fixation cross and placeholders. The dashed rectangle and the arrows (here drawn on top of the background screen for illustrative purposes, not part of visual stimulation) highlight respectively the row in which visual motion cues were presented, and the two possible target locations in the left and right visual fields. **(B)** *Endogenous symbolic arrow-cues* (left, right or neutral) as presented in the centre of the screen. **(C)** Each trial began with a fixation cross (1000ms) and was followed by the presentation of an endogenous cue indicating the probable upcoming target location (here: neutral). The endogenous cue stayed on the screen until target presentation and throughout exogenous apparent motion cueing. *Exogenous motion cueing* began 1000ms after endogenous cue onset. Exogenous spatial cueing was implemented by successively flashing (for 35.3ms) each adjacent circle in the row below the endogenous cue from the left or right periphery towards the centre (i.e., leftward or rightward motion). Exogenous temporal cueing was implemented by presenting the motion cues in either a rhythmic or arrhythmic temporal structure. After a fixed ISI of 1294ms from motion cue onset (including 258.8ms after the last motion cue), the target appeared for 11.8ms either in or out of motion trajectory. Participants were asked to engage in endogenous orienting based on the symbolic cues, and to ignore the motion cues because they were task-irrelevant.

Procedure

The experiment took place in two sessions (1 hr per session) on two different days to avoid participants' fatigue. A training phase familiarized participants with the task. The first training block consisted of intermixed endogenous neutral-, left- or right-cues only (100% validity, number of trials: 24). Participants then completed a second training block, including motion (trajectory cues) in a rhythmic or arrhythmic pattern (50% validity), in addition to the 100% valid endogenous cues (number of trials: 32). This was followed by target titration, which served to individually adjust target luminance contrast to approximately 80% discrimination performance to avoid floor or ceiling effects. Overall, the experiment consisted of three endogenous symbolic cues (neutral, left and right), two exogenous motion directions (left to right and right to left) and two exogenous temporal structures (rhythmic or arrhythmic). All conditions were presented in an intermixed order in five blocks with breaks approximately every 6.5 minutes, resulting in a total number of 960 trials (80 trials per condition) per participant.

Statistical analysis

We subjected both discrimination accuracy (proportion correct) and reaction times (correct responses only) to two separate fully within-subjects design (repeated-measure) analysis of variances (ANOVAs). The factors of these 3x2x2x2 ANOVAs consisted of Endogenous Spatial Cueing (neutral vs. left vs. right), Exogenous Spatial Cueing (leftward vs rightward motion), Exogenous Temporal Cueing (rhythmic vs. arrhythmic) and Target Location (left vs. right). Significant main effects or interactions were followed up with simple effect tests. Calculation of the effect sizes for simple tests (Cohen's d) was based on correlated sample comparisons (within-subjects) (see Lakens, 2013) and we report their magnitude (not the sign).

2.3 Results

The data are represented in **Figure 3** (endogenous cueing effects) to **Figure 4** and **Figure 5** (exogenously driven spatial and temporal cueing effects and their interactions).

Endogenous cueing benefit on target discrimination and independence from exogenous cueing effects

In line with the participants following the instructions and engaging in the task (endogenous shifts of attention in response to the symbolic cues), we found both discrimination accuracy (**Figure 3** A) and reaction time (**Figure 3** B) to be influenced by endogenous cueing direction (left, neutral, right symbolic cues) as a function of target position (left visual field vs right visual field), which showed in a significant 2-way interaction of Endogenous Spatial Cueing x Target Location both for accuracy (F(2,48) = 13.32, p = .00003, $\eta p^2 = .36$) and reaction time (F(2, 48) = 83.08, p < .00001, $\eta p^2 = .78$). Follow-up simple tests showed significantly better performance levels (higher accuracy, faster RTs) for validly than invalidly cued targets in both the left visual field (accuracy L- vs R-cue: F(1,24) = 21.79, p = .00001, Cohen's d =.93; RT L- vs R-cue: F(1,24) = 80.18, p < .00001, Cohen's d =1.79), and the right visual field (accuracy R- vs. L-cue: F(1,24) = 5.05, p =.034, Cohen's d =.45; RT R- vs. L-cue: F(1,24) = 66.56, p < .00001, Cohen's d =1.63).

Importantly, there was no evidence for motion to affect any of the above endogenous cueing benefits at attended locations (no 3-way interaction of Endogenous Spatial Cueing x Target Location with neither Exogenous Spatial Cueing nor Exogenous Temporal Cueing, for any of the two measures (accuracy and RT) (both 3-way interactions non-significant: F(2,48) < 0.44, p > .646, $\eta p^2 < .02$). This speaks in favour of the participants maintaining endogenous attention throughout all conditions independently of the presence of simultaneous motion cues, i.e. for participants not dividing endogenous attention between the symbolic endogenous and the exogenous motion cues. Or in other words, this shows that participants effectively ignored the exogenous motion cues, as desired by instructions and design (motion flicker task-irrelevant and non-predictive as to forthcoming target location). As a consequence, any benefit from spatial or temporal trajectory cueing can be considered to reflect exogenously driven anticipation.

Finally but tangential to the questions of this study, the overall ANOVAs revealed a main effect of Endogenous Cueing for both performance accuracy (F(2,48) = 5.92, p =.005, $\eta p^2 = .20$) and reaction time (F(2, 48)=13.88, p = .00002, $\eta p^2 = .37$).

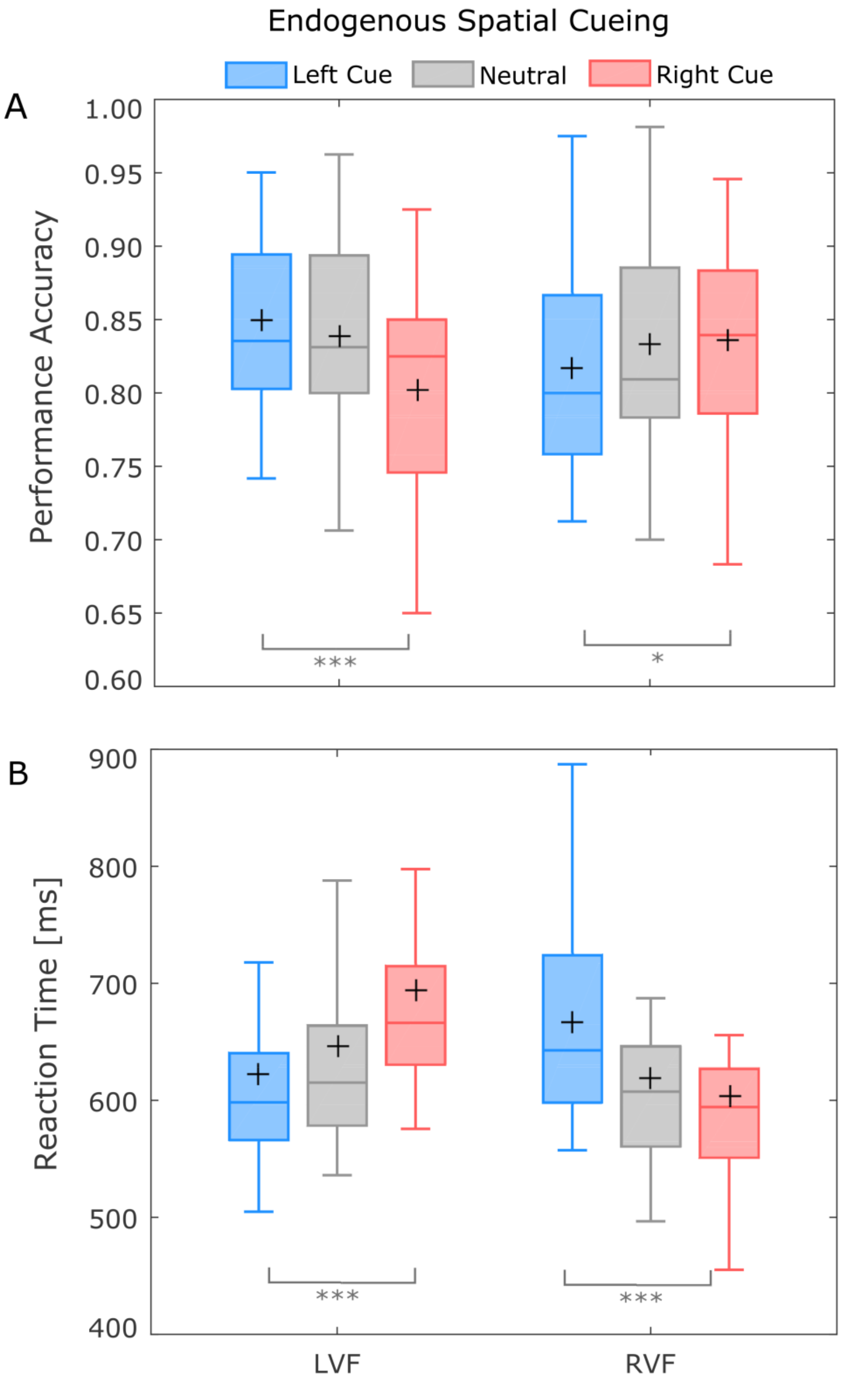


Figure 3: Behavioural results of endogenous spatial cueing. (A) Discrimination accuracy and **(B)** reaction time. The boxplots represent performance in response to symbolic leftward cues (blue), neutral cues (grey) or rightward cues (red) as a function of target presentation in the left visual field (LVF) vs. right visual field (RVF). Boxes show 25/50/75th percentile, whiskers enclose 1.5 * interquartile range, the cross represents the mean and circles show individual data points. Stars '*': simple tests significant at $p<0.05$ and '***' at $p < 0.001$.

Exogenous spatial extrapolation in response to the motion trajectory: Benefits of motion direction on target discrimination

Despite being task-irrelevant and non-predictive, the direction of exogenous motion cueing (leftward vs. rightward motion) significantly affected both target discrimination accuracy (**Figure 4** A) and reaction time (**Figure 5** A) as a function of target location (LVF vs. RVF), as revealed by significant 2-way interactions of Exogenous Spatial Cueing (i.e. motion direction) x Target Location (accuracy: F(1,24) = 10.14, p = .004, $\eta p^2 = .30$; RT F(1, 24) = 50.93, p < .00001, $\eta p^2 = .68$). Follow-up simple tests revealed significantly (or near-significantly) better performance levels (higher accuracy, faster RTs) for validly as compared to invalidly cued targets for both the right visual field (accuracy right- vs. leftward motion: F(1,24) = 6.80, p = .015, Cohen's d =.52/ RT right- vs. leftward motion: F(1,24)=10.18, p = .004, Cohen's d =.64) and the left visual field (accuracy left vs. rightward motion: F(1,24) = 3.94, p = .059, Cohen's d =.40; RT left vs. rightward motion: F(1,24)=31.22, p = .00001, Cohen's d =1.12). Thus, motion direction clearly benefitted target discrimination at motion-cued locations, with higher performance accuracy and faster reaction times for targets appearing in as compared to out of motion trajectory. This is evidence for motion trajectory exogenously driving spatial anticipation. Interestingly, this effect was independent of exogenous temporal cueing (rhythmicity) for both accuracy (F(1,24) = .18, p = .67, $\eta p^2 = .008$) and reaction time (F(1, 24) = .26, p = .62, $\eta p^2 = .01$) (see **Figure 4** B and **Figure 5** B).

Finally and again tangential to our question, there was a main effect of target location, with faster responses for targets in the right visual field relative to the left visual field (difference of 24.46 ms) (F(1,24) = 12.38, p = .002, $\eta p^2 = .34$).

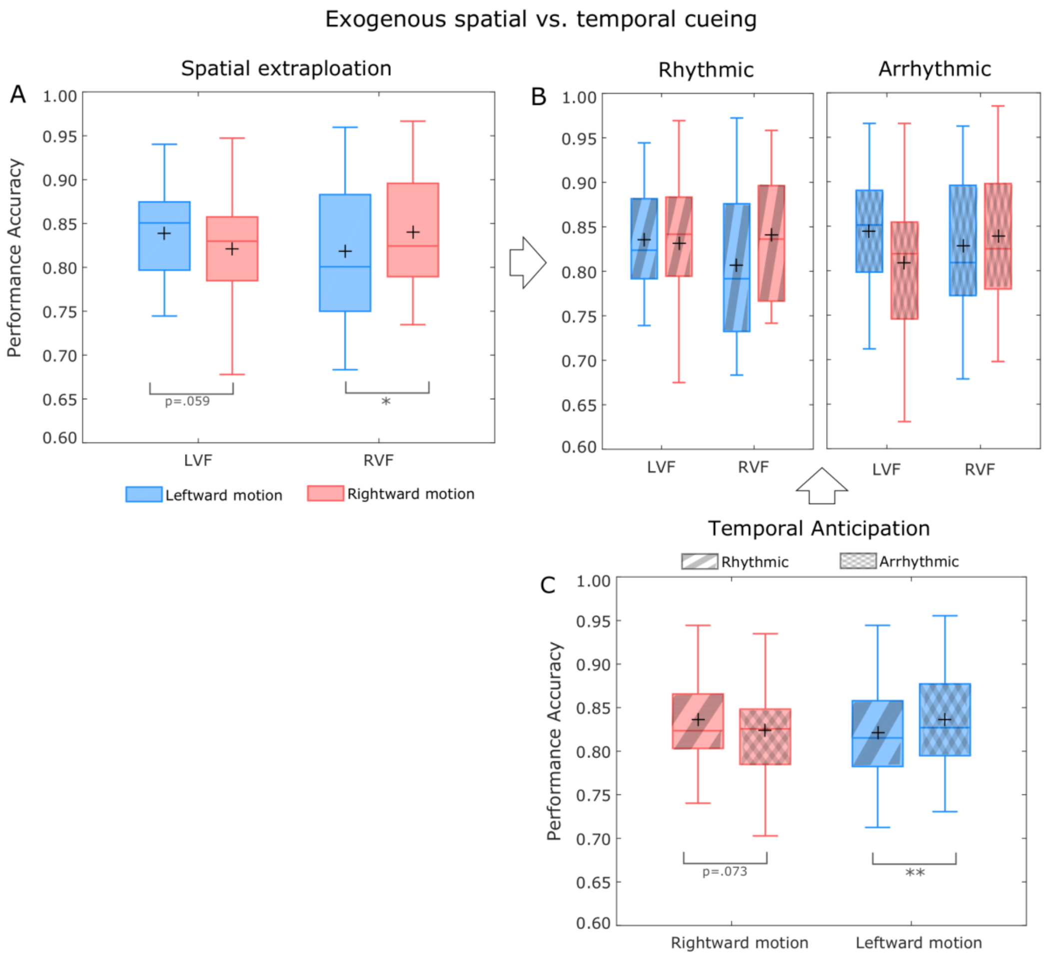


Figure 4: Performance accuracy as a function of exogenous spatial vs. temporal cueing conditions. (A) Boxplots represent performance during leftward (blue) and rightward (red) motion as a function of target locations in the left visual field (LVF) and right visual field (RVF). **(B)** shows the same as (A) but split between the two levels of temporal cueing (i.e. rhythmic vs. arrhythmic cueing). Note that the 2-way interaction of Exogenous Spatial Cueing x Target Location [illustrated in (A)] was statistically independent of Exogenous Temporal Cueing, i.e. there was no significant 3-way interaction [illustrated in (B)]. **(C)** Separate bar plots for rhythmic (bold stripes) and arrhythmic (chequered) cueing, per motion cueing direction, illustrating the significant 2-way interaction between temporal trajectory cueing and motion cueing direction. Boxes show 25/50/75th percentile, whiskers enclose 1.5 * interquartile range, the cross represents the mean and circles show individual data points. Stars '*': simple tests significant at p<0.05 and '**' at p < 0.01.

Exogenous temporal anticipation in response to the motion trajectory: Benefits from the temporal structure of motion stimuli

Overall responses to rhythmic cueing were slightly faster relative to arrhythmic motion cues (difference of 5.3 ms) (F(1, 24) = 4.72, p = .034, ηp^2 = *.16*). More importantly exogenous temporal cueing (rhythmicity) influenced target discrimination but differently from exogenous spatial cueing. We expected that the benefit from exogenously driving spatial anticipation by motion (as revealed above in the 2-way interaction Exogenous Spatial Cueing x Target Location) would be enhanced by temporal cueing (rhythmic vs arrhythmic condition), which was however not the case (no 3-way interaction of Exogenous Temporal Cueing x Exogenous Spatial Cueing x Target Location, see above). Instead, temporal trajectory cueing benefits were limited to discrimination accuracy and depended on motion direction (significant 2-way interaction of Exogenous Temporal Cueing x Exogenous Spatial Cueing (F(1,24) = 16.16, p = .0005, $\eta p^2 = .40$) (**Figure 4** C). This effect was absent for reaction times (**Figure 5** C). Follow-up simple tests on performance accuracy showed a trend for better performance when exposed to rhythmic as compared to arrhythmic rightward motion (F(1,24) = 3.53, p = .073, Cohen’s d =.38) and a significant advantage for arrhythmic as compared to rhythmic leftward motion (F(1,24) = 10.01, p = .004 , Cohen’s d =.63). This finding indicates asymmetric effects of exogenous temporal cueing (rhythmic vs. arrhythmic) for cueing towards the right vs. left visual fields.

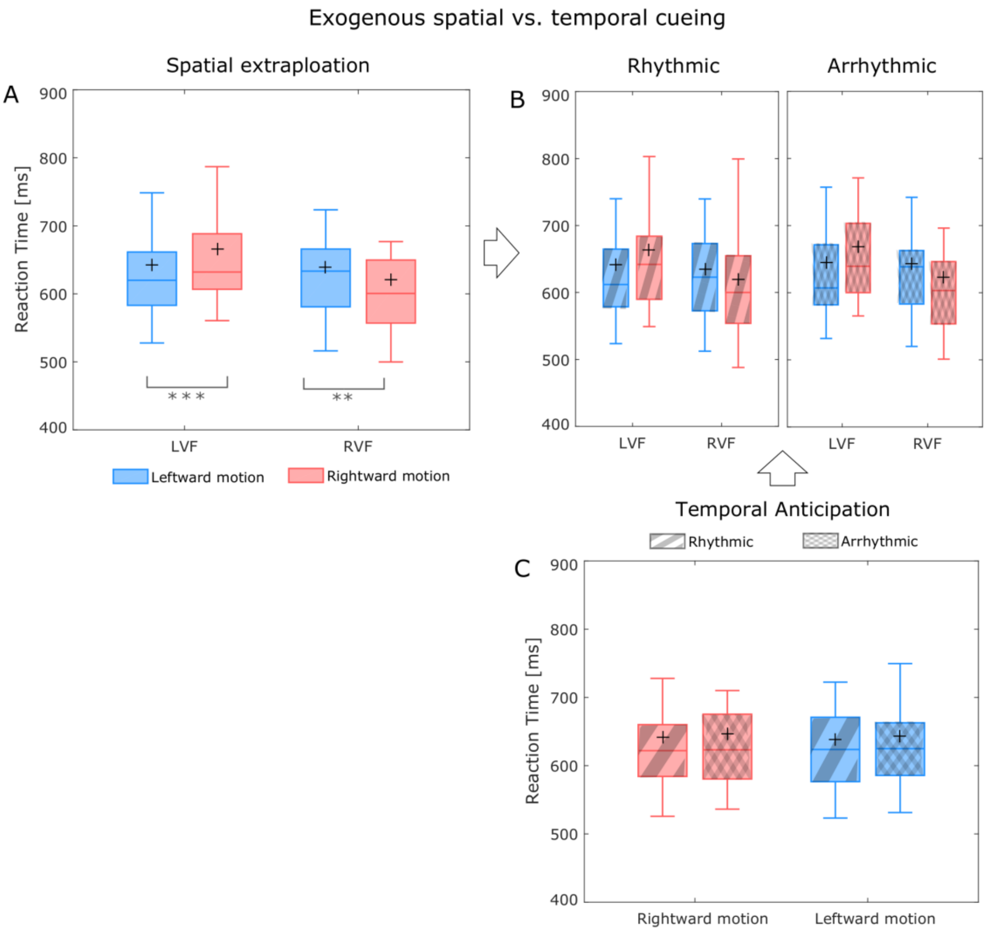


Figure 5: Reaction time as a function of exogenous spatial vs. temporal cueing conditions. (A) Boxplots represent reaction time during leftward (blue) and rightward (red) motion as a function of target locations in the left visual field (LVF) and right visual field (RVF). **(B)** shows the same as (A) but split between the two levels of temporal cueing (i.e. rhythmic vs. arrhythmic cueing). Note that the 2-way interaction of Exogenous Spatial Cueing x Target Location [illustrated in (A)] was statistically independent of Exogenous temporal cueing, i.e. there was no significant 3-way interaction [illustrated in (B)], as for accuracy (**Figure 4**). **(C)** Separate bar plots for rhythmic (bold stripes) and arrhythmic (chequered) cueing, per motion cueing direction. Boxes show 25/50/75th percentile, whiskers enclose 1.5 * interquartile range, the cross represents the mean and circles show individual data points. Stars '*': simple tests significant at $p<0.05$ and '***' at $p < 0.001$.

2.4 Discussion

To isolate the effects of exogenous processes putatively driven by the motion stream from those of intentional engagement of attention to the motion cues (i.e. endogenous attentional confounds), we asked participants to consider motion as task-irrelevant and to engage instead in an endogenous (and orthogonal) attention task. Our data revealed that this effectively avoided engagement of endogenous attention with the exogenous motion cues, given that motion did not affect the benefits of target perception at the focus of endogenous attention (no evidence for divided endogenous attention between the task and the motion stimuli). Therefore, effects of apparent motion on target processing are interpreted in the context of exogenously driven processes.

Specifically, we tested the interaction between exogenously driven temporal and spatial anticipatory processes in response to apparent motion stimuli by probing the effects of pre-target motion on target discrimination in or out of the motion path, at a rhythmic or arrhythmic rate. The main findings were three fold. First, we found that pre-target motion cues conveyed a benefit for target processing at spatially cued vs. un-cued locations in terms of both accuracy and reaction time. These benefits were however not influenced by the presence or absence of temporally valid cueing, here rhythmic or arrhythmic motion streams. This indicates that the inherently predictive spatial structure of motion exogenously facilitated perception at forthcoming locations along the motion trajectory, yet without strict temporal constraints. Second, we found that the temporal structures of the apparent motion stream conveyed perceptual benefits for target processing. While these perceptual benefits were independent of the presence of spatially valid motion cues, they depended on the direction of motion suggesting hemispheric lateralization. This indicates that spatial and temporal anticipatory processes in response to regular vs. irregular motion streams follows distinct rules by which visual perception is facilitated. Third, our finding that motion stimuli did not influence the effects of endogenous (orthogonal) expectations created by symbolic cueing suggests that exogenously driven anticipatory processes can be independent from intentionally driven (higher-order) processes.

This corroborates and extends previous research on entrainment of anticipatory processes by natural stimuli (such as motion) with a spatiotemporally predictive structure, which by definition convey behavioural relevance. Our findings support the notion that anticipatory sensory processes, while strongly influenced by internal goals likely involving higher level top-down attentional mechanisms (Lakatos et al. 2008), can also be exogenously driven in the presence of external events (Large and Jones 1999; Jones et al. 2002). Importantly, here we reveal for the first time the orchestration of exogenous spatial and temporal anticipatory processes, and show that these processes originate from partially distinct mechanisms (when investigated with behavioural measures). This possibly occurs bottom-up without the recruitment of higher level cognitive resources (see also, Breska and Deouell 2014). Apart from the processing of motion stimuli, such mechanisms may be engaged in speech communication, comprehension and attention, where timing is crucial for predicting internalized regularities of events (for reviews see, Arnal and Giraud 2012; Calderone et al. 2014).

Below, we discuss the dissociation between endogenous and exogenous processes, as well as the mechanisms that may underlie exogenously driven spatial and temporal anticipation and their relation in light of research on apparent motion and attentional cueing.

Behavioural dissociation between endogenous and exogenous attentional processes

The current experimental design successfully dissociated between endogenous and exogenously driven attentional effects. This behavioural independence has been reported before by employing different types of attentional paradigms such as attentional capture and visual search tasks (Pinto et al. 2013), by varying the predictability of spatial cues (Lupiáñez et al. 2004), when contrasting predictive central vs non-informative spatial cueing (Funes et al. 2007), but also in the temporal domain using rhythmic apparent motion (Coull et al. 2000; Rohenkohl et al. 2011). While most of these studies test and contrast endogenous vs. exogenous conditions separately (i.e., different trials, experimental blocks), one behavioural study also manipulated these processes concurrently within one trial (Berger et al. 2005). Similarly to our design, a trial started with an endogenous predictive cue, followed by a single non-predictive transient exogenous cue. This also resulted in independent behavioural effects, suggesting that separate mechanisms may underlie endogenous and exogenous attentional orienting (Berger et al. 2005). Yet, to what extent the underlying neural substrates implicated in endogenous and exogenous attention shifts are also independent or overlapping remains debated. Since this will be further tested and discussed in Chapter 3, the remainder of the discussion is focused on the effects of exogenously driven spatial vs. temporal attention.

Spatial extrapolation exogenously driven by apparent motion stimuli

We found that perceptual processing was clearly enhanced when targets appeared at spatially extrapolated locations in the motion direction, despite the fact that the apparent motion cues were task-irrelevant and non-predictive. This extends prior studies showing perceptual benefits when employing apparent motion stimuli (and also with attentive and/or passive object tracking paradigms), in which the observers traced (covertly) an object while perception of a target was probed in or out of the object’s motion path (Shioiri et al. 2002; Doherty et al. 2005; Hogendoorn et al. 2008; de Graaf et al. 2013). These perceptual benefits are likely conveyed through mechanisms for maintaining and updating the representation of a moving object along an apparent motion trajectory, serving motion extrapolation (Hogendoorn et al. 2008) and interpolation (Shioiri et al. 2000, 2002; Hogendoorn et al. 2008). In apparent motion this occurs even outside of the voluntary attentional focus (Hogendoorn et al. 2008). As an explanatory mechanism for the perceptual benefits, smooth shifts in the attentional focus along the motion path have been suggested, tracking the moving object and predicting future target locations (Cavanagh 1992; Shioiri et al. 2000, 2002). This could either be mediated by conscious prediction or an internal model (Shioiri et al. 2000), updating the motion path intentionally or exogenously. Alternatively, low-level motion processing could explain motion prediction mechanisms. As proposed by Nijhawan (Nijhawan 1994; Khurana and Nijhawan 1995), early visual structures may compensate for neuronal processing delays through extrapolation, attempting to predict future locations of a moving object. The present findings of spatial motion trajectory facilitating perception provide support for exogenous prediction mechanisms. This is also in line with prior findings showing that contrast sensitivity to moving objects is enhanced towards the end of the motion trajectory, interpreted to reflect automatic attention capture and prediction mechanisms (Verghese and McKee 2002), and that motion induces a forward prediction signal (Roach et al. 2011).

Temporal anticipation exogenously driven by rhythmic (versus arrhythmic) apparent motion stimuli is partially independent from spatial extrapolation

We found perception to be modulated by temporal trajectory cueing. Interestingly however, effects of temporal cueing were independent of spatial cueing, i.e. we did not find any synergy/additive effects of temporal (rhythmic) cueing on the spatial cueing benefit with our design. Instead, temporal cueing showed an unexpected pattern (not observed with spatial cueing): it depended on motion direction. That is, rhythmic cueing tended to benefit perceptual processing with rightward motion (relative to arrhythmic cueing), while arrhythmic cueing was associated with better performance in response to leftward motion (as compared to rhythmic cueing). This asymmetrical perceptual benefit driven by temporal cueing may suggest that distinct mechanisms are at play for spatial and temporal prediction. Importantly, their independence implies that these mechanisms do not interact in our design, i.e. at a purely unintentional/exogenous level (when endogenous spatial attention is saturated).

In contrast to our results, a recent series of studies that concurrently manipulated spatial and temporal attention have shown that temporal attention on its own is not effective in modulating visual performance (Rohenkohl et al. 2014) nor in modulating early visual evoked potentials typically associated with spatial attention (Doherty et al. 2005). Instead, these studies provide evidence for synergistic effects of temporal on spatial attention, i.e. for the need of spatial processes to be engaged so that temporal advantages can be expressed (Doherty et al. 2005; Rohenkohl et al. 2014). However, these results are not directly comparable to our findings because of differences in experimental design. Rohenkohl et al. (2014) manipulated temporal and spatial expectations in the endogenous dimension. Doherty et al. (2005) used apparent motion with an intrinsic, spatially and temporally predictive structure but did not control for intentional deployment of attention to these cues. As a consequence, participants may have engaged in endogenous anticipatory processes to deliberately use the apparent motion information for intentionally predicting the forthcoming events. Hence, synergistic interaction between these systems may require endogenous control to be expressed. Similar to our results, Jones (2015) found temporal and spatial cueing to convey independent attentional benefits. However, Jones (2015) studied the interaction between endogenous spatial attention and exogenous temporal expectations using symbolic spatial and central flicker cues, i.e. crossing the endogenous/ exogenous divide, again limiting comparison to our results. The discrepancy between our own and previous findings hence suggests that anticipatory processes in the spatial and temporal dimension may differ as to whether the cue is rhythmic or symbolic, as previously suggested (Coull and Nobre 1998; Triviño et al. 2010, 2011, Rohenkohl et al. 2011, 2014; Breska and

Deouell 2014), as well as whether the processes reflect intentional vs. exogenous mechanisms, as suggested here.

Possible neuronal substrates of dissociated exogenous spatial and temporal anticipation with apparent motion stimuli

It is well established that the left hemisphere is dominant for processing temporal information, whereas the right hemisphere is more specialized in processing spatial information (Kinsbourne 1977; Bradshaw and Nettleton 1981; Hammond 1982; Nicholls 1996). In line with this view, previous studies have associated temporal attention with left hemispheric activity (Coull and Nobre 1998; Doherty et al. 2005). Coull and Nobre (1998), for example, observed left intraparietal and premotor cortex activity for temporal orienting (i.e. in areas engaged in motor planning and attention (Rushworth et al. 2001) vs. right intraparietal activity for spatial orienting. Doherty et al. (2005), who found temporal attention to be associated with motor response-related EEG components, again interpreted this to reflect the engagement of left hemispheric resources with temporal attention deployment (in line with (Coull and Nobre 1998)). Our finding of a left-right asymmetry showing that perception tends to be enhanced by rhythmic (as compared to arrhythmic) motion but only for the rightward motion cues may hence suggest for the first time that hemispheric (left lateralized) differences may also come into play for exogenous temporal anticipatory mechanisms. By extension, our finding that perception was enhanced for arrhythmic (as compared to rhythmic) leftward motion may suggest a right hemispheric process. However, these findings on asymmetry should be interpreted with caution given that they were unexpected. In this light, it is of interest to note that most previous studies reporting perceptual benefits from temporal cueing with pre-target motion paradigms only employed rightward motion (albeit for testing more endogenous attention) (Doherty et al. 2005;

Rohenkohl and Nobre 2011a; Rohenkohl et al. 2011). One exception is De Graaf et al. (2013), who used a symmetric design (including left and rightward motion) but did not report an asymmetrical benefit in favour of rhythmic rightward motion (note that no arrhythmic condition was tested). However, the results of De Graaf et al. (2013) are likely to be confounded by intentional prediction mechanisms, which were not controlled for by design in contrast to the present study. Hence, comparisons to prior studies are limited and follow-up experiments are needed to confirm the hemifield asymmetry we found.

For a possible explanation of the observed hemifield asymmetry, we speculate that the entrainment of the attention focus to rhythmic cues may draw on similar resources as entrainment to rhythmic (and therefore predictive) speech signals (for review see Arnal & Giraud, 2012), for which a left hemispheric dominance, albeit not exclusively, can be assumed (Gross et al. 2013; Park et al. 2015). Alternatively, directional preferences for rightward motion stimuli (Halpern and Kelly 1993; Müller and von Mühlenen 1996), or a larger rightward shift of attention for rightward (but not leftward) motion (Kerzel 2003), may be due to internalized/learned reading habits and thus preferential visual rightward scanning. However, such a bias should be observed not only for temporal but also spatial processes, which was not the case here. Indeed, research on participants with native languages read/written from left to right (e.g. English) has shown that their perceptual span is asymmetrically shifted to the right around the fixation point (Rayner et al. 1980), while this effect is reversed for participants with native languages read/written from right to left (Pollatsek et al. 1981; Nachshon 1985). Thus, a bias from reading habits is unlikely to explain the dissociation we observe here between temporal and spatial anticipatory processes.

Conclusion

Prior findings suggest synergistic effects of endogenous temporal and spatial expectations (Coull and Nobre 1998; Doherty et al. 2005; Rohenkohl et al. 2014). In contrast, we here controlled for higher level (top-down) processes and found evidence for behaviourally dissociated processes of temporal and spatial anticipation when exogenously driven by motion stimuli. This establishes differences between endogenously and exogenously driven anticipatory mechanisms in response to predictive stimuli.

The implemented apparent motion paradigm, in combination with simultaneously presented endogenous cueing, effectively dissociated and controlled for potential endogenous engagement during exogenously driven attention shifts. I conclude that it is important to control for the different types of anticipatory processes (endogenous vs. exogenous) in order to better understand the interplay between the various top-down and bottom-up mechanisms of sensory prediction, and their effects on perception. Particularly, to better understand whether the behavioural dissociation between endogenous and exogenous visuospatial attention shifts revealed here are also reflected in separate and/or overlapping neuroanatomical substrates, is focus of the next chapter (Chapter 3).

Chapter 3

Interfering with dorsal and ventral attention network nodes during endogenous versus exogenous spatial orienting with Transcranial Magnetic Stimulation

3.1 Introduction

Even when engaged in exploring visual scenes based on current internal goals, we are required to concurrently react to sensory events that can suddenly occur in our environment and that may be task-irrelevant. It has been suggested that a partially segregated large-scale dorsal and ventral fronto-parietal network plays a crucial role in the orchestration of these processes, particularly in directing visuospatial attention when endogenously vs. exogenously driven (for review see Corbetta & Shulman 2002). While dorsal parietal and frontal regions, including the intraparietal sulcus (IPS) and frontal eye fields (FEF), have been associated with endogenous deployment of visuospatial attention, a ventral temporo-parietal and frontal network, including the ventral frontal cortex (VFC) and temporo-parietal junction (TPJ), have been related to exogenous visuospatial orienting (Corbetta and Shulman 2002; Kincade et al. 2005). In accordance with this dichotomy, numerous functional magnetic resonance (fMRI) studies have revealed evidence for a functional dissociation between dorsal and ventral attentional networks (Corbetta et al. 2000; Shulman et al. 2003; Hahn et al. 2006; Hu et al. 2009; Natale et al. 2009; Asplund et al. 2010), which can (partially) overlap depending on task settings, task demands and temporal dynamics of the task (Corbetta & Shulman 2002; Kincade et al. 2005; Peelen et al. 2004; Asplund et al. 2010).

Transcranial magnetic stimulation (TMS) on the other hand has revealed mixed results as to a functional dissociation of these networks. Although few TMS studies directly compare the dorsal and ventral system as to their implication in endogenous vs. exogenous attention, there is some agreement for a functionally distinct specialisation of these networks in attentional processes. For example, it has been shown that only right TPJ stimulation (as compared to right FEF stimulation) modulated attentional (re-)orienting towards distractors (Chang et al. 2013). In terms of feature-based attention, a TMS study has revealed distinct contributions of right IPS and right TPJ in attentional capture vs. suppression of distractors (Painter et al. 2015). Dissociated involvement of other sub-regions of the posterior cortex in attention has also been identified, where TMS of the supramarginal gyrus affected spatial attention only, and TMS of the anterior intraparietal sulcus interfered with spatial and feature-based attentional selection (Schenkluhn et al. 2008). Chica et al. (2011) instead tested the involvement of both dorsal and ventral network nodes (i.e., right IPS and right TPJ) in classical visuospatial cueing paradigms. They reported both IPS and TPJ to be implicated in exogenous attention (for inhibition of return specifically; see also Bourgeois et al. 2013), whilst IPS (but not TPJ) was associated with endogenous control (Chica et al. 2011). This finding is further supported by studies that combine fMRI-TMS and TMS-EEG, revealing that right IPS may serve as a functional node for coordinating both endogenous control and exogenously triggered attention shifts (Heinen et al. 2011; Capotosto, Babiloni, et al. 2012; Capotosto, Corbetta, et al. 2012).

Whilst these studies employed typical non-predictive cues to trigger exogenous attention shifts and predictive cues to engage endogenous attention control, their experimental designs invariably test each type of attention in separate experimental sessions (or block designs). However, as discussed in Chapter 2, when attempting to test exogenous shifts in particular, it is difficult to avoid higher-order cognitive anticipation effects, likely engaging endogenous attention processes that can modulate exogenous capture (see also, Folk et al. 1994; Ansorge & Heumann 2003; Berger et al. 2005; for review see, Ruz & Lupiáñez 2002). That is, participants may intentionally or unintentionally adopt strategies to predict events based on the exogenous cue information (even if not predictive). Hence, this endogenous engagement with the exogenous cues likely confounds the to-be-isolated, exogenous mechanisms in terms of behaviour but also (co)-activated attentional networks, unless controlled for (see also, Breska and Deouell 2014). Here, we sought to test to what extent there is a segregation, vs. an overlap, of the dorsal and ventral attention network nodes, while controlling for confounding effects of endogenous on exogenous attention processes. To this end, we combined TMS with the same visuospatial attention paradigm as implemented in the previous chapter. In this paradigm, endogenous expectations are created by employing symbolic spatial cues that are predictive of the upcoming target position (left vs. right). Simultaneously, non-predictive and task-irrelevant apparent motion cues are presented in the background moving towards the same target positions, triggering exogenous attention shifts (leftward vs. rightward path extrapolation). The design avoids endogenous engagement of attention with the exogenous motion cues, due to the need to engage voluntary attention elsewhere (i.e. in response to the symbolic cues). The paradigm results in perceptual benefits from both endogenous and exogenous cueing which are independent, hence dissociating endogenous control from exogenous attentional processes and vice versa.

To investigate to what extent endogenous and exogenous visuospatial orienting processes have common vs. dissociated neuronal substrates, we interfered with the nodes of the dorsal and ventral attention network, using neuronavigated double-pulse TMS over either the right IPS (rIPS) or right TPJ (rTPJ) or using sham-TMS, while participants performed the above task. We sought to: Firstly, replicate our previous findings from Chapter 2 in the absence of TMS-interference (i.e. in the sham-TMS condition). Secondly, identify shared or dissociated effects of active-TMS on endogenous vs. exogenous attention processes. More specifically, we hypothesised that if the two attention systems are distinct, endogenous cueing benefits should be abolished during active rIPS-TMS (as compared to active rTPJ-TMS), whereas exogenous cueing benefits should be abolished during active rTPJ-TMS (as compared to active rIPS-TMS). Alternatively, exogenous attention may be abolished during both, active rTPJ- and/or rIPS-TMS, supporting common/overlapping substrates (in line with, Chica et al. 2011; for review see Vossel et al. 2014) after controlling for confounding effects of endogenous and exogenous attentional processes.

3.2 Methods

Participants

A total of twenty-two healthy adult volunteers (average age ± SD: 23.9 ± 4.5, 19 female, 3 male) participated in the experiment. All participants had no previous psychiatric or neurological history, were right handed and had normal or corrected-to normal vision. Before taking part in the experiment, all participants provided written informed consent. None had contraindication to TMS (established with a safety questionnaire (Rossi et al. 2009)). Ethical approval was provided by the College of Science and Engineering Ethics Committee of the University of Glasgow.

Two participants were excluded from further testing after the first session (task-familiarization) as they experienced TMS discomfort. Three further participants had to be excluded from the statistical analysis after completion of the second session (the actual data recording session): one because of an experimenter recording error, one as more than 50% of the responses had been missed and one because of performance at chance level. Hence a total N of 17 was included in the statistical analysis.

Apparatus

The experiment was presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) on a LCD monitor (ASUS ROG Swift PG278Q, ©ASUSTeK Computer Inc.) with 100Hz refresh rate and a spatial resolution of 1280 x 1024. A chin rest maintained a constant viewing distance of 35cm to the screen. A CCTV camera was used to monitor eye movements to ensure participants maintained fixation during the task (covert attention shifts). A TMS stimulator (Magstim Rapid^2) in combination with a figure of 8-shaped coil (Double 70mm Alpha Coil) (The Magstim Company Ltd, UK) was used for double-pulse delivery. TMS Navigation (Brainsight® TMS, Rogue Resolutions Ltd) was used to determine stimulation locations, to guide the placement of the TMS coil and to allow online tracking for minimizing deviations from the optimal site of stimulation during the experiment.

Stimuli and Task

The same visuospatial attention paradigm using simultaneously presented endogenous symbolic cueing and exogenous apparent motion cueing was implemented as in Chapter 2 (originally adapted from de Graaf et al. 2013). However, note that here the main interest was the perceptual benefit of spatial orienting only, hence the temporal factor was excluded (no arrhythmic condition). Identical to the previous paradigm, a matrix of 5x9 circles (gray placeholders) together with a central fixation cross (white) was presented at all times on a black background (**Figure 6**, **A**). The diameter of the placeholders was 1.2cm, with a vertical distance of 3cm and a horizontal distance of 3.4cm. In order to manipulate endogenous attention shifts, central symbolic cues consisting of arrows were presented on top of the fixation cross (**Figure 6, B**). These arrows were predictive as to the upcoming target location (i.e., 75% cue-validity at the left or right target location). Participants were asked to covertly shift attention towards the indicated target position, while keeping their fixation at the central fixation cross. Simultaneously to endogenous cueing, and in order to manipulate exogenous attention, five placeholders from the row below the fixation cross flashed briefly (for 30ms) in succession, starting with the rightmost circle and ending at the central circle directly underneath the fixation cross, or starting with the leftmost circle and ending at the same central circle. These motion stimuli flashed rhythmically at 4Hz, giving the impression of apparent motion (i.e., at a stimulus-onset-asynchrony (SOA) of 250ms). This was followed by a target presented for 10ms (1 refresh rate) in the adjacent placeholders, either in or out of the motion path (i.e., to the left or right of the last apparent motion stimuli). Importantly, target appearance in the motion path (congruent) or out of the path (incongruent) was equally probable (i.e., the motion path was uninformative as to the upcoming target locations). The instructions given to the participants declared these exogenous motion cues as task-irrelevant.

The target consisted of a ‘+’ or ‘x’ and participants were asked to discriminate the target as accurately and rapidly as possible by button press (keys: 1 for ‘x’, 2 for ‘+’; counterbalanced across participants). The engagement of endogenous and exogenous attention was indexed by the advantage of target discrimination at the cued vs. the un-cued position and at the motion-cued vs. the uncued position respectively. As shown in Chapter 2, this experimental design allows to simultaneously manipulate both endogenous and exogenous attention shifts. For the timeline of events within a trial, see **Figure 6B** below.

In order to interfere with ongoing attention shifts, a double-pulse TMS (100ms inter-pulse-interval) was delivered between the last motion stimuli and target onset (specifically at -175ms and -75ms prior to target presentation) over either the right intraparietal sulcus (rIPS), right temporo-parietal junction (rTPJ) or sham (block design, counterbalanced across participants; see TMS procedure below for details).

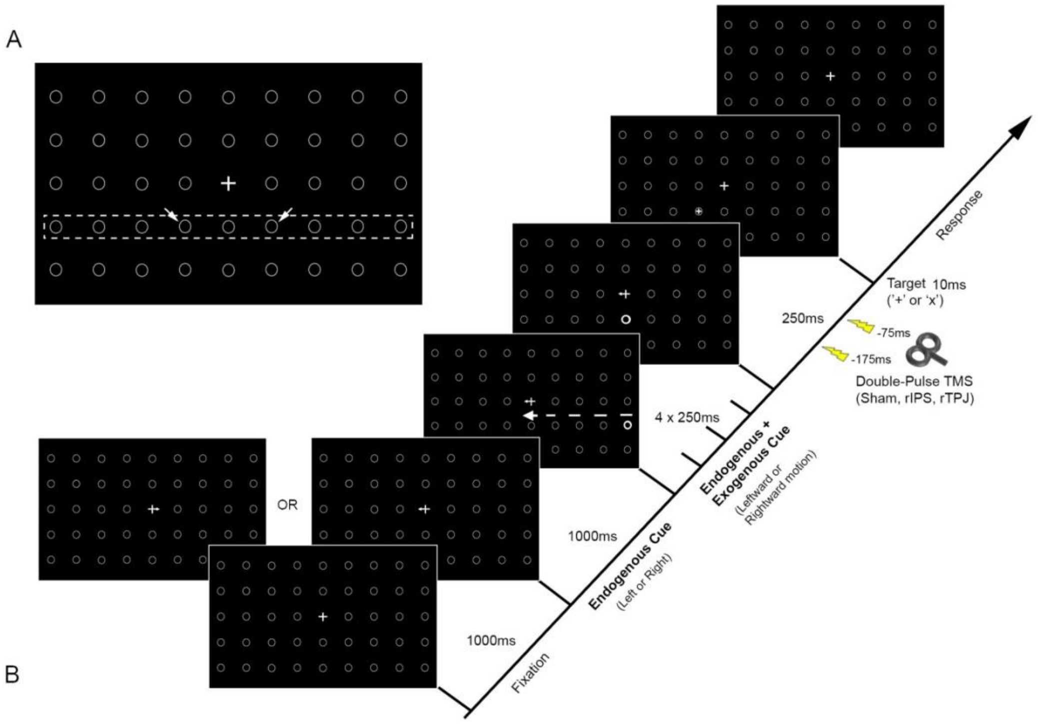


Figure 6: Schematic representation of the experimental design. (A) Fixation cross and placeholders. Dashed rectangle and arrows drawn for illustrative purpose. Arrows indicate the two possible target locations in the left and right visual field. Dashed rectangle indicates the row of placeholders where the apparent motion stimuli were presented. (B) Example trial sequence (note that the timeline is not drawn to proportion).

Trials started with a fixation cross (1000ms), followed by an endogenous cue (left or right symbolic arrow; 75% predictive) indicating the probable target location (here left cue). Exogenous cueing consisted of apparent motion stimuli (leftward or rightward). Five adjacent stimuli briefly flashed successively from gray to white at a rate of 4Hz (4 inter-flash intervals of 250ms) giving the impression of apparent motion (50:50 non-predictive as to upcoming target location; here dashed arrow drawn for illustration purpose showing leftward motion). After the last motion stimulus and before target presentation, double pulse TMS was delivered (100ms inter-pulse interval) over either right intraparietal sulcus (rIPS), right temporo-parietal-junction (TPJ) or sham. The target consisted of a '+' or 'x' and participants were asked to discriminate the target as accurately and rapidly as possible by button press.

Experimental procedure

Participants were asked to visit the laboratory on two separate days for two sessions. Session one served for training of the task and familiarization with the experiment. Participants performed two short training blocks (covert attention shifts with target discrimination). The first training block consisted of endogenous left and right cue trials only, during which participants were instructed to deploy attention covertly and to discriminate targets at both cued and uncued positions (20 trials). In the second block, exogenous motion cues were added but participants were informed that these stimuli were task-irrelevant (32 trials). These training blocks ensured participants understood the concept of the task (covert attention shifts without eye movements). In addition, participants were familiarized with the TMS (namely the TMS sensation and click noise). This session lasted for approximately 40 minutes. Session two consisted of the actual experiment. First, visual targets were individually adjusted to near-threshold levels (80% discrimination rate) via modulation of the luminance contrast with the background, to avoid ceiling or flooring effects. This was followed by the determination of the individual TMS resting motor thresholds and co-registration of the participants head position with the anatomical MRI scan for TMS neuronavigation (see below for details on TMS procedure). The experiment consisted of a total of 480 trials (20 trials x 2 endogenous cues (left and right arrows) x 2 exogenous cues (leftward and rightward motion) x 2 target locations (left and right visual field) x 3 TMS locations (Active-TMS over rIPS and rTPJ and sham-TMS). Active-TMS and sham-TMS trials were distributed across 3 experimental blocks (160 trials per block) with breaks every 80 trials to avoid fatigue (i.e. approximately every 6 minutes). The order of TMS and sham blocks were randomized and counterbalanced across participants. All trials within each block were randomized and presented in an intermixed order. The second session lasted for approximately 1.5 hours. The perceptual measures of interest were discrimination accuracy and reaction time.

TMS and neuronavigation procedure

Resting motor threshold (rMT) was determined over the right motor cortex to individually adjust TMS-intensity during the task (set to 100% individual rMT; average rMT ± SD: 53.3% ± 7.0 of maximum stimulator output). Individual anatomical T1 weighted MRI scans were acquired at the Centre for Cognitive Neuroimaging (CCNi) (University of Glasgow) using a 3T MR scanner (Magnetom Trio Siemens, Erlangen, German) and a magnetiziation-prepared rapid gradient echo sequence (MPRAGE) (Parameters: voxel size = 1 x 1 x 1mm; TR = 1900ms, TE = 2.52ms; inversion time (IT) = 900ms; slice thickness = 1mm; FoV = 256mm; matrix size = 256 x 265; excitation angle = 9°; 192 axial slices). The TMS target sites were based on Talairach coordinates (group averages) obtained from previous fMRI-guided TMS studies on orienting of visuospatial attention: rIPS (x = 16; y = -63; z = 47) and rTPJ (x = -51; y = -51; z = 26) (Kincade 2005; Chica et al. 2011; Bourgeois et al. 2013) (**Figure 7**). Brainsight® TMS Navigation was used for TMS coil positioning. rIPS and rTPJ coordinates were first projected on each individual reconstructed 3D anatomical MRI scan (i.e., the stimulation target coordinates were de-normalized for rIPS and rTPJ respectively and projected into native space for each individual anatomical brain scan). The anatomical MRI scans were then co-registered with the participant’s head to allow for precise positioning and online guiding of the TMS coil. For Active-TMS, the coil was held tangentially to the skull and was oriented such that the coil-centre was overlaying the target site, and the TMS-induced current was running perpendicular to the stimulated gyrus. For sham-TMS, the coil was turned perpendicular to the surface of the participant's head (between rIPS and rTPJ target locations), such that the current was discharged away from the cortex (**Figure 7** shows one example participant).

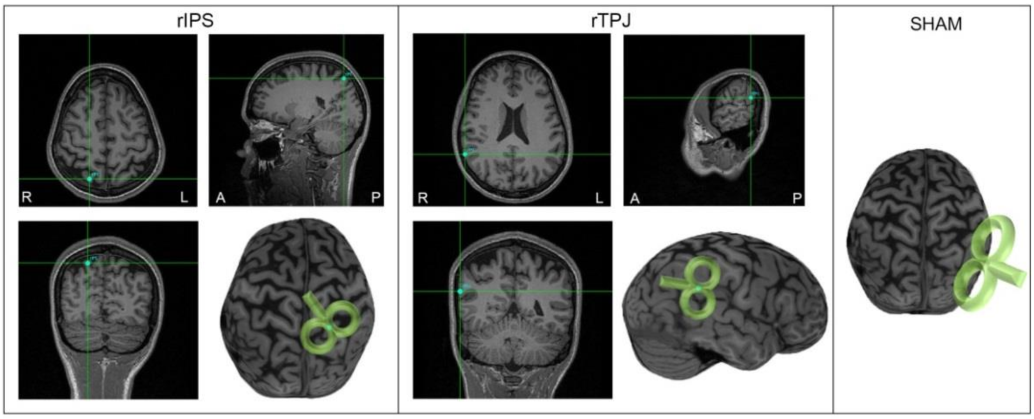


Figure 7: TMS coil orientation and localization of right intraparietal cortex (rIPS), right temporo-parietal junction (rTPJ) and sham stimulation for an example participant. (R=Right; L=Left; A=Anterior; P=Posterior). Slices represent sagittal-, transverse- and coronal- views (T1 structural MRI scans) as well as 3D surface reconstructions of the brain.

Statistical analysis

Discrimination accuracy (performance accuracy) was subjected to a fully within-subject (repeated-measure) analysis of variance (ANOVAs) with the factors Stimulation site (sham- vs. rIPS- vs. rTPJ-TMS), Endogenous cues (Left vs. Right), Exogenous cues (Leftward vs. Rightward motion) and Target Location (Left vs. Right visual field). Likewise, reaction times were subjected to the same ANOVA design, but are not further described here and instead added as an appendix to this chapter, as there were no effects of stimulation on neither endogenous nor exogenous cueing benefits/costs in the RT data ($F(2, 32) < 0.6$, $p > 0.5$, $\eta p^2 < 0.04$) (see 3.5 Appendix).

For performance accuracy, main effects and interactions of interest were followed up with simple tests. Since our expected cueing effects were derived from the behavioural results obtained previously (Chapter 2), we planned one-sided simple tests.

Additionally, given this prior evidence, we ran a Bayesian factor analysis (according to Verhagen and Wagenmakers 2014) to provide additional information on how strong the evidence was for the alternative (H_1) or the null hypothesis (H_0). This was tested separately for sham- and active-TMS: First, in accordance with the Bayesian replication test, we tested whether the effects of sham-TMS were similar or different to the cueing effects observed in the original experiment (Chapter 2). To test this, the original experiment was re-analysed by conducting a Bayesian paired-samples T-test (two-sided, default Cauchy prior distribution centred at zero, width=0.36) for each main effect of interest. The resulting posterior distributions served as informed prior distributions to establish whether sham-TMS resulted in a successful replication (i.e., H_0: no replication/cueing effects absent; H_1: replication/cueing effects present). The resulting replication posterior distributions (i.e., the accumulated evidence brought by the data from the original experiment and sham-TMS), served as an informed prior to test whether the cueing effects were similar or different during active-TMS. Specifically this means, if active-TMS has a detrimental effect on performance, we expected evidence for H_0 (cueing effects absent). We report Bayes factors (BF) reflecting the probability of the data given H_r relative to H_0 (i.e., $BF < 1/3$ strongly favour H_0; $BF > 3$ strongly favour H_r; $1/3 < BF < 3$ indicates data insensitivity) (Verhagen and Wagenmakers 2014; Dienes and Mclatchie 2017). The ANOVA and Bayes factor analyses were performed using JASP (JASP Team 2018; Version 0.8.2; open source; https://jasp-stats.org/).

3.3 Results

Endogenous cueing benefits on target discrimination: effects are present during Sham-TMS and unaffected by Active-TMS over rIPS- or rTPJ.

Endogenous cueing led to the expected benefit for discriminating targets at cued vs. uncued positions, as revealed by a significant 2-way interaction of Endogenous Cueing (left vs. right cue) x Target Location (left vs. right visual field) (F(1,16) = 10.90,p = 0.005, $\eta p^2 = 0.41$) (**Figure 8** A, left panel). There was a higher accuracy for discriminating validly as compared to invalidly cued target locations for both the left visual field (t(16) = 2.66 , p = 0.009, Cohen's d = 0.64), and the right visual field (t(16) = -.56, p = 0.011, Cohen's d = -.62). Notably, this endogenous cueing benefit did not depend on the TMS conditions, i.e. was not differentially affected by Sham-, rIPS- or rTPJ-TMS (no 3-way interaction of Stimulation Site x Endogenous Cueing x Target Location: F(2,32) = 0.16, p = 0.85, $\eta p^2 = 0.01$; see **Figure 8** A, right panels).

These findings were supported by the Bayesian analysis (BF-analysis), showing substantial evidence for a replication (H_1: cueing effects present) for both the left visual field and right visual field effects ($BF_{10} > 9$) across sham- and active-TMS, i.e. averaged across conditions did not annihilate any VF effect (stimulation conditions collapsed, see Endogenous Cueing; Overall average in **Table 1**). When considering each stimulation condition separately (i.e., sham-, rIPS-, rTPJ-TMS), there was evidence for a replication of the cueing effects (H_1) in both visual fields during sham-TMS ($BF_{r0} > 5$). During active-TMS, there was evidence for H_1 in the right visual field ($BF_{10} > 3$), while the data were insensitive for either hypothesis in the left visual field ($BF_{r0} < 1$ but > 1/3) (Endogenous cueing; see active-TMS in **Table 1**).

Thus, taken together, the results from the classical ANOVA analysis and evidence revealed by the BF-analysis indicate that the endogenous cueing benefits did not show a statistically different pattern across the three stimulation conditions. This speaks in favour of maintained/unaffected endogenous cueing benefits across sham- and active-TMS.

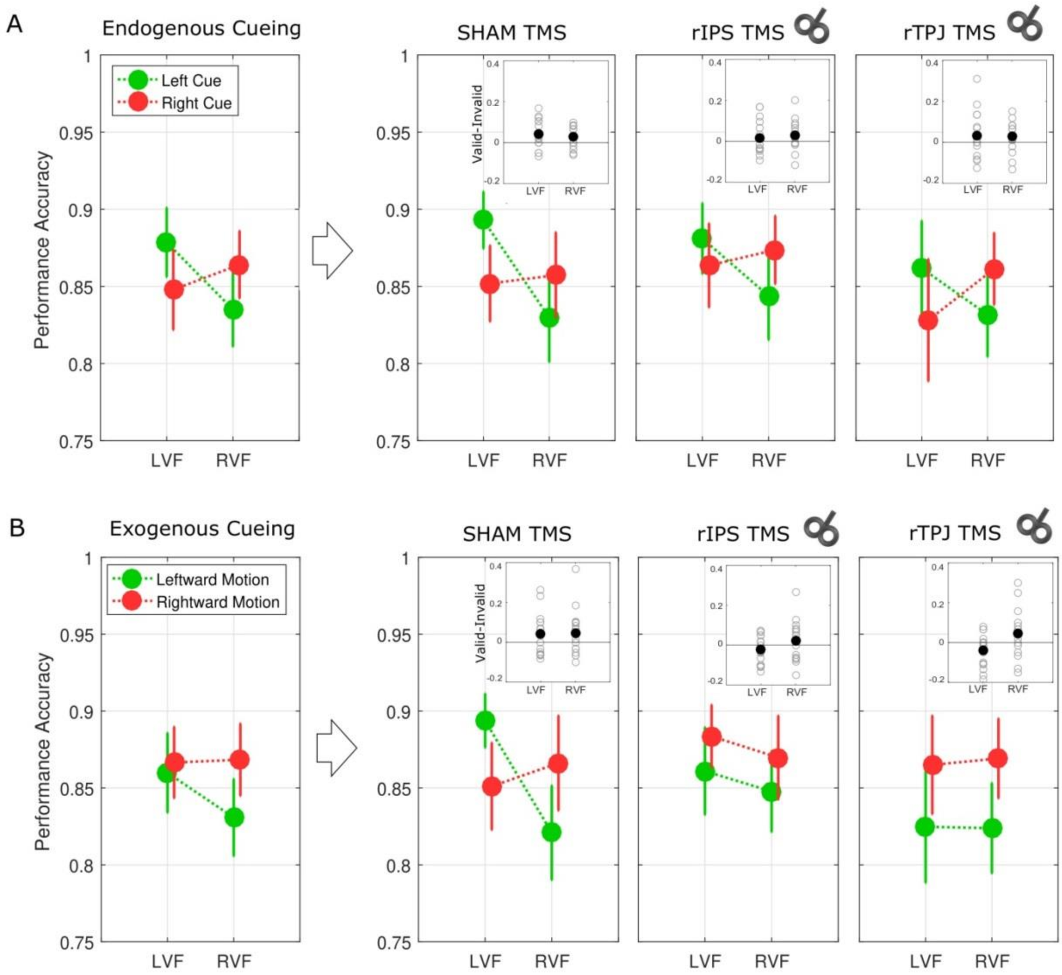


Figure 8: Performance accuracy as a function of cueing type (endogenous vs. exogenous) and TMS conditions (sham vs. rIPS vs. rTPJ). (A) Left panel: Grand averaged performance during endogenous cueing (left or right cue) as a function of target location in the left visual field (LVF) and right visual fields (RVF) illustrating endogenous cueing benefits. Right panels: These benefits (2-way interaction) were independent of the TMS conditions (sham, rIPS, rTPJ) i.e., there was no 3-way interaction. (B) Identical to (A) but for exogenous cueing. Exogenous cueing benefits depended on the TMS stimulation condition (3-way interaction). The error bars indicate the standard error of the means (± SE). Subplots show pairwise differences of the individual participants (gray circles) and the grand average (solid black circles) for valid minus invalidly cued targets in the LVF and RVF respectively, where positive values indicate a cueing benefit (higher accuracy) and negative values a disadvantage (lower accuracy).

Exogenous cueing benefits on target discrimination: effects are abolished during Active-TMS over rIPS- and rTPJ

Unlike the endogenous cueing benefits, we found the exogenous benefits to be affected by active-TMS (**Figure 8** B, right panels). Cueing effects depended on TMS conditions (marginally significant 3-way interaction of Stimulation Site x Exogenous Cueing x Target Location: F(2,32) = 3.10, p = 0.059, $\eta p^2 = 0.16$) (**Figure 8** B, right panels), while no overall effect of exogenous cueing on target discrimination was observed (no overall Exogenous Cueing x Target Location interaction: F(1,16) = 1.33, p = 0.27, $\eta p^2 = 0.077$) (**Figure 8** B, left panel). Following-up the 3-way interaction, we first established that exogenous cueing benefits were present during sham-TMS. The corresponding 2-way interaction of Exogenous Cueing x Target Location was significant (sham-TMS: F(1,16) = 5.94, p = 0.027, $\eta p^2 = 0.271$), explained by a higher accuracy for targets appearing in- as compared to out- of motion trajectory in both the left visual field (t(16) = 1.75, p = 0.050, Cohen's d = -0.42), and the right visual field (t(16) = -1.65, p = 0.059, Cohen's d = 0.4). This was also supported by the BF-analysis, showing that during sham-TMS there was evidence for a replication of cueing effects for both, the left visual field and right visual field ($BF_{r0} > 3$; Exogenous Cueing; see sham-TMS, **Table 1**). In contrast, during active-TMS, the 2-way interactions of Exogenous Cueing x Target Location were absent for both rIPS-TMS (F(1,16) < 0.001, p = 0.98, $\eta p^2 < 0.0001$) and rTPJ-TMS (F(1,16) = 0.016, p = 0.90, $\eta p^2 = 0.001$). This confirms that exogenous cueing benefits were only present during sham-TMS, but abolished during both active-TMS conditions.

Interestingly, the absence of the 2-way interactions during active-TMS appeared to be driven primarily by an impaired modulation of exogenous cueing in/towards the left visual field. As corroborated by follow-up simple tests, this translated in a lack of cueing benefits for LVF-targets appearing in the motion trajectory (i.e., leftward motion) as compared to out of the motion trajectory (i.e.

rightward motion) (see **Figure 8** B, rightmost two panels: relative leftward motion cueing disadvantage for LVF targets), which was observed for both rIPS-TMS (LVF: $t(16) = 1.31$, $p = 0.89$, Cohen's $d = 0.3$) and rTPJ-TMS (LVF: $t(16) = 2.05$, $p = 0.97$, Cohen's $d = 0.4$). Also note that the effect sizes for LVF discrimination were reversed by active-TMS (Cohen's $d > 0.3$) as compared to sham-TMS (Cohen's $d = -0.42$). In contrast, cueing benefits during active-TMS appeared qualitatively unchanged in the RVF (rTPJ-TMS, RVF: $t(16) = 1.59$, $p = 0.07$, Cohen's $d = 0.36$; rIPS-TMS, RVF: $t(16) = 0.92$, $p = 0.19$, Cohen's $d = 0.22$) as compared to sham-TMS (Cohen's $d = 0.4$). Importantly, the BF-analysis further supported this finding by revealing evidence for H_0 (i.e., evidence against exogenous cueing effects) during both active-TMS conditions in the LVF ($BF_{10} < 1/3$) but not the RVF ($BF_{10} > 1$ but < 3) (Exogenous Cueing; see active-TMS, **Table 1**). In fact, this lack of cueing benefit in the LVF was 8.3 times more likely during IPS-TMS and 14.29 more likely during TPJ-TMS under H_0 than under H_1. While the Bayes factor for the RVF effect showed data insensitivity when broken down by active-TMS conditions, the evidence against cueing effects during active-TMS in the LVF supports our finding that the modulation of exogenous cueing towards/in the left visual field was impaired by rIPS- and rTPJ-TMS.

Hence, taken together, the results of the classic ANOVA analysis and the evidence revealed by the BF-analysis indicate that active-TMS affected performance by abolishing the exogenous cueing benefits and this effect appeared to be visual field specific (lateralised to the LVF).

Independence between endogenous and exogenous cueing

In line with the original findings from Chapter 2 using the same task design but without TMS, we found no interaction between endogenous and exogenous cueing, as shown by the absent 3-way interaction of Endogenous Cueing x Exogenous Cueing x Target Location ($F(1,16) = 0.82$, $p = 0.38$, $\eta p^2 = 0.05$). This indicates that the design effectively isolates endogenous from exogenous shifts of attention and that any benefits resulting from exogenous cueing can be interpreted to reflect automatically driven processes, with no contamination of deployment of endogenous processes in response to the exogenous cues. By extension, this also suggests that participants followed the instructions and engaged with the task (endogenous shifts of attention), whilst ignoring the exogenous cueing (as by design exogenous cues were task-irrelevant and non-predictive). Also note that the absence of the 3-way interaction was independent of stimulation condition (no 4-way interaction of Stimulation x Endogenous Cueing x Exogenous Cueing x Target Location; $F(2,32) = 0.26$, $p = 0.77$, $\eta p^2 = 0.02$).

Table 1: Bayes Factor Analysis for Endogenous and Exogenous cueing

	Endogenous Cueing				Exogenous Cueing			
	δ Value		$BF_{1\|0}$		δ Value		$BF_{1\|0}$	
	LVF	RVF	LVF	RVF	LVF	RVF	LVF	RVF
Original Exp. (Chapter 2)	.65	-.34	-	-	-.30	.38	-	-
Replication*								
Overall average	.65	-.43	**16.15**	**9.25**	-.21	.42	**.31**	**4.53**
Sham-TMS	.64	-.40	**11.88**	**5.91**	-.33	.40	**3.44**	**3.07**
Active-TMS**								
rIPS-TMS	.51	-.41	*.45*	**3.65**	-.22	.36	**.12**	*1.10*
rTPJ-TMS	.55	-.40	*.98*	**3.26**	-.20	.40	**.07**	*2.93*

Note: Bayes Factor (BF) > 3 indicates strong evidence in favour of the alternative hypothesis (**marked in bold**), BF < 1/3 can be considered as strong evidence in favour of the null hypothesis (**also marked in bold**), whereas 1/3 < BF < 3 indicates data insensitivity in support for neither hypothesis (***marked in italic***) (Verhagen & Wagenmakers 2014; Dienes 2014).Original experiment: Bayesian paired-samples T-Test (two-sided test, default Cauchy prior centred at 0, width=0.36). *Replication of Sham-TMS: Bayesian paired-samples T-Test (one-sided test; posterior distributions obtained from the Original Exp. served informed priors). **Active-TMS: Bayesian paired-samples T-Test (one-sided test; posterior distributions obtained from Sham-TMS served as informed priors). δ-Value = effect size; $BF_{1|0}$ = Bayes Factor; LVF = Left Visual Field; RVF = Right Visual Field; rIPS = right inferior-parietal sulcus; rTPJ = right temporo-parietal junction.

3.4 Discussion

The present results provide evidence for differential neural substrates underlying endogenous and exogenous attention orienting, but no evidence for an isolated implication of the dorsal (rIPS) and ventral attention system (rTPJ) in endogenous and exogenous attention orienting respectively. There was no evidence for TMS to affect endogenous orienting, but evidence for impaired exogenous orienting by TMS over both rIPS and rTPJ. Unlike previous TMS studies (Chica et al. 2011; Capotosto, Corbetta, et al. 2012), we tested both types of attention simultaneously which allowed us to exclude, by experimental design, the confound of potential endogenous engagement during exogenous orienting. Hence, the implication of the dorsal (rIPS) system in exogenous orienting was unlikely due to unintentional co-activation of endogenous processes. Furthermore, our results revealed that active-TMS over rIPS and rTPJ regions induced left lateralised effects, in line with previous findings showing contralateral impairment after right hemispheric TMS over the posterior parietal cortex (Pascual-Leone et al. 1994; Fierro et al. 2000; Müri et al. 2002; Thut et al. 2005; Dambeck et al. 2006). These results are discussed below for exogenous and endogenous processes of attention orienting separately.

Dorsal- and ventral attention network nodes both drive exogenously driven attentional orienting

Our findings provide further evidence of rTPJ being causally involved in exogenously driven shifts of attention as exogenous cueing benefits were abolished by rTPJ-stimulation. This supports the neuroanatomical model that the ventral fronto-parietal network is implicated in exogenous orienting (Corbetta and Shulman 2002; Corbetta et al. 2008) and is in line with previous findings showing that rTPJ is particularly important for detecting novel and behavioural relevant stimuli (e.g., Asplund et al. 2010).

Most importantly though, our results revealed that rIPS was also engaged in exogenous orienting, as interferences with TMS abolished the respective cueing benefits. At first sight, this appears to contradict the evidence of rIPS being a key node predominantly associated with endogenous (top-down) modulatory influence on visual activity, as revealed across different neuroimaging modalities including fMRI (Bressler et al. 2008; Vossel et al. 2012), fMRI-TMS (Ruff et al. 2008), MEG (Siegel et al. 2008) and EEG-TMS (Capotosto et al. 2009; Capotosto, Babiloni, et al. 2012). Interestingly though, some studies have reported an association of the right IPS with the exogenous attention system using TMS (Chica et al. 2011), EEG-TMS (Capotosto, Corbetta, et al. 2012) or fMRI-TMS (Heinen et al. 2011), in line with our results. In contrast to our experimental design, however, these studies have always tested exogenous attention in isolation. As a consequence, participants may have (unintentionally or intentionally) engaged higher-order endogenous control mechanisms, which are difficult to dissociate from exogenous processes unless controlled for by design. This in turn may have led to a co-activation of rIPS in addition to rTPJ, and to a contribution of endogenous attention to the cueing benefit. Thus, it is conceivable that endogenous (top-down) control has confounded exogenous attentional processes in these studies, i.e. that a combination of both attentional processes were at play. For example, the study by Chica et al. (2011) employed a classical exogenous visuospatial cueing paradigm. The results showed that after long cue-target intervals (at 800ms), TMS over both rIPS and rTPJ network nodes affected exogenous cueing. Whilst excluding possible endogenous attention confounds on exogenous processes in the current study, we corroborate these findings by showing that both network nodes are indeed involved during exogenously driven orienting. Hence, our finding shows that rIPS is implicated in exogenous processes, which extends the classical view of rIPS being the source of top-down influence on visual areas during endogenous attention. Additionally, since rIPS and rTPJ were mutually implicated in exogenously driven orienting, this strongly supports the notion of a collaborative role of both dorsal and ventral attention network nodes, in line with studies demonstrating an interplay between dorsal fronto-parietal and ventral fronto-parietal attention networks (Chica et al. 2011; Parks and Madden 2013; Vossel et al. 2014). Causal directional influences between these two networks have been demonstrated before in both directions by the analysis of functional and effective connectivity in fMRI (Vossel et al. 2012; Wen et al. 2012) and by a combined TMS-fMRI study (Leitao et al. 2015). In further support of a collaborative role of the two systems, anatomo-clinical data have revealed that re-orienting deficits in spatial neglect, which usually occur after damage of the right ventral network, can be accompanied by lesions in the dorsal system (Marshall et al. 2002; Halligan et al. 2003). Interestingly, impairments in re-orienting have also been reported after focal IPS lesions without ventral damage (Gillebert et al. 2011). Although our results corroborate these findings, we cannot pinpoint exactly if TMS over IPS affected the ventral attention system, or TMS over TPJ influenced the dorsal system through network effects.

No effects of TMS over rIPS or rTPJ on endogenous spatial attention shifts: Consideration of compensatory mechanisms and methodological limitations

There is consistent evidence from both neuroimaging and TMS studies for the implication of rIPS in endogenous control of visuospatial attention (Corbetta and Shulman 2002; Kincade et al. 2005; Chica et al. 2011). In contrast, our data revealed no TMS effects on behaviour after rIPS stimulation. This appears contradictory to previous findings and may suggest no rIPS involvement in endogenous attention shifts. However, alternative considerations and methodological limitations are likely to explain the absence of this effect in the current study.

Neuroimaging has shown that the endogenous control system activates a large-scale bilateral, dorsal fronto-parietal network (Corbetta and Shulman 2002). Additionally, EEG studies have revealed that this activity is accompanied by specific scalp ERP components and oscillatory responses that evolve at different stages during attentional orienting (e.g., Nobre et al. 2000; Siegel et al. 2008; Rihs et al. 2009). For example, Simpson et al. (2011) showed by employing fMRI and MEG, that after the presentation of an endogenous spatial cue (150-1000ms post-cue), activity steadily increased, spreading from the cuneus over both lateral intraparietal areas. This was followed by co-activation of multiple dorsal fronto-parietal regions (including fontal eye fields, middle-frontal gyrus, and superior frontal gyrus). This temporal progression over different parts of the dorsal fronto-parietal network possibly reflects initial extraction of the cue information, shifting covert attention and finally transitioning into sustained deployment of attention (see also, Grent-’t-Jong & Woldorff 2007; Green & McDonald 2008; Lauritzen & Silver 2010; Siegel et al. 2008; Simpson et al. 2011). In the current study, we presented the TMS pulses 2075-2175ms after endogenous cue onset (175-75ms before target presentation). Hence, the time of the TMS administration fell into an interval when multiple, bilateral brain regions of the dorsal fronto-parietal network likely already had been recruited for task execution. It is therefore conceivable that the TMS over rIPS was ineffective because ipsi- and contralateral parts of this network were able to compensate for the disruption at the time of TMS delivery, maintaining endogenous cueing benefits without significant performance costs. Moreover, in combination with the increased activity across brain regions, the stimulation intensity may have been sub-threshold in order to interfere with endogenous orienting.

While the involvement of different brain regions at the time of TMS delivery may be responsible for the null effect in the IPS condition, we also need to consider the temporal dynamics underlying sampling of information during attention orienting. Previous research has shown that visuospatial attention is sampling information periodically at theta and alpha frequency (Landau and Fries 2012; Song et al. 2014; Dugué et al. 2015), even when attention is sustained (Fiebelkorn et al. 2013). For example, using TMS over visual cortex, a recent study on endogenous attention orienting revealed a periodic pattern of visual disruption at theta frequency (5Hz) suggesting cyclic sampling also during endogenous attention shifts (Dugué et al. 2016). In light of our null effects as to rIPS-TMS interference in the endogenous condition, we can therefore not exclude that our stimulation may have fallen into a low-sensitive sampling phase, although the chosen double pulse TMS design (with 100ms inter-pulse interval) should have minimized this scenario. Given that 100ms covers half a 5Hz (theta) cycle, it is likely that either of the two pulses coincided with a high sensitivity sampling phase and hence that our TMS design should have affected voluntary orienting even if cyclic.

Dissociated effects of endogenous and exogenous attention orienting

While during sham-TMS, endogenous cueing benefitted perception at cued locations (relative to uncued locations) as expected, simultaneously presented exogenous cues also enhanced performance despite being task-irrelevant and non-predictive as to upcoming target location. Importantly, and replicating the findings from Chapter 2, exogenously driven attention benefits occurred independently of the endogenous process, i.e. did not interact with endogenous orienting. This therefore further adds to the evidence that these two processes may be dissociated in terms of neural substrates, in line with our findings of rIPS- and rTPJ-TMS affecting exogenous cueing benefits, whilst endogenous benefits were maintained, and is in support of previous research (Coull et al. 2000; Lupiáñez et al. 2004; Berger et al. 2005; Hopfinger and West 2006; Funes et al. 2007; Pinto et al. 2013).

Conclusion

By excluding confounding effects of endogenous processes on exogenous attention benefits, we provide conclusive evidence against independent involvement of the dorsal and ventral attention network nodes (i.e. rIPS and rTPJ) in exogenous orienting. This highlights that the dorsal and ventral attention network can be activated in conjunction by exogenous events, suggesting that the functional roles of the ventral and dorsal attention system overlap.

3.5 Appendix

No effects of TMS on reaction times for neither endogenous cueing nor exogenous cueing

As revealed for performance accuracy in response to endogenous cueing, reaction times (RT) were unaffected by TMS. Instead, endogenous cueing benefits were maintained and led to overall faster RT at cued vs. uncued positions, as revealed by a significant 2-way interaction of Endogenous Cueing (left vs. right cue) x Target Location (left vs. right visual field) (F(1,16) = 10.88, p = 0.005, $\eta p^2 = 0.40$) (**Figure 9** A, left panel). Follow-up simple tests showed RT benefits for validly as compared to invalidly cued target locations for both the left visual field (t(16) = -4.01, p = < 0.001, Cohen's d = -0.97), and the right visual field (t(16) = 2.40, p = 0.01, Cohen's d = 0.58). Again, this endogenous cueing benefit did not depend on the TMS conditions (no 3-way interaction of Stimulation Site x Endogenous Cueing x Target Location: F(2,32) = 0.37, p = 0.70, $\eta p^2 = 0.02$; see **Figure 9** A, right panels).

Unlike the observed TMS effects on accuracy for exogenous cueing, RTs were unaffected by active-TMS (no 3-way interaction of Stimulation Site x Exogenous Cueing x Target Location: F(2,32) = 0.59, p = 0.56, $\eta p^2 = 0.04$; **Figure 9** B, right panels). Instead, there was a 3-way interaction of Endogenous Cueing x Exogenous Cueing x Target location (F(1,16)=6.27, p=0.023, $\eta p^2 = 0.28$) which depended on stimulation condition as revealed by a 4-way interaction of Stimulation Condition x Endogenous Cueing x Exogenous Cueing (F(2,32)=4.60, p=0.018, $\eta p^2 = 0.22$). These complex interaction were driven by an overall exogenous cueing bias with faster RT for rightward motion as compared to leftward motion (F(1,16)=8.08, p=0.012, , $\eta p^2 = 0.34$) and a visual field bias with overall faster RT to RVF as compared to LVF targets (F(1,16)=5.49, p = 0.032, $\eta p^2 = 0.26$). The visual field biases in RT may be explained by a contribution of non-specific TMS effects, as has been shown by previous work where the lateralised click of (sham-)TMS over one hemisphere can introduce RT biases towards the visual field ipsilateral to click (i.e., here right visual field) (Duecker and Sack 2013).

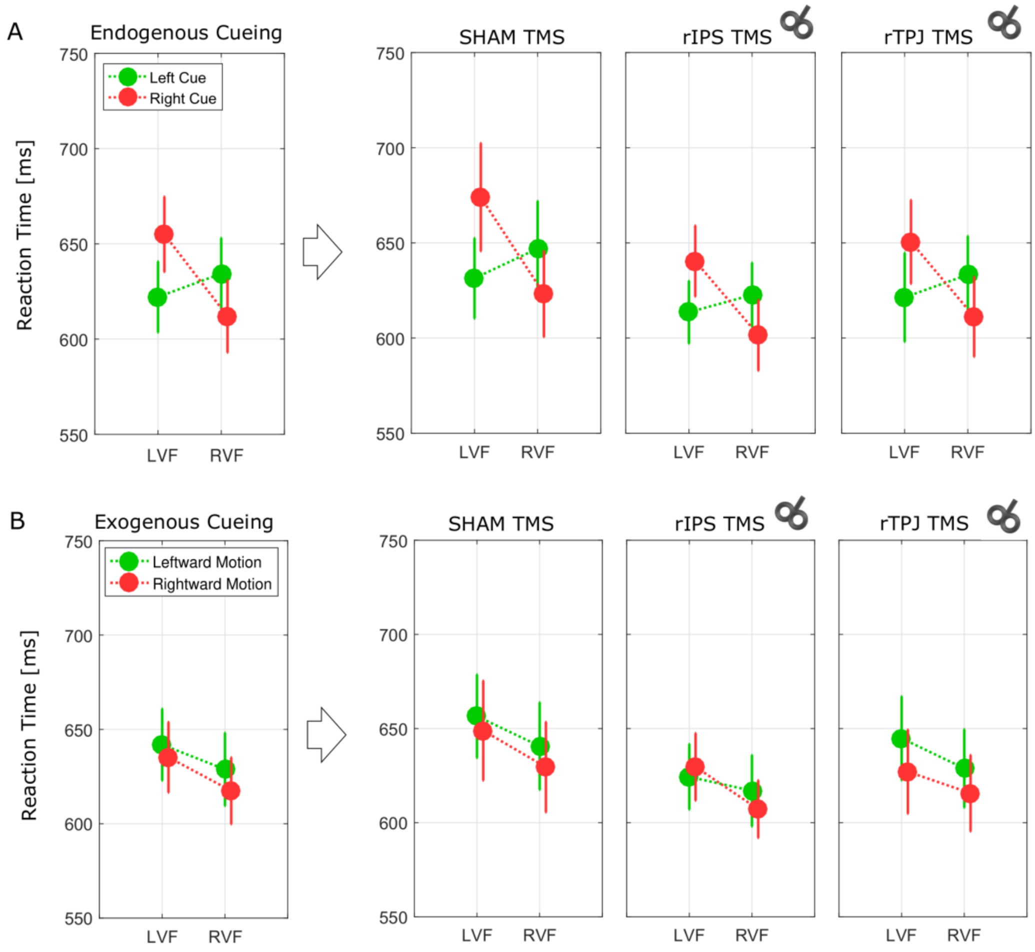


Figure 9: Reaction time as a function of cueing type (endogenous vs. exogenous) and TMS conditions (sham vs. rIPS vs. rTPJ). **(A)** Left panel: Grand averaged performance during endogenous cueing (left or right cue) as a function of target location in the left visual field (LVF) and right visual fields (RVF) illustrating endogenous cueing benefits. Right panels: These benefits (2-way interaction) were independent of the TMS conditions (sham, rIPS, rTPJ) i.e., there was no 3-way interaction. **(B)** Identical to (A) but for exogenous cueing. Exogenous cueing benefits were also independent of the TMS stimulation condition (no 3-way interaction; right panels). The error bars indicate the standard error of the means (± SE).

Chapter 4

Investigating the oscillatory signatures of exogenous visuospatial attention shifts in Electroencephalography

4.1 Introduction

Visual perception is influenced by a variety of different factors, each engaging distinct attentional and cognitive control processes. As mentioned and discussed in previous chapters, attentional factors include endogenous, exogenous and anticipatory processes that follow distinct temporal dynamics: Endogenous deployment of attention gradually enhances perception based on expectations and internal goals and is typically more sustained. In contrast, exogenous orienting of attention is triggered by unexpected external events, transiently enhancing perception at its position and as time progresses, this initial facilitation turns into an inhibition (reduced performance) at the same location (known as inhibition of return (IOR)) (Posner et al. 1985; Klein 2000; Lupiáñez et al. 2001). Exogenous attention is typically tested by manipulating the time interval between non-predictive, lateralised cues and the appearance of a target (for reviews see

Klein 2000; Lupiáñez et al. 2006). Transient, unexpected events also evoke alertness, allowing individuals to reach or maintain an attentive state in order to effectively process potential upcoming events (e.g., Fan et al. 2007; Petersen & Posner 2012). Additional key factors that influence perception are cognitive control processes, which allow monitoring and resolving potential conflicts between competing sensory inputs, different task demands and motivational systems (Cohen 2014a, Cavanagh et al., 2013). Together, these attention and control processes represent key mechanisms for the selection or inhibition of relevant vs. irrelevant environmental information, in order to guide adaptive behaviour (see also, Fan et al. 2007; Fan et al. 2009; Petersen & Posner 2012).

Recent neuroimaging and neurophysiological studies have suggested that distinct neural networks over fronto-parietal regions and oscillatory activity in the theta-, alpha-, beta- and gamma-frequency bands may play a role in the implementation of these attentional and cognitive control processes (Fan et al. 2007; Womelsdorf and Fries 2007; Hipp et al. 2011; Bauer et al. 2014; Clayton et al. 2015; Fries 2015). For example, a fronto-subthalamic circuit including lateral prefrontal cortex, medial prefrontal cortex and anterior cingulate cortex has been associated with cognitive control engagement (Kerns et al. 2004; Ridderinkhof et al. 2004; for review see, Cavanagh & Frank 2014). The communication within this circuit appears to be facilitated via oscillatory ***theta-band*** (2-8Hz) activity resulting in pronounced mid-frontal theta scalp topographies (Cohen 2011), which has been revealed by converging neurophysiological evidence in human and non-human primates (Womelsdorf et al. 2010; Voloh et al. 2015; Cohen 2016; for reviews see, Cavanagh & Frank 2014; Clayton et al. 2015). Various situations have been identified where such mid-frontal theta activity possibly reflects increased demand of control. This includes processes of signalling behavioural errors and resolving upcoming conflicts (e.g., Cohen 2011; Cohen & Donner 2013; Cavanagh et al. 2012), adjusting behaviour when correcting errors

(Cavanagh et al. 2009, 2010), avoiding impulsive (error-prone) responses (Cavanagh et al. 2009, 2012; Nigbur et al. 2011) or when overcoming behaviourally strong habitual biases (Cavanagh et al. 2013). Hence, it has been suggested that the degree of relative theta-band power over mid-frontal regions indexes the recruitment of cognitive monitoring and control processes when in demand of adaptive behaviour (Cavanagh et al. 2009; Cavanagh et al. 2013; for reviews see, Cohen 2014a; Cavanagh & Frank 2014). While theta-band activity appears to be a key correlate of cognitive performance, gamma- and alpha-band activity have been suggested to reflect attentional processes for selection and inhibition of information (for review see, Clayton et al. 2015). For instance, gamma-band (>30 Hz) activity increases with attention possibly to enhance behaviourally relevant signals (Fries et al. 2001; Jia and Kohn 2011). Additionally, it has been shown that in response to spatially cued discrimination tasks, gamma-band activity reflects the degree of surprise when events are less predictable during stimulus processing (i.e., decreased gamma-band activity with increasing stimulus predictability) (Bauer et al. 2014). In contrast, changes in pre-stimulus alpha/beta-band desynchronization reflect the anticipation of upcoming events (Bauer et al. 2014). In fact, numerous studies have associated changes in the ***alpha-band*** (8-14) over occipito-parietal regions with anticipatory endogenous attention orienting towards predictable visual events (e.g., Foxe & Snyder 2011; Thut et al. 2006; Kelly et al. 2006; Worden et al. 2000). To briefly recapitulate from the general introduction (Chapter 1, 1.3), the typical alpha-band modulations observed during endogenous deployment of spatial attention are reflected in an increase of alpha power (synchronization) ipsilateral to the attended position and a decrease in alpha power (desynchronization) contralaterally, which is most pronounced over occipito-parietal areas (Worden et al. 2000; Kelly et al. 2006; Thut et al. 2006; Foxe and Snyder 2011). While there is consensus that this alpha lateralization acts as a suppression mechanism of irrelevant, distracting information (Foxe and Snyder 2011), the oscillatory signatures underlying exogenous spatial attention and its underlying temporal dynamics remain less well investigated. Nevertheless, recent work has suggested that the same brain oscillations in the alpha-band are also implicated in exogenous attentional processes (Feng et al. 2017; Harris et al. 2017).

Inspired by substantial research on the oscillatory correlates of endogenous attention control (for reviews see e.g., Foxe & Snyder 2011; Clayton et al. 2015), I here sought to identify the less known oscillatory signatures of exogenous attention processes. To this end, I examined the EEG responses to a single visual stimulus in a widely used task thought to trigger exogenous alerting and orienting processes (introduced by Posner 1980) in order to establish links between these EEG responses and the known behavioural effects associated with this paradigm. In the current work, typical non-predictive and task-irrelevant cues were presented which are known to evoke alertness (irrespective of space), and trigger exogenous spatial orienting in response to the cue (left or right visual field) and affect the processing of lateralized targets. Reaction times (RTs) were measured at four different cue-target delays to determine the engagement of exogenous attention processes over time in behavioural measures (Posner et al. 1985; Peterson & Posner 2012; Klein 2000; Lupiáñez et al. 2001). In terms of alertness, I expected an early behavioural facilitation (faster RT) in response to cued trials (relative to no-cue). Likewise, exogenous spatial orienting typically leads to an early advantage at short cue-target intervals, followed by later inhibition (slower RT) at cued (relative to un-cued) spatial locations (i.e., IOR) (Posner et al. 1985; Klein 2000; Lupiáñez et al. 2001). Concurrently recorded EEG served to identify the corresponding neural correlates in oscillatory activity. Based on previous neurophysiological findings on endogenous and exogenous attention processes (Thut et al. 2006; Foxe and Snyder 2011; Feng et al. 2017; Harris et al. 2017), I was particularly interested in the response of oscillatory alpha-band activity (8-14Hz) over occipito-parietal regions. In response to alerting I expected general alpha-band desynchronization over occipital areas, whereas in response to spatial cueing I expected alpha-band desynchronization to be lateralised shortly after cue presentation (in line with early benefits for target processing at short cue-target intervals), and to then change to alpha-band synchronization with the same lateralization at later cue-target intervals (in line with IOR). In addition, as previous research indicates, more complex oscillatory activity patterns in other frequency bands may also be associated with the various types of attentional processes (e.g., Fan et al. 2007). Hence, I also investigated broad band (1-40Hz) oscillatory responses across the whole scalp. Importantly, the experiment was designed such that the EEG analysis could focus on cue-related activity prior to target presentation, i.e., oscillatory response un-contaminated by target-evoked potentials.

The results revealed a partial implication of alpha-band activity in exogenously triggered attention (in line with Feng et al. 2017; Harris et al. 2017). Notably, the analysis showed that even during this classic exogenous cueing task, control processes are co-activated together with exogenous attentional mechanisms. These control processes were indexed by mid-frontal theta-band activity that heavily influenced task performance by overriding reflexive attentional capture. Hence, the results indicate that there is an interplay between ongoing higher-level processing and exogenous alerting and spatial orienting mechanisms even in a classical paradigm widely thought to study exogenous attention orienting in isolation.

4.2 Methods

Participants

A total of fifteen participants took part in this study (age range: 18-33; average ± SD: 25.7 ± 4.5; gender: 8 female, 7 male). One participant did not complete the full experimental session (missing data for more than half the experiment) and two datasets had to be excluded due to having >50% of highly artefactual EEG epochs (muscle artefacts and lateral eye movements). This resulted in a total of twelve participants (n = 12) being included in the final analysis. All participants were right handed, had normal or corrected-to normal vision and provided written informed consent before taking part in the experiment. Ethics approval was given by the College of Science and Engineering ethics committee of the University of Glasgow.

Apparatus, Stimuli and Task

The experimental task was presented using E-Prime 2.0 software (Psychology Software Tools Pittsburgh, PA) on a CRT monitor (Samsung Sync Master 1100MB, 20 inch diameter, pixel resolution 1280 x 1024, refresh rate 85Hz). A chinrest maintained a constant head position at a viewing distance of 57 cm. Stimuli consisted of a central black fixation cross presented on a grey background (RGB: 191, 191, 191) together with two square placeholders in the left and right lower visual field (distance from centre of the placeholder to fixation cross: horizontal dimension: 7°, vertical dimension: 5°) (**Figure 10**; adapted from the classic cued visual detection task (Posner 1980)). The placeholders indicated the two possible target locations and served as cues by briefly flashing their outline from black to white for 58.8ms. To manipulate exogenous orienting and alerting mechanisms, cues were non-predictive as to the upcoming target position (50:50) and declared as task-irrelevant. Following four different cue-target intervals (T1 = 105.8, T2 = 305.8, T3 = 505.8 and T4 = 705.8 ms, randomized across trials), a target consisting of a small black dot (5x5 pixels) was presented at the centre of one of the placeholders (note: participants were not informed about the different time intervals). A no-cue condition was included in order to measure the effect of phasic alerting (cue relative to no-cue irrespective of spatial location). Participants were asked to maintain fixation throughout the experiment and to detect the target as accurately and quickly as possible via button press. This design allowed us to quantify the engagement of two exogenous attention processes via behavioural measures, namely: (a) phasic alertness (by comparing behavioural responses to cued vs. no-cued targets independently of spatial locations) and (b) spatial (re)-orienting (by comparing responses to targets at cued vs. uncued locations).

Overall, the experiment consisted of 960 trials, 50% of which included both cues and targets (target-present trials; **Figure 10** A) allowing us to measure behavioural effects. The other 50% of trials included cues only (target-free trials; **Figure 10** B) to allow the analysis of cue-related EEG activity unperturbed from target processing (and associated EEG activity). For the behavioural trials, the conditions consisting of two spatial cues (left and right) or no-cue, four cue-target intervals (105.8-705.8ms) and two possible target locations (left and right visual field) which resulted in a 3x4x2 design with 24 conditions and 20 trials per condition cell (in total 480 target-present trials). The remaining 480 target-free trials were split such that 160 trials were presented per cue condition (left-cue, right-cue or no-cue). Note that in half of these trials (n = 240), a single TMS pulse was delivered over right intraparietal sulcus at 705.8ms (the expected onset of T4). For the scope of this thesis, I here analysed only the 240 target-free trials with no TMS (i.e., 80 trials per each of the 3 cue conditions). Hence, the TMS-EEG data was excluded from the current analysis and will be subject to a separate analysis on TMS-evoked potentials and TMS induced oscillatory activity not part of this thesis. All conditions were presented in an intermixed order with breaks approximately every 10 minutes to mitigate participant fatigue.

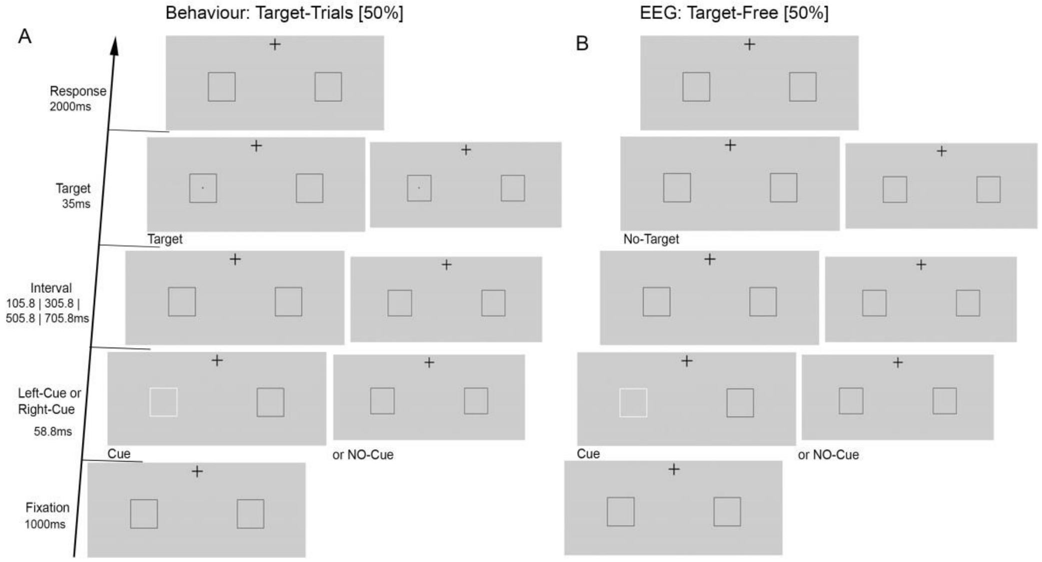


Figure 10: Trial sequence and study design. (A) Behavioural trials. Each trial started with a fixation cross (1000ms) and two black placeholders appearing on the screen indicating the two possible target locations in the left and right visual field. Following the fixation, either no-cue or a non-predictive, task-irrelevant cue (left, right) briefly flashed for 58.8ms (example trial shown: left-cue). After a variable interval of either 105.8, 305.8, 505.8 or 708.8ms, a target appeared at the centre of one of the two placeholders (target-trials). This was followed by a fixed response period of 2000ms. Participants were asked to always maintain fixation and to detect the target as accurately and quickly as possible. **(B)** EEG Trials. The same trial sequence was presented for the EEG trials except that no target was presented (target-free trials). Participants were instructed to only give a response when they detected a target.

Behavioural statistical analysis

The behavioural measure of interest was reaction times (RTs) (correct responses only, RTs faster than 100 ms or slower than 1200ms were excluded). RTs were subjected to 3x4 repeated-measures ANOVAs where the factors consisted of Cueing (no-cue vs. valid vs. invalid cue) and Cue-Target Interval (four intervals 105.8-708.8ms). Significant main effects or interactions were followed up with simple effect tests where appropriate and of interest (i.e., Alerting: $\text{Cue}_{(\text{valid+invalid})}$ vs. No-cue; Spatial orienting: Valid vs. Invalid cues). We also checked for potential overall differences between left and right visual field target RTs. To test this, RTs were subjected to a 2x2x4 repeated-measures ANOVA which consisted of the factors Visual field (left vs. right), Validity (valid vs. invalid) and Cue-Target Interval (four intervals 105.8-708.8ms). The same analysis was conducted for the no-cue condition resulting in a 2x2x4 ANOVA which consisted of Visual field (left vs. right), Cueing (Cue$_{(valid+invalid)}$ vs. No-Cue) and Cue-Target Intervals (T1-T4).

EEG data acquisition

EEG was recorded from 62 channels (including an ocular electrode) and a standard electrode montage according to the official 10-10 System (J.Clin.Neurophysiology Vol 8, No 2, 1991: American Electroencephalographic Society Guidelines for Standard Electrode Position Nomenclature). The reference electrode was positioned at ‘AFz’ and the ground electrode was over the left mastoid bone (‘TP9’). The electrode cap was connected to two 32-channel BrainAmp DC amplifiers (Brain Products GmbH) (filters: DC to 1000Hz, sampling rate of 5000Hz and 0.1µV resolution). We used TMS compatible Ag/AgCl ring electrodes (‘Multitrodes’) and abrasive abralyt electrode paste to keep the skin resistance below 5kOhm (electrodes and electrode paste, EasyCap GmbH).

EEG analysis: Time-frequency analysis and correlation with behaviour

Pre-processing. EEG pre-processing and analysis were performed using Fieldtrip (Oostenveld et al. 2011, http://www.ru.nl/neuroimaging/fieldtrip) and custom-written scripts for MATLAB (MATLAB R2013b, The MathWorks, Inc., Natick, Massachusetts, United States). Offline, EEG data were high-pass filtered at 0.1 Hz and re-referenced to the average of all 62 scalp channels. Line noise was removed using a band-stop filter (49-51Hz). Epochs were centred on the hypothetical T4 onset, and extracted from 1700ms before up to 1500ms after (to cover twice the full length of the longest cue-target interval; total epoch length 3200ms). An initial visual inspection of the EEG epochs was performed to remove highly artefactual trials and channels (muscle artefacts, sweating artefacts). The data were then subjected to an independent component analysis (ICA; fastICA algorithm) in order to remove residual blink artefacts, eye movements and muscle artefacts (on average 12.1 components removed ± 4.2 SD). Following ICA, missing channels from the previous rejection were interpolated using a spherical spline method (on average 2.8 electrodes ± 1.02 SD). In total, 13.30% of trials were excluded from the analysis.

Time-frequency analysis. I was interested in cue-related activity in the window preceding a potential target onset, i.e. activity that may influence and be predictive of target processing. To avoid contamination of the cue-related EEG response by target-evoked potentials, EEG analysis was performed on target-free trials. Behavioural relevance of this activity for target processing was then assessed in a second analysis step (see below), by examining correlations of the activity in target-absent trials with the behavioural effects extracted from target-present trials. Time frequency representations of power were calculated using a Hanning taper and a fixed time window of 500ms in steps of 20ms (1 to 40Hz frequency range). Changes in power were computed relative to the baseline (-900: - 200ms relative to cue onset) in each electrode according to the following formula:

Baseline corrected data = (data - mean(baseline period)) / mean(baseline period)

(as implemented in fieldtrip see function: ‘ft_freqbaseline’, method ‘relchange’). To examine alpha-band activity, we extracted the mean power between 8-14Hz for different electrodes of interest (EOIs) separately in response to alerting and exogenous spatial orienting. While for alerting, the EOI consisted of occipital channels, independent of hemisphere (i.e. POz, PO3, PO4, PO7, PO8, O1, O2, Oz), symmetrical EOIs were created for exogenous spatial orienting (i.e., left hemisphere: P3, P5, P7, PO3, PO7, O1; right hemisphere: P4, P6, P8, PO4, PO8, O2).

Since I was also interested in examining power differences in a wider spectrum of frequencies, I decided to implement a mass univariate approach, testing for statistical effects in the broad-band (1-40Hz), including a longer time range (Cue onset to 1500ms post-T4) across all electrodes. To this end, non-parametric cluster-based Monte Carlo permutation testing was performed in order to detect significant differences between conditions (i.e., comparisons of interest: No-Cue vs. Cue and Left-Cue vs. Right-Cue) and corrected for multiple comparisons (see Maris & Oostenveld, 2007 for details). Initially, paired-sample t-tests were performed at all data points and all t-values which matched a criterion of $p<0.05$ (uncorrected) were built into clusters based on spatial, spectral and temporal adjacency (with a minimum of one adjacent significant neighbouring electrode required in order to be included in a cluster). The cluster statistic was then computed as the sum of the t-values within each identified cluster (original cluster-level t-score). Then, a null hypothesis distribution of cluster statistics was built by extracting the maximum cluster statistic on each of 2500 random permutations of the data (Maris and Oostenveld 2007; Oostenveld et al. 2011). If the original cluster statistic was lower or higher than 97.5% of the respective null distribution t-scores, then this was considered a significant effect (5% alpha level). To examine the effect of alerting, we compared the relative power change between No-Cue and Cue trials (note: Cue trials were created by collapsing 50% left cue and 50% right cue trials: Left- and Right-Cue trials were randomly selected within each individual participant in order to equalise the number of trials between No-Cue and Cue conditions). To investigate the effect of exogenous spatial orienting, we compared relative power changes between Left- and Right-Cue trials.

Correlations between EEG power and behaviour. In order to investigate the behavioural relevance of the identified EEG power changes across conditions for the RT measures of the attention processes across participants, between-subject correlations (Spearman’s rank and Pearson correlation analyses was performed). It is important to note that, while EEG power was obtained from target-free trials, RT measures were obtained from target trials (see **Figure 10** for experimental design). This design allowed to the keep cue-related EEG response free from contaminations by target evoked potentials and therefore to test whether the cue-related neural response could predict behavioural responses to targets.

Alerting effect: The alerting effect was indexed by the RT difference of No-Cue minus Cue such that positive values reflect faster RT to the cue (relative to no cue) (**Figure 11** A). The averaged relative EEG power change was indexed by the Cue minus No-Cue difference such that negative values reflect a decrease in power in response to the cue (relative to No-Cue), which was then correlated with the alerting effect at the shortest cue-target interval (T1). This correlation was performed separately for alpha-power (8-14Hz) over occipital electrodes (occipital EOI, see above) and for the significant power difference clusters revealed by cluster-based permutation testing.

Spatial orienting: To investigate the relationship between EEG power and *spatial orienting* over time, cueing intervals and laterality were taken into account (i.e., cue-target intervals, visual fields and hemispheres) (**Figure 11** B). The spatial orienting effect was indexed by RTs to invalidly minus validly cued targets such that positive values reflect faster RT and negative values reflect slower RT in response to validly cued targets (relative to invalidly cued targets). This was computed for targets in the left and right visual field respectively. The spatial orienting effects were correlated with the averaged relative power change of the EOI in the contralateral hemisphere (see above for LH- and RH-EOIs). Specifically, the LVF orienting effect was correlated with the averaged relative power difference in the RH (indexed by the Left-Cue minus Right-Cue difference such that negative values reflect a power decrease and vice versa). The RVF orienting effect was correlated with average relative power difference in the LH (indexed by the Right-Cue minus Left-Cue difference, again such that negative values reflect a power decrease and vice versa). These correlations were performed for the shortest and longest cue-target intervals (T1, T4) in the alpha-band (8-14 Hz) as well as for the significant power difference clusters revealed by cluster-based permutation testing.

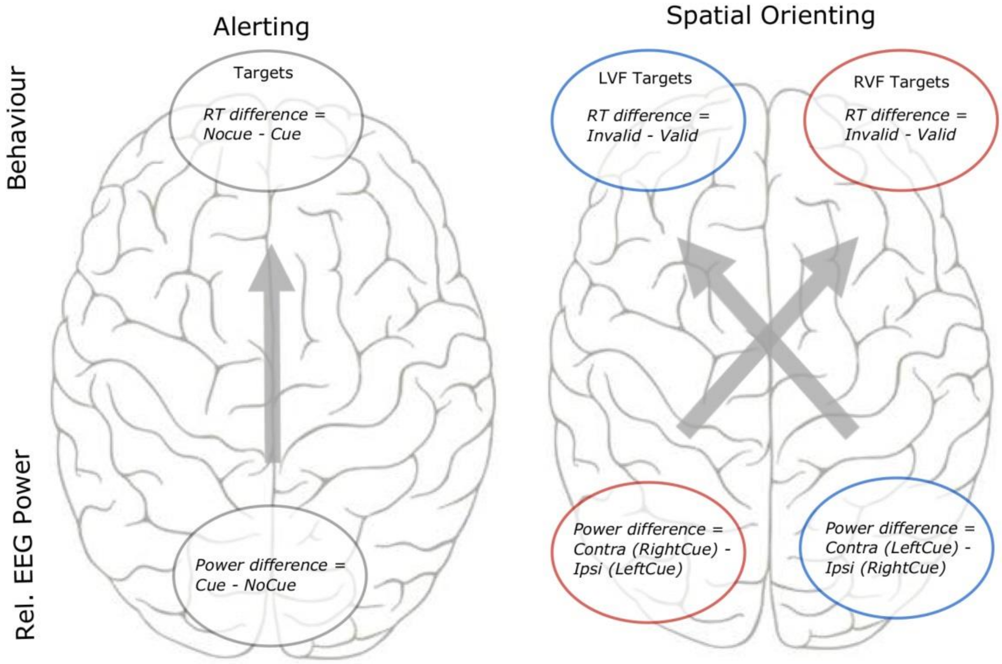


Figure 11: Schematic representation of the correlations between relative EEG power and behavioural cueing effects (RT). (A) Alerting: The alerting effect (RT difference of No-Cue minus Cue) at the shortest cue-target interval (T1) was correlated with the relative EEG power difference (Cue minus No-Cue difference) collapsed across both hemispheres. **(B)** Spatial orienting: Behavioural attention benefits per visual field targets (left, right) were each correlated with attention-related power changes in the contralateral hemisphere respectively, i.e. the left visual field (LVF) spatial orienting effect (RT difference: invalidly minus validly cued) was correlated with the relative power change of the right hemisphere (RH) electrodes of interests (EOI) and the right visual field (RVF) spatial orienting effect was correlated with the relative power change of the left hemisphere (LH) EOI. Note: Behaviour indexes were always computed such that positive values reflect faster RT while negative values reflect slower RT. For the relative power changes, indexes were always computed such that negative values reflect power decease while positive values reflect power increase.

Spearman’s rank and Pearson correlation analyses between behavioural and neural data were computed at each time point (cue-onset to 705.8ms post-cue, i.e. up to the longest cue-target interval at T4) and were corrected for multiple comparisons using non-parametric cluster-based permutation testing. This was performed according to the same principle as described above for testing significant differences between conditions, except that significant clusters were formed based on temporal adjacency only (minimum of two adjacent time points required to be considered a cluster). First, we performed the real correlations separately at each time point and then created a null hypothesis distribution by randomly permuting the neural data across participants at each time point and again performing the correlations at each time point on each iteration (2500 iteration). For a given correlation to be included in a temporal cluster, it was required to have a t-value lower or higher than 97.5% of the null hypothesis distribution and at least one significant adjacent time point. Following this temporal cluster forming procedure, cluster statistics were established (i.e., by extracting the maximum cluster statistic), for both the original correlation data and across the surrogate correlation data from the 2500 random permutations. If an original cluster statistic was lower or higher than 97.5% of the respective null distribution cluster t-scores, then this was considered a significant effect (5% alpha level).

EEG signal of induced and evoked oscillatory response collapsed. Note that the time-frequency analysis was performed on the total EEG signal comprising both induced and evoked response. In order to investigate the induced oscillatory response in isolation, a differentiation needs to be made between non-phase locked power (i.e., induced power) and phase-locked power (i.e., evoked power). Non-phase locked power is usually computed by subtracting the averaged ERP from single trials before performing time-frequency (TF) analysis to remove the evoked contribution (e.g., Cohen & Donner 2013; Cohen 2014b). Thus, induced power reflects the TF-representations of the task-related oscillatory dynamics only, whilst phase-locked power contains the evoked responses. This distinction between induced and evoked power is particularly useful when there is interest in the differences and similarities of the information contained in TF-power as compared to ERPs. Importantly, either approach removes potentially task related key information from the EEG signal and assumes that the physiological origin between evoked and induced power is based on different underlying mechanisms. This assumption makes it difficult to interpret differences between the two approaches (see also discussion, Cohen 2014b, Chapter 20). Hence, in the current study I decided to perform the TFR analysis on the total EEG power changes (i.e., consisting of both, induced and evoked response).

4.3 Results

Whilst EEG was recorded, participants performed a classic cued visual detection task for assessing exogenous orienting (Posner 1980), in which the influence of a non-informative, task-irrelevant cue on detection of an upcoming visual target is assessed. In half of the trials, only cues were presented (target-free trials) which allowed us to identify EEG correlates of cue-induced activity that were devoid of confounding target-related activity (such as target-evoked potentials, motor-evoked activity) over a window of >1000ms. In the other half of trials (target-present trials), cues were followed by targets presented at cued or uncued positions in one of four different cue-target intervals (T1 – T4) or targets were presented without preceding cues (no-cue trials). After quantifying the engagement of alertness and spatial (re)-orienting in the behavioural data (Figure 12), the EEG signatures of exogenous attention were identified in cue-related EEG activity by analysing the corresponding EEG responses in target-free trials (extracted from time-frequency analysis). By using correlational analysis, it was tested whether the respective EEG responses predicted the behavioural difference measures of alerting and spatial orienting in target-present trials across participants (Figures 13-17).

Behavioural effects: Replication of the known alerting and spatial (re-)orienting effects

The first aim was to verify the well-established behavioural effects of phasic alertness and spatial orienting in response to non-predictive cueing. Thus, reaction time (RT) data were subjected to repeated-measures ANOVAs. The overall 3x4 ANOVA on the data of all conditions (see **Figure 12** A) with the factors of Cueing (valid vs. invalid vs. no-cue) and Cue-Target Interval (T1-T4) revealed a significant 2-way interaction (F(6,66) = 15.81, p<0.0001, $\eta p^2=0.59$) suggesting that Cueing effects depended on the Cue-target Interval. To break down this interaction in terms of evidence for known alerting and spatial orienting effects, follow-up analysis were performed as follows.

First, it was verified that the cues induced phasic alerting effects by establishing that RTs to targets were faster following cues relative to no-cue trials (valid and invalid cues collapsed, see **Figure 12** B, left panel) as a function of cue-target interval. The corresponding follow-up simple tests revealed significantly faster RTs in cue trials as compared to no-cue trials at the three shortest cue-target intervals with decreasing effect sizes with delay from cue ($\text{cue}_{(\text{valid+invalid})}$ vs. no-cue at T1: F(1,11) = 73.23 p < 0.0001, Cohen's d = 2.11; T2: F(1,11) = 47.86, p < 0.0001, Cohen's d = 1.63; T3: F(1,11) = 11.94, p = 0.005, Cohen's d = 1.07) but not at the longest interval (T4: F(1,11) = 2.90, p = 0.12, Cohen's d = 0.65). Thus, non-predictive cueing evoked a transient (phasic) reduction in RT relative to the no-cue condition (**Figure 12** B, right panel). This cueing advantage, which was strongest at the shortest cue-target interval (T1), is in line with the classical effect of phasic alertness (Fan et al. 2002, Fan et al. 2009). For the subsequent correlation analysis with EEG (see below), we quantified the *effect of alertness* per participant by subtracting RTs in no-cue trials from cue trials (at T1) such that positive values indicated a cueing advantage (faster RT), while negative values would indicate a cueing disadvantage (**Figure 12** B, right panel).

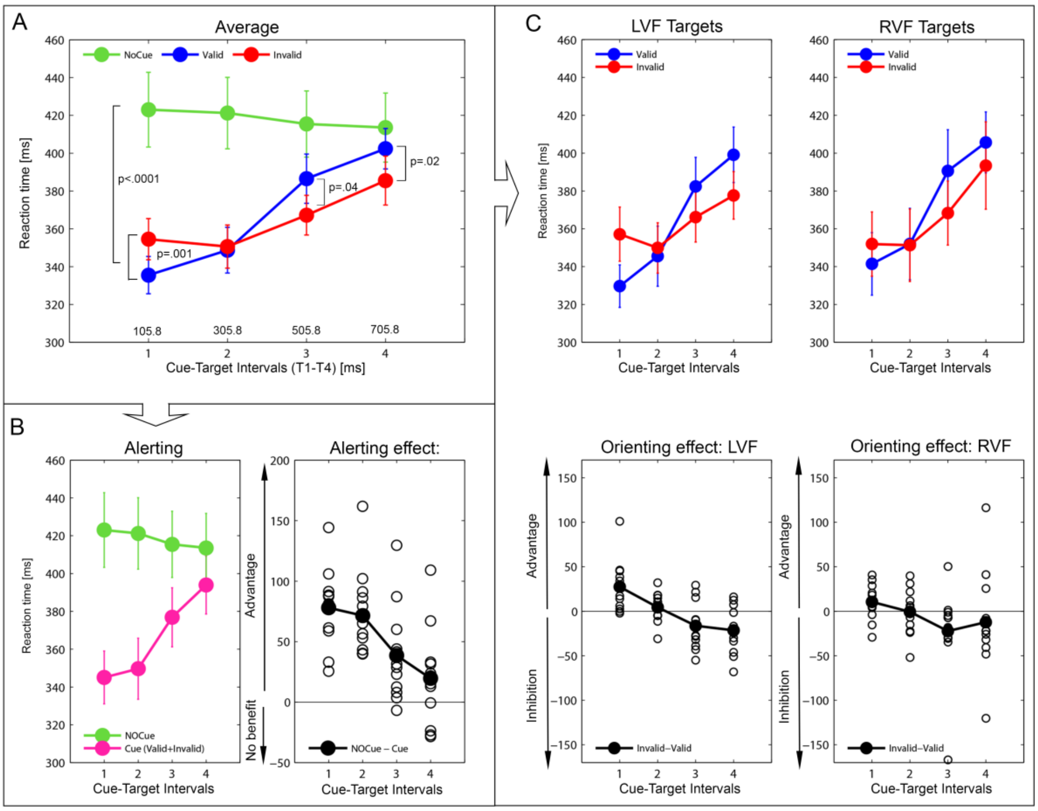


Figure 12: Behavioural replication of exogenous cueing on alertness and spatial (re-)orienting. (A) The line plots represent grand averaged reaction time (RTs) in response to no-cue (green), valid cue (blue) and invalid cue (red) conditions as a function of cue-target interval (T1-T4). **(B)** Alerting effect. Grand averaged RTs in response to no-cue and cue (pink) conditions irrespective of cue validity (left panel) and corresponding differences where positive values indicate faster RTs (advantage) in cue relative to no-cue (alerting effect; right panel) trials. **(C)** Spatial orienting effect illustrated separately for the left and right visual fields (LVF, RVF) for valid and invalid cues (upper panel) and corresponding differences between invalid and valid cues (cueing effects; lower panels) as a function of cue-target delay. Positive values indicate faster RTs in valid relative to invalid cue trials (advantage), while negative values indicate slower RTs (inhibition) in valid relative to invalid cue trials. Error bars indicate standard error of the mean (± SE). Single white dots (difference plots) represent individual participants and solid black dots represent grand averages.

Second, it was verified that the cues triggered exogenous spatial orienting processes by establishing that RTs differed significantly depending on whether targets appeared at validly cued or invalidly cued locations (see **Figure 12** C, upper panels). This was confirmed by follow-up simple tests, showing significantly faster reaction times for validly as compared to invalidly cued targets at the early cue-target interval (valid vs. invalid cues at T1: F(1,11) = 18.43, p = 0.001, Cohen's d = 1.54, **Figure 12** C). This effect was reversed for the two longest cue-target intervals, showing significantly slower RTs for validly cued targets as compared to invalidly cued targets (valid vs. invalid at T3: F(1,11) = 5.25, p = 0.04, Cohen's d = 0.70; at T4: F(1,11) = 6.99, p = 0.02, Cohen's d = 0.81, **Figure 12** C). Thus, due to the cue being non-informative in regards to upcoming target position and hence being task-irrelevant, these reversed cueing effects are indicative of exogenous orienting to the cued location at the early interval, followed by re-orienting to uncued positions as time progresses (an effect known as inhibition of return; IOR) at the later interval (Posner et al. 1985; Klein 2000; Lupiáñez et al. 2001; Tipper and Kingstone 2005). For the subsequent correlation analysis with EEG, we quantified per participant the *effects of spatial orienting* on the one hand and *reorienting* on the other hand by computing the difference between invalid and validly cued targets at T1 and T4 respectively, such that positive values represent a cueing advantage (faster RT), while negative values indicate an inhibition (i.e., slower RT) of return (IOR) (**Figure 12** C, lower panel).

Importantly, note that both effects of phasic alerting and spatial (re-)orienting were independent of the visual field (VF) in which the target appeared. This was tested by subjecting RTs to two separate repeated-measure ANOVAs. First, for *alertness* RTs in response to cued and no-cue targets were entered into a 2x2x4 ANOVA with the factors Target Location (LVF vs. RVF), Cueing ($\text{Cue}_{\text{(valid+invalid)}}$ vs. No-Cue) x Cue-Target Intervals (T1-T4), which revealed no 3-way interaction (F(3,33) = 0.18, p = 0.91, $\eta p^2 = 0.016$). Secondly, for *spatial (re-)orienting*, RTs in response to the cue were subjected to a 2x2x4 ANOVA with the factors Target Location (LVF vs. RVF), Cue Validity (valid vs. invalid) and Cue-Target Intervals (T1-T4). This revealed no main effect of visual fields (LVF vs. RVF) (F(1,11) =

0.73,$p = 0.41$, $\eta p^2 = 0.062$*) and no* 3-way interaction of Cue (LVF vs. RVF) x Validity (valid vs. invalid) x Cue-Target Interval (T1-T4) (F(3,33) = .42, p = .74, $\eta p^2 = 0.04$).

EEG-signatures of alertness: Occipito-parietal alpha-band desynchronization predicts the effect of phasic alertness (Cue vs. No-Cue)

Next, I sought to identify EEG time-frequency predictors of the behavioural effect of alerting, i.e. to identify the cue-induced EEG activity in the interval prior to target onset that correlates with the strongest cue-related changes in behavioural performance to this target (with no-cue trials as the control). The initial analysis was focused on the alpha-band activity (8-14Hz) over occipito-parietal electrodes of interest (EOI based analysis).

To identify cue-related EEG changes, the time-frequency spectra were compared between cue and no-cue trials. This analysis revealed a decrease in alpha power (alpha desynchronization) in cue relative to no-cue trials from 300ms to 880 ms post-cue onset over occipital electrodes (**Figure 13** A). To test whether this alpha-band decrease could predict the behavioural alerting effect (estimated at T1), between-subject correlations were computed between the relative alpha desynchronization over time (cue minus no-cue, **Figure 13** A) and the early alerting effect (i.e., RT advantage at T1, 108.5ms post-cue, **Figure 12** B right panel). The analysis revealed a significant negative correlation prior to the expected target onset (Spearman's: Rho = -0.60 and Pearson's correlation; Rho = -0.59, both $p < 0.05$ cluster-corrected; Rho-values averaged across significant time points). Those individuals who displayed the strongest alpha-band desynchronization at early time points also showed the fastest cue-induced RT advantage (see **Figure 13** B illustrating Spearman's correlation results). Hence, the degree of cue-induced alpha power decrease over occipital electrodes prior to target onset predicted the early RT advantage across participants.

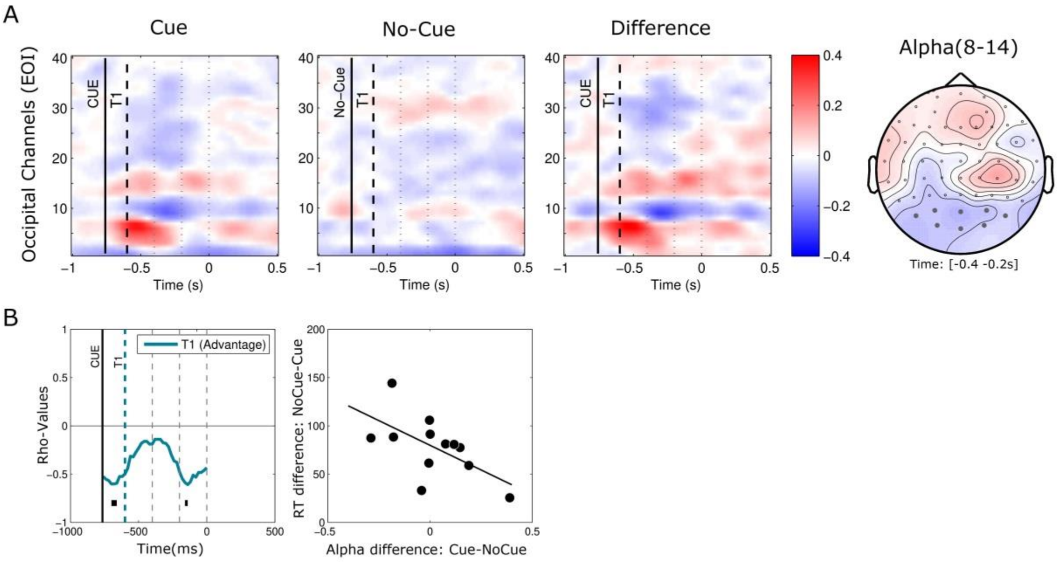


Figure 13: EOI Time-frequency representations (TFRs) in EEG and relation to phasic alertness (Cue relative to No-Cue trials). **(A)** TFRs averaged over occipital electrodes of interest (EOI) in response to Cue, No-Cue and the difference between the two (Cue minus No-Cue). Solid black line represents cue onset, dashed black line represents target onset at the shortest-cue target interval (T1), dashed grey lines represent remaining target onsets (T2-T4), zero corresponds to the last cue-target onset; note that targets were absent in these trials and onsets are shown for illustrative purpose. Highlighted electrodes (in grey) on the scalp topography correspond to the occipital EOIs. The topography represents the difference in alpha power (8-14 Hz) between the Cue and No-Cue conditions at the time points corresponding to the biggest difference between conditions. **(B)** Between-subject correlations: Spearman correlations between relative occipital alpha-band desynchronization (Cue minus No-Cue) and RT difference (No-Cue minus Cue) at T1 computed at each EEG time point (from cue-onset to 705.8ms post-cue at T4). Scatter plots show the relationship averaged over significant time points. Black bars represent significant correlations (p<0.05, cluster-corrected). Note: See 4.5 Appendix 4.5 for corresponding Pearson's correlations.

Mid-frontal delta/theta-band synchronization counteracts phasic alertness effects (Cue vs. No-Cue)

Because previous literature has revealed the involvement of other frequency bands than alpha in different types of attentional processes (e.g., Fan et al. 2007; Bauer et al. 2014), I also examined broad-band activity (1-40Hz) across the whole scalp in a second analysis step. Again, cue-induced EEG changes were identified first, before establishing correlations with the alerting effect. After selecting an a-priori time window of interest (covering the window from cue-onset up to 500ms post-T4), cluster-based permutation testing revealed a significant difference in relative power change across delta/theta-band frequencies (1-8Hz) with an increase in power in cue relative to no-cue trials ($p < 0.05$, cluster-corrected) (**Figure 14** A, black contour). This significant theta synchronization extended from 40ms up to 1170ms post-cue (maximal synchronization at 240ms post-cue) and was most pronounced over mid-frontal electrodes (**Figure 14** A, topography). Note that the time-course of this theta response (extending over ~1000ms) indicates a sustained oscillatory activity and hence is unlikely to exclusively reflect a cue-evoked potential. To test whether the increase in theta power was predictive of the early behavioural alerting effect at T1, we computed between-subject correlations between the relative theta-band synchronization over time (cue minus no-cue) and the early RT advantage (no-cue minus cue). This resulted in significant negative correlations prior to and around the expected target onset at T1 (Spearman's correlation: Rho = -0.62, $p < 0.05$, cluster-corrected; Pearson's correlation: Rho = -0.58, $p = 0.047$, uncorrected; Rho-values averaged across significant time points). Those individuals who displayed the strongest early theta-band synchronization also showed the weakest cueing effect (**Figure 14** B). This indicates that theta-band synchronization around cue onset may have impaired/abolished the behavioural early advantage (faster RT) at the shortest cue-target interval. Thus, theta-band synchronization showed the opposite effect as compared to the alpha-band desynchronization; being associated with reduction of the cue-induced early alerting effect.

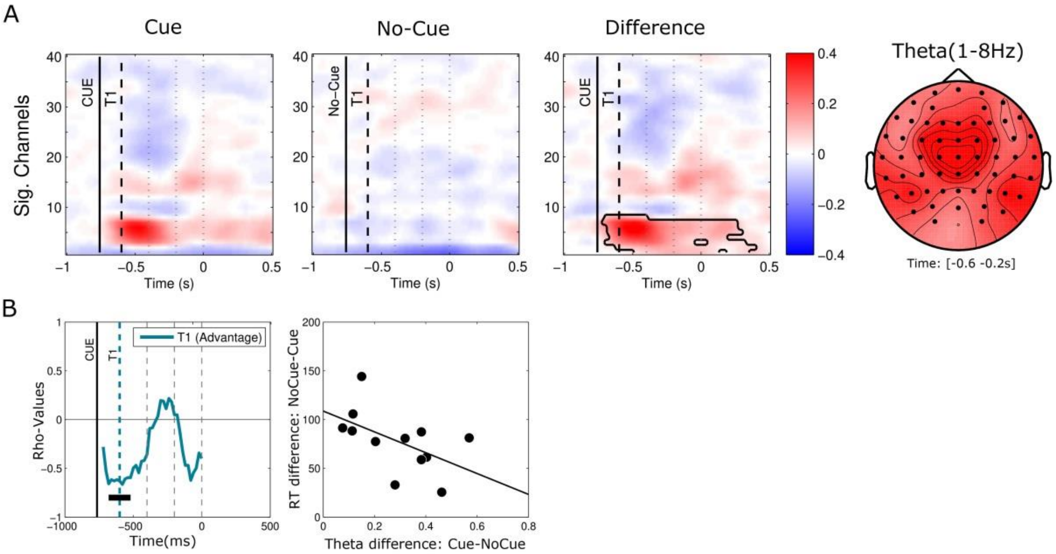


Figure 14: Time-frequency representations (TFRs) in EEG and relation to phasic alertness (Cue relative to No-Cue trials). (A) TFRs averaged over significant electrodes revealed by whole-scalp cluster-permutation testing. The black contour represents a significant difference in power change between the Cue and No-cue conditions ($p<0.05$, cluster-corrected). Solid black line represents cue onset, dashed black line represents target onset at the shortest cue-target interval (T1), dashed grey lines represent remaining target onsets (T2-T4), zero corresponds to the last cue-target onset; note that targets were absent in these trials and onsets are shown for illustrative purpose. Significant channels are highlighted (in black) on the corresponding scalp topography, representing the difference of Cue minus No-Cue theta-band power (1-8Hz) at the time point showing the biggest difference between conditions (maximal synchronized state). **(B)** Between-subject correlations: Spearman correlations between the relative significant theta-band synchronization (Cue minus No-Cue) revealed by the cluster-permutation testing (see subfigure A for the cluster) and RT difference (No-Cue minus Cue) at T1 computed at each EEG time point (from cue-onset to 705.8ms post-cue at T4). Scatter plots show the relationship averaged over significant time points. Black bars represent significant correlations ($p<0.05$, cluster-corrected). Note: See 4.5 Appendix 4.5 for corresponding Pearson's correlations.

EEG-signatures of spatial cueing: Lateralized occipito-parietal alpha-band desynchronization in response to exogenous spatial (re-)orienting, but no apparent correlation with behavioural attention effects (Left- vs. Right-Cue)

Following the same principle as described for the phasic alerting effect, I sought to investigate whether alpha lateralization is similarly implicated in exogenous spatial orienting, as evoked by non-predictive (spatial) cueing. Hence, I tested whether there is an association between EEG changes and the known early behavioural benefits and later costs on target processing. To this end, time-frequency representations were computed in left-cue relative to right-cue trials, focusing first on alpha-band activity (8-14Hz) over occipito-parietal regions. Lateralization was taken into account by selecting symmetrical electrodes of interest (EOIs) over left and right occipito-parietal sites respectively (**Figure 15** A, highlighted electrodes in grey). The results revealed a stronger alpha/beta (8-18Hz) power decrease over contralateral electrodes (as compared to ipsilateral electrodes) to the cued location from approximately 60 to 800ms post-cue onset (**Figure 15** A).

To test whether this cue-related alpha-band change is predictive of the early spatial cue benefits and/or the late costs (IOR) in behaviour, between-subject correlations were computed between lateralized alpha-band desynchronization (always measured relative to the cue presented contralateral to the hemisphere of interest) and the spatial orienting effects. More specifically, relative alpha-band desynchronization in the *right hemisphere EOI* (left relative to right cue trials) was correlated with relative RT effects for LVF targets when validly vs. invalidly (i.e. left- vs. rightward) cued (i.e., benefits at T1 and costs at T4 relative to RVF targets). Similarly, relative alpha-band desynchronization in the *left hemisphere EOI* (right relative to left cue trials) was correlated with relative RT effects for RVF targets when validly vs. invalidly (i.e. right- vs. leftward) cued (i.e., benefits at T1 and costs at T4 relative to LVF targets) (see **Figure 11** for a schematic representation of the correlation between RT measures and EEG power for spatial orienting). In contrast to the analysis of the alerting effect and unexpectedly, the results revealed a positive correlation between lateralized relative alpha changes and early cueing benefit (T1) at two time points for only the left visual field targets (Spearman's Correlation: Rho = 0.60; Pearson's Correlation: Rho = 0.61; $p<0.05$, cluster-corrected) (**Figure 15** B, green line in LVF). However, note that the correlation is in the opposite direction of what would be expected, i.e., individuals who displayed stronger alpha-band desynchronization showed slower RTs (in the LVF). In addition, the correlation is observed 200ms after the expected T1 target onset (i.e., ~300ms post-cue) which would suggest that cue-related alpha-activity postdicted (as opposed to predicted) target processing. Hence, this is likely to reflect a spurious result. The analysis revealed no other significant correlation (Spearman's or Pearson's correlations) between lateralized alpha changes and either of the behavioural effects (cue-induced RT facilitation or inhibition) (**Figure 15** B).

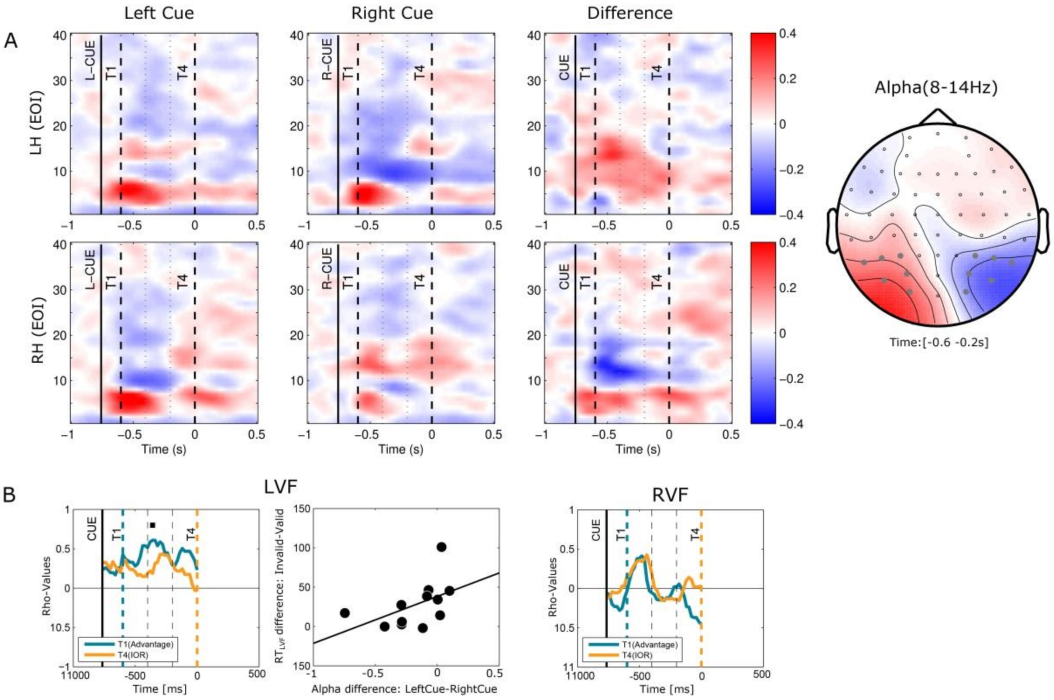


Figure 15: EOI Time-frequency representations (TFRs) in EEG in relation to exogenous spatial orienting (left vs. right cues). (A) TFRs averaged over left and right occipito-parietal electrodes of interest (EOIs) in response to left cues, right cues and the difference (contrast: left minus right cue). The topography reflects relative left posterior synchronization and right posterior desynchronization due to the direction of contrast. Highlighted electrodes (grey) in the scalp topography correspond to the occipital EOIs in the left and right hemisphere respectively. The scalp topography represents the difference in alpha power (8-14 Hz) between the Left-Cue and Right-Cue conditions at the time points showing the biggest difference (maximal desynchronized state). Solid black line represents cue onset, dashed black lines represents target onset at the shortest-cue target interval (T1) and longest cue-target interval (T4), dashed grey lines represent remaining target onsets (T2, T3), zero corresponds to the last cue-target onset; note that targets were absent in these trials and onsets are shown for illustrative purpose. **(B)** Between-subject correlations: Spearman correlations between the difference in relative alpha-band desynchronization (contralateral minus ipsilateral relative to the cues) and the RT difference (Invalid minus valid cues) for the left and right visual fields at both the shortest and longest cue-target intervals (T1 = green, T4 = orange) respectively. Scatter plots show the relationships averaged over corresponding significant time points. Black bars represent significant correlations (p<0.05, cluster-corrected). Note: See 4.5 Appendix 4.5 for corresponding Pearson's correlations.

Mid-frontal theta-band synchronization counteracts the effect of late costs from exogenous spatial (re-) orienting (Left vs. Right-Cue)

In accordance with the analysis of the alertness effect, I also considered broad-band activity (1-40Hz) to investigate whether any alternative frequencies may predict the exogenous spatial orienting effect in behaviour. Again a cluster-based permutation test was performed (left vs. right cue) including 1-40Hz across the whole scalp. This analysis revealed a significant difference between the left and right cue (positive cluster, $p<0.05$, cluster-corrected) conditions across the theta-, alpha- and beta-bands (2-18Hz), extending from cue-onset to 1160ms post-cue (**Figure 16** A, black contour). Within this extended cluster, a distinction was apparent between high and low frequency bands, covering different time periods and with differing topographical distributions: While higher frequencies (~8-18Hz) extended from 200ms to 550ms post-cue and were most pronounced over occipito-parietal channels in the left hemisphere, lower frequencies in the theta-band (2-8Hz) extended from cue-onset to 1160ms and were most pronounced over mid-frontal electrodes (**Figure 16** A, topography). Note, that in further support of this distinction, the analysis also revealed a second significant (negative) cluster which was lateralized over right occipital-parietal electrodes across the higher frequencies bands (9-18Hz) and extending from cue-onset to approximately 500ms post-cue (**Figure 16** B, gray contour; negative cluster, $p<0.05$, uncorrected). Taken together, this indicates that there were two distinct spatial cueing difference patterns, one in the alpha (extending to the beta) band showing a lateralized modulation over occipital-parietal electrodes, and another in the theta-band (2-8Hz) which was most prominent over mid-frontal regions (**Figure 16** A, B; topographies).

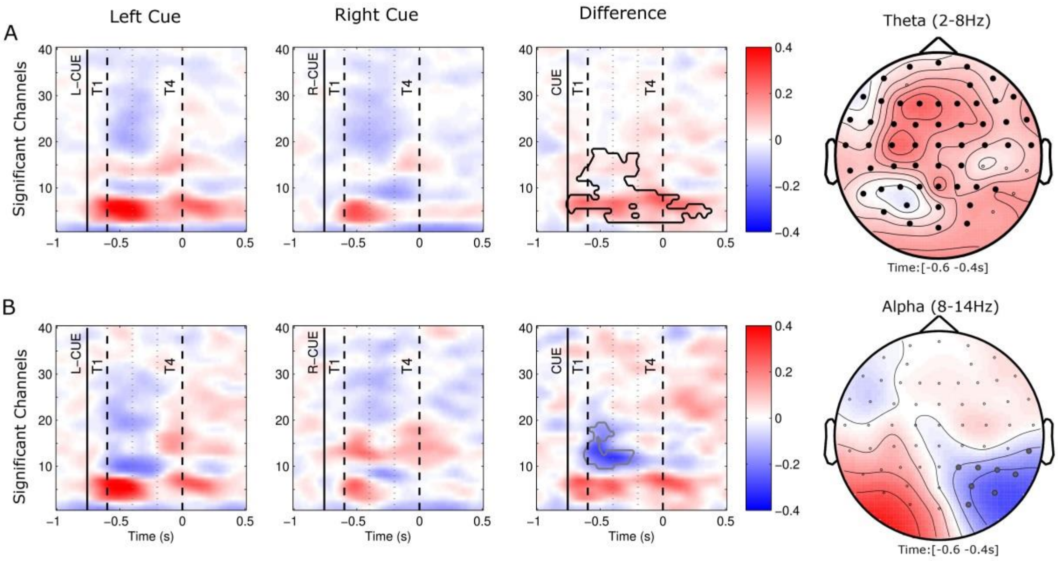


Figure 16:Time-frequency representations (TFRs) in response to Left-Cue and Right-Cue: distinction between high and low frequency bands. TFRs averaged across significant channels revealed by cluster-permutation testing. **(A)** Significant positive cluster. The black contour represents significant difference in relative power change between Left-Cue and Right-Cue (positive cluster, cluster-corrected p<0.05). **(B)** Significant negative cluster. The grey contour represents significant difference in relative power change between Left-Cue and Right-Cue (negative cluster, uncorrected p<0.05). Significant channels are highlighted in black and grey respectively on the corresponding scalp topographies. The solid black line represents cue onset, dashed black lines represents target onset at the shortest-cue target interval (T1) and longest cue-target interval (T4), dashed grey lines represent remaining target onsets (T2, T3), zero corresponds to the last cue-target onset; note that targets were absent in these trials and onsets are shown for illustrative purpose.

To test whether this mid-frontal theta synchronization could predict either the early RT benefit (at T1) and/or late cost (at T4), I followed the same correlation analysis as described for the lateralized alpha-band desynchronization. Between-subject correlations were computed between relative theta-band synchronization and both the RT benefits and costs (i.e., advantage at T1 and inhibition at T4) in the LVF and RVF respectively. While no significant correlation was revealed for the early behavioural benefits, significant positive correlations were revealed between the degree of relative theta-band synchronization prior to the last possible target onset at T4 and the relative RT costs (difference between valid and invalid trials) for this target (i.e. T4), corresponding to the IOR. The effect was significant in both visual fields (LVF Spearman's correlation: Rho = 0.69, Pearson's correlation: Rho = 0.61; RVF: Spearman's correlation: Rho = 0.67, Pearson's correlation: 0.66; all p<0.05, cluster-corrected; Rho-values averaged across significant time points) (**Figure 17** B, orange lines). These correlations show that the individuals who displayed stronger relative theta-band synchronization also showed a reduction of inhibition of return (re-orienting) in both the left and right visual field respectively (**Figure 17** B). Therefore, mid-frontal theta seems to counteract the behavioural consequences of both exogenous alertness and re-orienting.

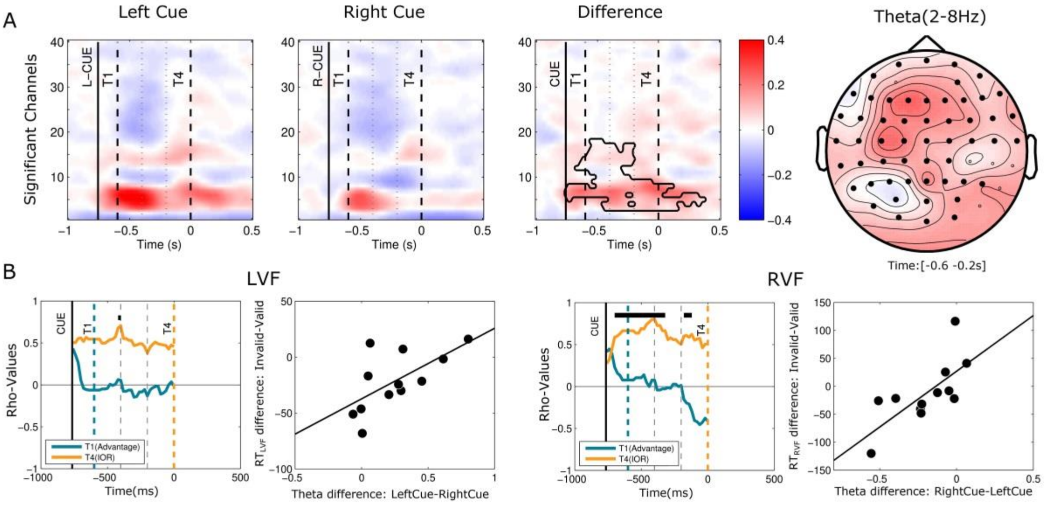


Figure 17: Time-frequency EEG representations (TFRs) in relation to exogenous spatial orienting (left vs. right cues). (A) TFRs averaged across significant channels revealed by whole-scalp cluster-permutation testing. The black contour represents a significant difference in power change between the Left-Cue and Right-Cue conditions (p<0.05, cluster-corrected). The corresponding scalp topography represents the difference of Left- minus Right-Cue theta-band power (2-8Hz) at the maximal synchronized state. Significant channels are highlighted in black. Solid black line represents cue onset, dashed black lines represents target onset at the shortest cue-target interval (T1) and longest cue-target interval (T4), dashed grey lines represent remaining target onsets (T2, T3), zero corresponds to the last cue-target onset; note that targets were absent in these trials and onsets are shown for illustrative purpose. Note: Lower frequencies (2-8Hz) in the significant cluster were distributed over mid-frontal electrodes, while higher frequencies (>8Hz) were distributed over occipital regions. **(B)** Between-subject correlations: Spearman correlations between the difference in relative theta-band synchronization (contralateral minus ipsilateral relative to the cues) and the RT difference (Invalid minus valid cues) for the left and right visual fields at both the shortest and longest cue-target intervals (T1 = green, T4 = orange) respectively. Scatter plots show the relationships averaged over corresponding significant time points. Black bars represent significant correlations (p<0.05, cluster-corrected). Note: See appendix 4.5 for corresponding Pearson's correlations.

4.4 Discussion

The current experiment aimed to investigate how cue-related (pre-target) oscillatory activity in the alpha-band (8-14Hz) as well as cue-related broad-band activity (1-40Hz) relates to performance measures in a task thought to primarily manipulate exogenous attentional processes (i.e., alertness and spatial (re-)orienting). First, the classic patterns of behavioural results were replicated (Posner 1980; Petersen and Posner 2012), showing strong modulations of RTs to targets in response to cue-related alerting (i.e., early advantage) and spatial (re-)orienting (i.e., early advantage and later inhibition). Second, the EEG results revealed cue-related changes in alpha and theta-band activity. Importantly, these EEG results reflect the cue-related responses, uncontaminated by target-evoked responses, since TFR analysis was performed on target-free trials. Third, correlation analyses between the cue-related oscillatory changes and the attention effects in behaviour demonstrated a partial link of alpha-band changes with exogenous attention processes, as revealed by a correlation between alpha-desynchronization and phasic alertness measures. This result is consistent with previous findings linking preparatory alpha-band activity to enhanced visual processing. Furthermore, the correlation analyses revealed an inverse relationship of mid-frontal theta-band synchronization and exogenous attention processes. Mid-frontal theta-activity counteracted exogenous attentional capture by abolishing both phasic alertness and later components of exogenous (re-)orienting. These findings are discussed in light of previous studies showing that engagement of higher-level (top-down) processes (such as cognitive control), which has been associated with theta activity over mid-frontal regions, can override automatic processes. The results suggest that the classic, exogenous attention manipulation task we employed does not exclusively involve exogenous processes, but also recruits other endogenous control mechanisms which can suppress exogenous capture.

Alpha-band desynchronization may serve as a general mechanism to facilitate visual processing

By employing a typical experimental design to trigger exogenous attention shifts, we reveal an association between the strength of relative preparatory (pre-target) alpha power desynchronization over occipital regions and the level of ***phasic alerting***. The stronger the alpha-band desynchronization, the faster the RTs. This in line with previous studies showing that anticipatory alpha-band desynchronization facilitates visual processing during non-spatial (e.g., Ergenoglu et al. 2004; Hanslmayr et al. 2007; van Dijk et al. 2008) and spatial attention shifts (e.g., Babiloni et al. 2006; Thut et al. 2006; Gould et al. 2011; for review see Foxe & Snyder 2011).

In addition, the analysis revealed that in response to spatial cues that induced ***exogenous (re-)orienting***, alpha-band activity showed differential modulations over the two hemisphere, with desynchronization dominating over occipito-parietal regions contralateral to the cued visual field. This asymmetric alpha topography is typically observed when contrasting left vs. right cue conditions (or vice versa) during deployment of endogenous spatial attention (e.g., Worden et al. 2000; Sauseng et al. 2005;Kelly et al. 2006; Thut et al. 2006;Gould et al. 2011; Samaha et al. 2016). However, unlike previous results showing that the alpha-band lateralisation prior to target presentation is predictive of task performance both when modulated by endogenous attention (e.g., Thut et al. 2006; Gould et al. 2011) or as a function of spontaneous neural variability (no cueing involved: see e.g. Ergenoglu et al. 2004; Babiloni et al. 2006; Hanslmayr et al. 2007; Benwell et al. 2017), we did not observe a relationship between cue-related lateralised alpha-band changes prior to expected target presentation and target processing. Instead, and unexpectedly, we only found a relationship between lateralised alpha-band desynchronization and the earlier cueing advantage (to T1) for EEG activity in a late time-interval (~300ms post-cue and thus ~200ms post-target T1), i.e. EEG postdicted (as opposed to predicted) target perception, and this in the opposite direction as expected (i.e., RT slowing), and only for left visual field targets. Hence, we consider this latter, unexpected and inconsistent result as inconclusive in regards to a behavioural relevance of the lateralized alpha-band changes we observed during exogenous spatial (re-)orienting.

Our findings of an association between alpha-band desynchronization and behavioural alertness effects, and of lateralised alpha-band desynchronization contralateral to the cue inducing exogenous spatial (re-)orienting, are in line with recent work suggesting that alpha-band modulations are not only involved in endogenous but also exogenously triggered shifts of attention (Feng et al. 2017; Harris et al. 2017). More specifically, Feng et al. (2017) showed improved visual perception at validly (relative to invalidly) cued locations in response to a non-predictive auditory cue, which was linked to sound-induced lateralized alpha desynchronization over occipital areas and predicted correct task performance. Interestingly and distinct to endogenous orienting, non-predictive auditory cues did not induce any alpha-band synchronization ipsilateral to the cued locations, possibly suggesting a lack of 'active' suppression towards the un-cued visual field for exogenous orienting. Similarly to cross-modal cueing (as employed by Feng et al. 2017), exogenous visual cueing also facilitated visual processing in the current experiment but regardless of visual field (alpha-band desynchronization associated with alertness). Another relevant study conducted by Harris et al. (2017) showed a distinct lateralized alpha desynchronization when attention was captured involuntarily by non-predictive but goal-relevant features of the cue (i.e., color). While this study also speaks to the notion that alpha-band modulations are implicated in exogenous capture, this task still relies on feature-based properties of the cue which engage goal-directed (top-down) components. It therefore does not test exogenous processes exclusively but also contingent endogenous processes (Folk et al. 1994). Nonetheless, these findings altogether suggest that cue-induced alpha changes over occipito-parietal regions are not exclusively modulated during goal-directed (top-down) shifts of attention, but likewise during exogenous processes, hence indicating that alpha-band desynchronization serves as a common mechanism to facilitate visual processing (Feng et al. 2017; Harris et al. 2017).

Evidence of higher-level processing (cognitive control) reducing exogenous attentional capture

Instead of facilitating perception (as revealed for alpha-band desynchronization), relative mid-frontal theta increases were associated with the opposite effect, i.e. with reduction of both the behavioural measures of phasic alertness as well as of later components of exogenous spatial (re-)orienting (i.e, IOR). Note that the TFR was performed on the total EEG signal (i.e., without removal of the cue-evoked potential prior to TFR analysis; see also methods). However, as the differences in relative theta-band power showed long lasting changes (>1000ms), they seem unlikely to be explained by evoked responses only. Hence, we interpret the majority of the effects to reflect induced oscillatory changes, with only a partial contribution from evoked responses. Interestingly, these observed mid-frontal theta increases are consistent with engagement of higher-level (top-down) processes such as cognitive control and action-monitoring (Cavanagh and Frank 2014; Cohen 2014a; Clayton et al. 2015), which have been shown to help overcoming behaviourally strong, automatic biases (Cavanagh et al. 2013).

Situations that have been linked to mid-frontal theta activity and the recruitment of cognitive control demands include those for which behavioural adjustments are needed, such as when correcting errors, avoiding impulsive (error-prone) responses (Cavanagh et al. 2009, 2012; Nigbur et al. 2011) or when in need of overriding strong habitual behaviours (Cavanagh et al. 2013). Interestingly, these studies also showed that the degree of relative theta-band power predicted the adjustment of behaviour, reflected in RT slowing (Cavanagh et al. 2009, 2013). For instance, the latter study recorded EEG whilst participants performed a learning task. In this task, participants were first trained to internalise optimal action-outcomes based on reward, followed by a forced-choice testing phase which created conflicts between the learned reward and best outcome, to establish the individual ability to overcome the previously internalised biases. The results showed that when conflicts arise between competing motivational systems, theta-band activity increased when the habitual/internalised behaviours needed to be overridden. While overcoming such habitual biases requires endogenous goal-directed control, our results revealed that even in a task thought to primarily trigger exogenous processes, relative mid-frontal theta power increased, and was associated, with impairing both exogenous processes of alertness and IOR. It is conceivable that this likewise reflects the recruitment of higher-level processes, possibly to overcome the exogenous attentional capture by the cue that may not always be adaptive, and certainly was not in the current experimental context. As the non-predictive cues provide no spatial or temporal information, it is conceivable that individuals may adapt a strategy to supress the (distracting) cue transients in order to optimize behaviour towards upcoming targets. This account would be in line with Cavanagh et al. 2013, showing that increases in theta-band activity were related to the success of overcoming strong habitual/inherent biases (Cavanagh et al. 2013). Thus, mid-frontal theta activity may also be indicative of the degree of cognitive control engagement in the current task (for reviews see, Cohen 2014a; Cavanagh & Frank 2014).

In addition to overcoming the capture by the cue, other factors inherent to this task may also increase the demand for control, and hence increase mid-frontal theta. Since the cues are spatially and temporally ambiguous, upcoming target events are highly uncertain. For instance, distributing attentional allocation across multiple potential target locations (e.g., left and right visual fields) increases the difficulty to engage local processing demands, as attentional resources must be diffused over two locations (Weinbach and Henik 2011). Moreover, it has been shown that the longer the cue-target interval (>400ms), the more time the participants have to engage control processes in order to prevent and resolve anticipated conflicts during target presentation (Fan et al. 2009; Weinbach and Henik 2013; Asanowicz and Marzecová 2017). Together, these factors increase the demand for cognitive control, in order to reduce the performance costs associate with high target uncertainty (see also Mackie et al. 2013), and hence may also explain the present results. Indeed, a link of mid-frontal theta to target uncertainty is supported by recent studies reporting mid-frontal theta-band increase during the anticipation of upcoming conflicts (van Driel et al. 2015) and during highly ambiguous trials, such as during non-informative cueing when target and distractor were very similar (van Diepen et al. 2016).

A third alternative explanation of the mid-frontal theta activity may involve inhibition of (micro-) saccades. Saccades and micro-saccades inevitably occur towards unexpected irrelevant stimuli whilst participants need to maintain fixation. For example, investigations with EEG into the reflexive nature of saccades directed towards a stimulus vs. anti-saccades (in the direction opposite to a stimulus), revealed an increase in evoked frontal theta-band activity particularly in the period prior to correct anti-saccades (Clementz et al. 2001). Similarly, intracranial recordings in primates have revealed increased coherence in the theta-band (and beta-band) between anterior cingulate cortex and frontal eye fields prior to pro- and anti-saccade initiation (Babapoor-farrokhran et al. 2017). The period prior to an anti-saccade reflects a phase of increased demand for control (i.e., overcoming a saccadic reflex, and instead initiating a saccade into the opposite direction). Thus, the evoked theta increases possibly relate to this enhanced demand for control and the ability to inhibit/overcome the reflexive saccadic response. Since participants were required to inhibit reflexive saccades towards cues, overcoming this reflex may partially explain the increased theta-band activity in the current experiment. However, note that the relationship with both behavioural measures of alerting and spatial orienting speaks for the notion that the theta response had a strong impact on those behavioural outcomes, regardless of whether saccadic inhibition may partially be involved.

Design considerations

As implemented in the current experimental design and numerous previous studies (for reviews see, Petersen & Posner 2012; Chica et al. 2014), tasks for studying exogenous attention shifts are typically thought to manipulate exogenous attention in isolation from endogenous attention processes. However, the current experiment reveals that one of the most widely used and classic non-predictive cueing task does not exclusively involve exogenous processes, but also recruits other endogenous processes which can counteract or reduce exogenous capture and this in anticipation of targets. In fact, as has also been discussed in previous chapters, unless dissociated by experimental design, engagement of endogenous and exogenous attention processes are likely to co-occur (Chapter 2, 3; Breska & Deouell 2014; Berger et al. 2005). Despite many studies demonstrating that endogenous and exogenous processes are dissociated in terms of behavioural and/or neural effects (e.g., Coull et al. 2000; Berger et al. 2005; Chica et al. 2013; see also Chapter 2,3), the present data indicate that task-circumstances that increase the demand for control will likely elicit a competition between endogenous and exogenous processes (see also, Berger et al. 2005; for reviews see, Awh et al. 2012; Macaluso & Doricchi 2013), mediated by mid frontal theta. Irrespective of the functional origin of this mid-frontal theta activity (e.g. whether due to the need for overcoming exogenous capture by the cues and/or reducing task uncertainty and/or inhibition of reflexive saccades), the mid-frontal theta activity is likely to reflect increased demand for control processes. Thus, our results show that even when investigating exogenous shifts of attention in isolation, endogenous control mechanisms are likely to be engaged prior to upcoming events. It is conceivable that the increased mid-frontal theta activity reflects the degree of such higher-level engagement, suppressing/counteracting exogenous processes. This also supports the concept that attentional control can interact with exogenously driven attention (Fan et al. 2009; Berger et al. 2005; for reviews see, Awh et al. 2012; Macaluso & Doricchi 2013) and highlights an interplay between higher-level and exogenous attention mechanisms.

Limitations: Motor inhibition and TMS-pulse as possible confounds of the results

The EEG analysis was performed on target-free trials. Thus, participants may have actively inhibited their manual response on those trials (due to the absence of a button press). By extension, ***motor inhibition*** may be considered an alternative explanation for the increase in theta-band activity (as opposed to cognitive control). However, theta-band increases with stopping or suppression of a manual response seem unlikely due to the following reasons: First, the time period of interest focused on pre-target activity. As implemented in the experimental design, target and target-free trials were presented in a randomized order and there was no signal (go/no-go) indicating the type of trial. Thus, it appears unlikely and non-beneficial for participants to prepare for the next (possibly target-fee) trial by inhibiting a response. Second, and more importantly, distinct oscillatory activity patterns have been related to different components of movement control such as preparation/intention, execution, and inhibition of motor responses, none of which appear to be associated with mid-frontal theta-activity (Alegre et al. 2004). Previous evidence suggest that motor inhibition in particular is associated with fronto-central oscillatory activity in the ***beta-band*** (Alegre et al. 2008; Krämer et al. 2011; Swann et al. 2013, for see review, Huster et al. 2013). More recently, a clear distinction has been proposed between the 'control of action' (e.g., motor response) and the 'control of cognition' (e.g., conflict): Within a (partially) overlapping fronto-subthalamic circuit, fronto-central beta-band activity appears to be associated with the inhibition of a motor response (i.e., the implementation of control over an action/no-action), whilst low frequency theta-band activities (2-8Hz) have been linked to the need of control during cognitive processes such as conflict (Aron et al. 2016). This speaks towards the notion that the mid-frontal theta response revealed in this experiment is likely due to increased demand for control rather than motor inhibition.

Another factor to consider in the interpretation of the results is a potential expectancy effect of the ***TMS single-pulse***. On a subset of trials (240 out of a total 960 trials), concurrent single-pulse TMS was delivered at the last expected target onset (i.e., 708.8ms post-cue) over right parietal cortex. The analysis of this subset of TMS-EEG trials is beyond the scope of this thesis. However, it needs to be considered to what extent TMS-trials may have impacted on TMS-free trials (i.e., target-free EEG trials and/or behavioural target-trials). These TMS-trials can be considered as rare events, randomly interleaved with TMS-free trials; hence expectancy effects of the forthcoming TMS click and sensation may have occurred during EEG and behavioural trials. However, even in case of such expectancy effects, it appears unlikely that these would have differed systematically between the cueing conditions. Instead, any consequences of expectancy should be similar across all trials and throughout the experiment, as there was no information regarding the likelihood of the TMS-pulse. Hence expectancy of the pulse appears unlikely to explain the oscillatory and behavioural differences observed in the analysis of the target-free EEG signal and the behavioural target-trials.

Asymmetric theta-band activity in response to exogenous spatial orienting

Note that in response to spatial cueing, the cluster-based permutation testing revealed a significantly stronger theta-band power increase in response to left cues as compared to right cues (**Figure 17** A). Functional asymmetries between incoming information from the left and right visual fields have been observed before, where left visual field stimuli are processed faster and more accurately than right visual field stimuli (e.g., Nicholls et al. 1999; Suzuki & Hoshiyama 2011; Voyer et al. 2012; Newman et al. 2017). For example, left visual stimulation (as compared to right visual field stimulation) has resulted in a left visual field bias associated with a larger P300 amplitude in the ERP response (Suzuki and Hoshiyama 2011). This left visual field bias may reflect a stronger engagement with left cues (or stronger difficulty to disengage from left cues) (Śmigasiewicz et al. 2015, 2017). Thus, visual field asymmetries appear to be reflected in the underlying EEG response and they emerged as an increased theta response to LVF cues in the current study. Regardless, of this asymmetry the revealed *relative increase* in mid-frontal theta-band power correlated with the expected target T4 onset (i.e., IOR) in both left and right visual fields.

Conclusion

Our findings inform the following three points. First, the results provide partial evidence of alpha desynchronization reflecting a general mechanism to facilitate visual perception, including in response to cues inducing exogenous attention processes. Second, the findings provide evidence of theta-band activity being predictive of the ability to overcome the influence of exogenous attentional capture, which is not task-relevant in the experimental setting (as non-predictive of target position). Third, the experiment provides information on the latent interplay between endogenous and exogenous attention. Typically, experiments are designed in an attempt to investigate exogenous and endogenous processes affecting perception in isolation. Yet, in real-world situations they are likely to interact and compete for limited attentional resources (Berger et al. 2005; Fan et al. 2009; Awh et al. 2012; Scalf et al. 2013). Hence, this study highlights the interplay between higher-level processes and exogenous attention mechanisms, with cognitive control overriding the latter processes even in tasks that supposedly trigger primarily exogenous processes selectively.

4.5 Appendix

Pearson’s correlation analyses

For completeness, **Figure 18** shows the Pearson’s correlation analyses corresponding to the correlations presented in the main text. Note that the effects are identical to the results revealed by the Spearman’s rank analyses, except for the correlation between relative alpha-band desynchronization and spatial orienting effect (comparison **Figure 18** C and **Figure 15** B from main text). Here, the Pearson’s correlation revealed the same effect in terms of directionality and limitation to left visual field, however much later in time (~550ms post-cue). Again this speaks towards the fact that this correlation is considered inconclusive (see discussion). All other effects are consistent across both analyses.

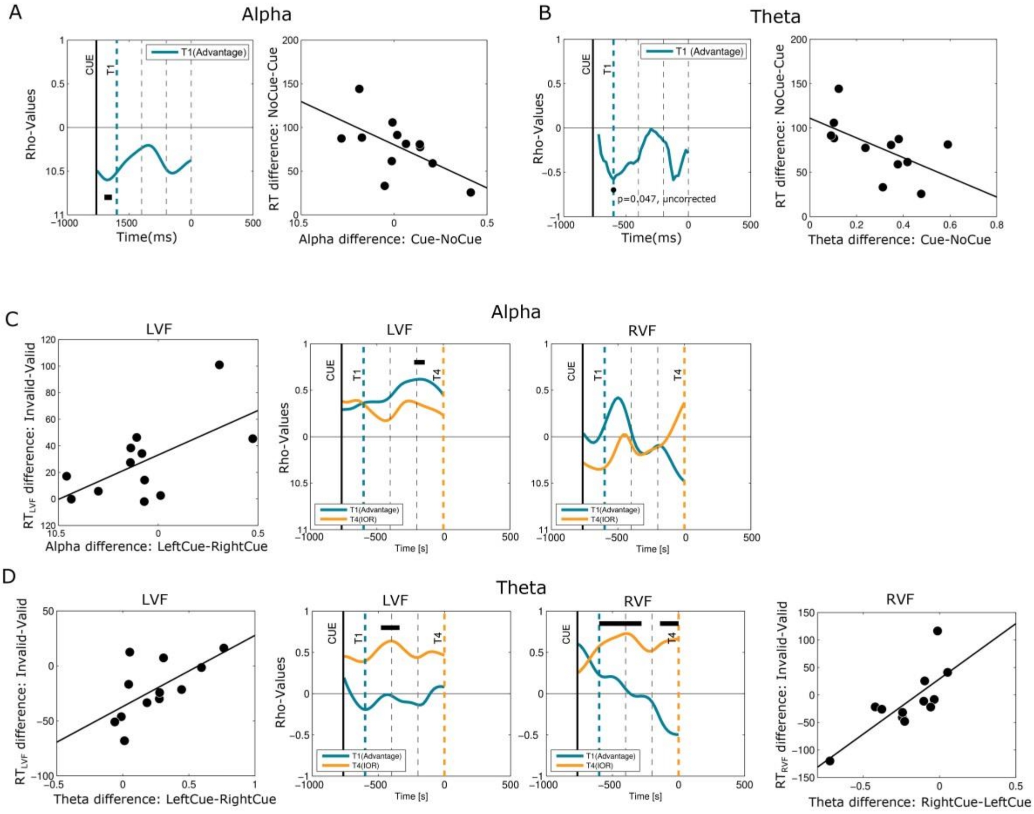


Figure 18: Between-subject Pearson’s correlation analyses. (A) Correlations between the difference in relative alpha-band desynchronization and alertness. **(B)** Same as in (A) correlation between relative theta-band synchronization and alertness. **(C)** Correlation between the relative alpha-band desynchronization (contralateral minus ipsilateral relative to the cues) and spatial orienting effects for the left and right visual fields at both the shortest and longest cue-target intervals (T1 = green, T4 = orange) respectively. **(D)** Same as in (C) but for relative theta-band synchronization and spatial

orienting effects. Scatter plots show the relationships averaged over corresponding significant time points. Black bars represent significant correlations ($p<0.05$, cluster-corrected). Solid black line represents cue onset, dashed black lines represents target onset at the shortest-cue target interval (T1) and longest cue-target interval (T4), dashed grey lines represent remaining target onsets (T2, T3), zero corresponds to the last cue-target onset.

Chapter 5

General Discussion

The current series of experiments shed light on the neuroanatomical substrates and oscillatory correlates related to different aspects of visuospatial attention. The results showed that despite robust behavioural dissociations between endogenous and exogenous attention processes, both processes appear to partially overlap on a neural level. Furthermore, the findings call into question the ability to dissociate both types of orienting within typically utilised spatial attention tasks.

Visuospatial attention is influenced by both endogenous and exogenous factors. In the experimental design implemented in **Chapter 2,** behavioural dissociation of both types of attention was achieved when manipulating them simultaneously, which effectively avoided mutual confounds. By utilizing the same task with concurrent MRI-guided TMS in **Chapter 3**, a potential functional overlap was revealed in that both, the ventral (i.e., rTPJ) and dorsal attention network node (i.e., rIPS) were implicated in exogenously driven attention. Furthermore, investigation of the extent to which oscillatory signatures in different frequency bands predict behavioural outcome during exogenous attentional orienting (**Chapter 4**) revealed that cognitive control mechanisms, as indexed by mid-frontal theta oscillations, heavily influence the degree of automatic attentional capture even in tasks which putatively trigger exogenous processes in isolation.

Reflecting on the current and previous findings, it appears that the endogenous and exogenous attention systems are not as strictly separated as often assumed; rather they likely complement each other in a flexible way depending on the experimental context. Below, I discuss the behavioural and functional dissociation vs. interaction of the endogenous and exogenous attention systems, and how future experimental designs may effectively manipulate both processes simultaneously (instead of in isolation) to reveal the full extent of interplay at both the behavioural and neural levels.

5.1 A flexible visuospatial attention system

Endogenous and exogenous attention processes have been behaviourally dissociated both in the current experiments and in numerous previous studies (**Chapter 2 and 3**; Lupiáñez et al. 2004; Berger et al. 2005; Funes et al. 2007; Rohenkohl et al. 2011; Pinto et al. 2013). This independence likely underlies our ability to maintain and act in accordance with (internal) behavioural goals whilst also effectively reacting to salient (unexpected, external) sensory events.

Given the behavioural dissociation, it is conceivable that the two attention systems may also be implemented in functionally distinct neural circuits. This may go along with a segregation of brain networks and distinct neurophysiological responses that are potentially implicated at different stages. However, while functional neural distinctions have been reported (Coull et al. 2000; Mayer et al. 2004; Natale et al. 2009; for review see, Corbetta and Shulman 2002; see also Bartolomeo and Chokron 2002 for clinical-anatomical data review), for both attentional systems to operate effectively they must also interact. This could result in partially overlapping brain regions being implicated in both types of attention, yet with specific regions being exclusively involved in only one attentional process (see also Chica et al. 2013). The most prominent neuroanatomical model posits a ***dorsal fronto-parietal network*** mainly implicated in endogenous orienting and a ***ventral fronto-parietal network*** mainly implicated in exogenous (re-)orienting (Corbetta and Shulman 2002). Interestingly, potential **interactions/convergences** between the dorsal and ventral network have been reported (for reviews see, Chica et al. 2013; Vossel et al. 2014). In line with this work, **Chapter 3** highlighted a joint implication of rIPS and rTPJ during exogenous orienting (see also Chica et al. 2011). Extending previous findings, this suggests that the parietal part of the dorsal network (i.e., rIPS; but not rTPJ) may act as a node implementing not only endogenous attentional control as shown by others (Capotosto et al. 2009; Chica et al. 2011; Capotosto, Babiloni, et al. 2012; Vossel et al. 2014), but also attentional responses to exogenously driven signals (as shown in **Chapter 3**; Chica et al. 2011; Capotosto, Corbetta, et al. 2012) (**Figure 19**, yellow/blue pattern). However, it is unclear whether the rIPS activation by exogenous signals occurs indirectly via the ventral system (Corbetta and Shulman 2002; Shulman et al. 2009; Vossel et al. 2012) or is directly driven via bottom-up input from the visual cortex (Buschman and Miller 2007; Ruff et al. 2008; Siegel et al. 2008). For instance, evidence for the former has been shown by Vossel et al. (2012) who investigated the functional architecture during visuospatial attention shifts with fMRI. They showed that invalid cueing increased effective connectivity from rTPJ to rIPS, in line with the suggestion that rTPJ signals the appearance of salient unexpected stimuli to rIPS in order to update ongoing activity and re-direct attention accordingly (Corbetta and Shulman 2002; Vossel et al. 2012). On the other hand, a TMS-fMRI study by Ruff et al. (2008) showed that rIPS-TMS induced BOLD changes in V1-V4 vs. V5/MT were strongly depending on concurrent visual input (visual stimuli absent vs. motion stimulation), highlighting the direct (feed-forward) projections between visual cortex and IPS. In contrast, the influence of FEF-TMS on visual cortex was independent of visual input, suggesting that FEF may primarily be involved in top-down attentional control (Ruff et al. 2008). Irrespective of whether IPS is directly or indirectly implicated in exogenous orienting, these findings collectively suggest a partial overlap where IPS integrates both bottom-up and top-down signals, in contrast to FEF which may exclusively signal top-down control (see **Figure 19** for a schematic illustration).

Interestingly, the distinction between parietal vs. frontal regions is in line with a recently proposed ***'hybrid model'*** of attentional control (Duecker and Sack 2015). This model proposes region-specific asymmetries along the dorsal fronto-parietal network in which frontal regions mediate a general top-down enhancement on perception with a right frontal hemispheric dominance coding for both visual fields, whereas the posterior parietal cortex of each hemisphere mediates attention to the contralateral visual field. In principle, the 'hybrid model' combines all three earlier proposed models of 'hemispheric dominance' (Heilman and Abell 1980), 'interhemispheric competition' (Kinsbourne 1970b) and the functional-neuroanatomical model of Corbetta and Shulman (Corbetta and Shulman 2002). However, it only accounts for the dorsal fronto-parietal network and its association with endogenous top-down control, not the ventral network and/or the potential overlap with exogenously driven attention. According to the findings described above, such overlap between both types of orienting may be implemented in posterior parietal regions (Figure 19). Note that other potential interactions/convergences (not depicted in Figure 19) between both systems have also been suggested to occur via the inferior frontal gyrus (IFG) (Fox et al. 2006; Asplund et al. 2010), the middle frontal gyrus (MFG) (Fox et al. 2006; He et al. 2007) and the SLF II, the latter providing a direct communication pathway between ventral parietal and dorsal frontal regions (Thiebaut De Schotten et al. 2011).

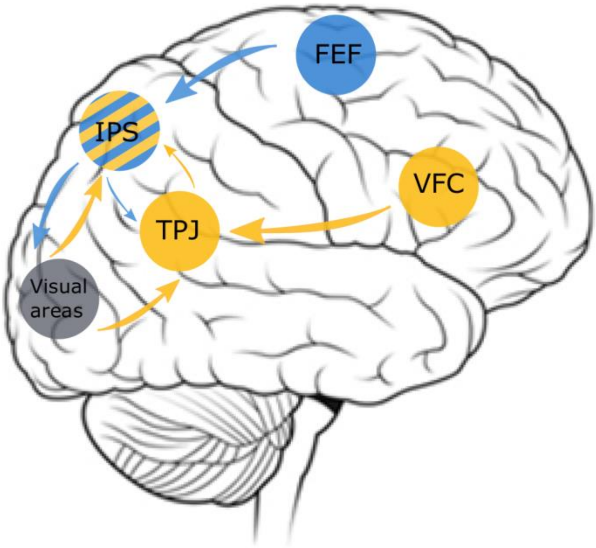


Figure 19: Adapted schematic neuroanatomical illustration of the dorsal and ventral fronto-parietal attentional network nodes of the right hemisphere (based on the model of Corbetta and Shulman 2002). The dorsal fronto-parietal network nodes are depicted in blue (IPS = intraparietal sulcus; FEF = frontal eye fields). The ventral fronto-parietal network nodes are depicted in yellow (TPJ = temporo-parietal junction; VFC = ventral frontal cortex). Potential *functional* overlap between both systems is depicted by yellow/blue pattern (IPS). Arrows indicate the main pathways of top-down (blue) and bottom-up control (yellow) (i.e., arrows indicate direct and indirect connections and do not represent a true reflection of anatomical connections).

Further evidence for this functional specialisation between visual, parietal and frontal regions has been provided by investigation of the oscillatory dynamics that mediate visuospatial attention shifts. Interestingly, endogenous attention shifts and exogenous (re-)orienting likewise result in widespread frequency-specific modulations with only a few differences across visual/parietal and frontal regions (cf. Siegel et al. 2008 on endogenus and Proskovec et al. 2018 on exogenous attention). For instance, the MEG study by Siegel et al. (2008) utilized spatial cues to induce endogenous attention shifts. The results showed that cue-induced (pre-target) alpha and beta-band responses were strongly suppressed contralateral to the attended visual field (most pronounced over occipital and parietal (IPS) regions), whereas during target processing gamma-band synchronization was strongly enhanced over the same regions. In contrast, frontal regions (FEF) showed beta-band suppression before and during target processing (independent of the analysis period, i.e. both pre- and post-stimulus). This highlights that endogenous control is mediated by frequency specific changes across the dorsal fronto-parietal network, where alpha-band suppression facilitates performance and gamma-band enhancement plays a crucial role in stimulus processing (Siegel et al. 2008). Instead of manipulating endogenous attention shifts, Proskovec et al. (2018) tested exogenously triggered attentional (re-)orienting by utilizing a classic Posner paradigm (similar to **Chapter 4**; Posner 1980) with MEG. Their results showed a recruitment of multiple regions that form part of the dorsal and ventral attention network, which were linked to distinct oscillatory responses in the theta-, alpha- and beta-band. Similar to the findings described by Siegel et al. (2008), alpha and beta-band power decreased over occipital/parietal regions during target processing. However, unlike the beta-band suppression over frontal regions during endogenous attention shifts, a general theta-band increase during target processing was observed over visual, ventral frontal (i.e., left prefrontal cortex, right inferior frontal gyrus) and dorsal frontal regions (right FEF). Yet over pre-frontal cortex, this theta-band increase was stronger in response to invalidly cued targets (relative to validly cued targets). The authors suggested that this could possibly be related to executive control and the need to (re-)orient attention towards un-cued target locations (Proskovec et al. 2018). However, their results did not allow conclusions to be drawn as to whether the observed increase in the theta-band was related to facilitation or inhibition of the respective target processing. Thus, this increase in theta-band may also have reflected the need to control the conflict created between cued vs. uncued target processing. This would speak towards increased engagement of control processes in order to overcome erroneous responses (also see discussion in **Chapter 4**).

In summary, it appears that even though at the behavioural level endogenous and exogenous attention can act independently, at the neural level this dichotomy may not be so clear. Rather, partially overlapping circuits are implicated that interact in a flexible way (Chica et al. 2013; Macaluso and Doricchi 2013; Vossel et al. 2014). More specifically, evidence from neuroimaging and TMS studies points to a neural overlap in parietal regions which respond to both endogenous (top-down) and exogenous (bottom-up) signals. Additionally, regardless of whether attention is endogenously engaged or exogenously driven, alpha/beta-band modulations over occipital and parietal regions show a similar pattern; with alpha/beta-band decreases enhancing visual perception (**Chapter 4**; Feng et al. 2017; Harris et al. 2017; Proskovec et al. 2018). This is in contrast to dorsal frontal regions (e.g. FEF) which may primarily implement top-down control (Corbetta and Shulman 2002; Ruff et al. 2008; Siegel et al. 2008). Further studies are required to test the extent of differences/similarities with respect to oscillatory dynamics over frontal regions (e.g., beta-band suppression over FEF during endogenous control vs. theta-band increases over frontal regions during exogenous (re-)orienting). Additionally, whether or not neural and/or behavioural interactions occur may depend on various factors, including task demands, temporal constraints, history of events and strategies employed during task performance (Awh et al. 2012; Macaluso and Doricchi 2013; Parks and Madden 2013; Vossel et al. 2014).

5.2 Design choices: Simultaneous (instead of isolated) manipulation of endogenous and exogenous attentional processes

Exogenous and endogenous attention shifts have classically been separated by experimental design, whereby the ***‘classic’ designs*** usually involve centrally presented endogenous cues (e.g., symbolic cue) predicting upcoming targets vs. non-predictive peripherally presented exogenous cues (e.g., brief change in luminance) (see Chapter 1 and reviews in Petersen and Posner 2012; Chica et al. 2014). The findings from these studies have informed (spatial) attention research and led to fundamental theories on how our senses may implement mechanisms to ‘filter’ relevant from irrelevant information. While these paradigms result in robust and well established effects, and are easily implemented in a laboratory setting, they necessarily reflect a simplification of complex attention processes that interact and compete for attentional resources in everyday life. This simplification (by separation) may lead to mutual confounding effects in terms of behaviour but also at the neural level. For instance, as discussed in previous chapters and by others (Folk et al. 1992; Ansorge and Heumann 2003; Breska and Deouell 2014; for reviews see Ruz and Lupiáñez 2002; Macaluso and Doricchi 2013), exogenous cues may still trigger control processes due to the adaptive/strategic behaviours (unintentional or intentional) in which participants may engage during task performance. Conversely, endogenous symbolic arrow cues are also likely to exogenously capture attention, possibly due to the overlearned and/or inherent meaning of the chosen cues (e.g., Hommel et al. 2001; Pratt et al. 2010; Reuss et al. 2011). To what extent this (co-)activation of both attentional processes occurs is challenging to estimate, unless it is taken into account by the experimental design.

Here, we sought to engage both the endogenous and exogenous attention system simultaneously within trials (as implemented in **Chapters 2 and 3**), instead of separating/isolating them by sessions, blocks or trial-by-trial. In the utilised design, the participant is endogenously engaged in a specific aspect of the task, whilst task-irrelevant distractors also exogenously drive attention. This controlled way of deploying attention and engaging the participant avoids unwanted strategies being adopted with regard to the exogenous cues. Thus, any attentional effects can more accurately be interpreted to reflect the desired processes respectively (if dissociated), and interactions/relationships between the attentional systems can be tested on both the behavioural and neural levels. Furthermore, the simultaneous testing of both types of attention reflects a more ecologically valid, ‘real-life’ situation, since we usually operate according to our internal goals, whilst unexpected events in our environment ***concurrently*** trigger exogenous shifts (not separately).

Thus, for simultaneously manipulating endogenous and exogenous attentional effects, the following four task variables are crucial to consider: Firstly, the ***cue-cue interval*** (i.e. the interval between endogenous presentation and exogenous cue onset). This interval should allow enough time for initial endogenous attention deployment. Thereafter, exogenous cue presentation can follow, whilst crucially however the endogenous cues should remain presented to discourage any disengagement from endogenous deployment. Secondly, the ***cue-target interval*** should allow for the endogenous deployment of attention to occur (> 300ms), but also trigger exogenous shifts (either facilitation <300ms or IOR >300ms as intended). Thirdly, the ***cue-predictability***: Whilst endogenous cues should be predictive, exogenous cues should be non-predictive of the upcoming target locations. This incentivises full deployment of endogenous attention to cued locations, and disengagement of voluntary attention from exogenous cues. Lastly, the ***task instructions*** given to the participants should encourage them to utilize the information provided by the endogenous cues whilst declaring exogenous cues as task-irrelevant, thereby avoiding strategic adaptations in response to the latter. As implemented in Chapters 2 and 3, this design allowed manipulation of both processes across a longer time window of ~2s, ensuring that endogenous attention was fully deployed, whilst exogenous attention was concurrently driven by apparent motion without tapping into IOR effects (see also Breska and Deouell 2014 for a similar design using centrally presented stimuli). With enhanced control over endogenous factors, it is unavoidable that the paradigm becomes more complex as a consequence of which other concerning/unwanted effects may arise. For instance, in case of long cue-target intervals, participants may try to adopt multi-tasking and/or task-switching strategies by distributing or splitting attention across both types of cues. However, if this were the case, I would expect a detrimental effect on one of the cueing effects, as this increases the demand for cognitive resources (Monsell 2003; Philipp et al. 2008). Importantly, if instructed appropriately, participants should have no incentive to do so and even if they did, the simultaneous modulation would still reflect a more realistic situation applicable to the real-world.

Interestingly, a few other studies have also tried to achieve a similar goal. For instance, a study by Thomsen et al. (2005) employed endogenous central cues simultaneously presented with exogenous peripheral cues. However, since the cue-target interval was fixed at 300ms, they did not account for the fact that both types of orienting evolve over different time scales (e.g., Klein 2000; Chica et al. 2014). Hence, for each process the cue-target interval should be optimized, otherwise attention (and/or potential interactive) effects may be missed. In addition, they only tested conflicting (incongruent) cue conditions (i.e., exogenous cue valid/endogenous cue invalid or exogenous cue invalid/endogenous cue valid), whereby neither of the cues predicted the upcoming target location (non-informative endogenous and exogenous cues). Two other studies also utilized a similar paradigm, accounting for the different cue-target intervals and cue-predictability. However endogenous and exogenous cues were presented consecutively as separate events (Berger et al. 2005; Natale et al. 2009) instead of simultaneously. The latter is crucial to discourage any potential engagement of endogenous deployment of attention with the exogenous cues.

5.3 Reflection and outlook

In the current experiments, I successfully replicated (internally) the behavioural cueing effects induced by the (rhythmic) visuospatial cueing paradigm (**Chapters 2 and 3**) originally reported by de Graaf et al. (2013), as well as the classic alertness and spatial cueing effects (**Chapter 4**) originally reported by others (Posner 1980; Petersen and Posner 2012). In addition, the EEG analysis in Chapter 4 revealed the previously reported attention-related lateralised alpha-band modulations over occipito-parietal regions (see Foxe & Snyder et al. 2011 for a review). This is important given that in recent years, numerous published findings have been found to be unreliable when attempts have been made to replicate them (Open Science Collaboration 2015). Surveys have suggested a variety of causes such as publication bias (the tendency for only significant effects to be published), pressure to publish, low power and insufficient replication attempts by the original researchers prior to publication (e.g., Baker 2016). To avoid biased reporting and to ensure the robustness of effects, it is crucial to report both successful and unsuccessful replication attempts (see Veniero et al. 2017). Importantly, replication of findings is only one way to avoid the above raised issues and this does not preclude reporting unexpected (new) findings. Additional preventive factors include pre-registration of study designs, open access to data and analysis pipelines (e.g. see ‘Open Science Framework (OSF)’ https://osf.io/) and employing a combination of different inferential statistical methods. For example, complementing classical frequentist with Bayesian statistical approaches, as implemented in Chapter 3, may be one helpful way forward (for a discussion see Leek et al. 2017; McShane et al. 2017). This combination is increasingly being applied and has recently been facilitated by open source software (e.g., JASP (JASP Team 2018); R code also available) which helps to disseminate and unify tools for best practice across researchers (Verhagen and Wagenmakers 2014; Dienes and Mclatchie 2017; Wagenmakers et al. 2018).

The findings presented in this thesis provide scope for potential follow-up experiments, regarding both the oscillatory signatures and neural substrates that underlie visuospatial attention. Regarding oscillatory signatures, it would be interesting to further investigate the top-down influence of theta-band power (Chapter 4), by manipulating exogenous cue predictability from non-predictive to 100% predictive. If the theta response reflects a control process that impairs exogenous attentional capture, I would expect a decrease in theta power with increasing predictability of the exogenous cue, as with enhanced predictability this cue becomes more task-relevant, which should reduce the need for engaging in cognitive control processes. In addition I would expect that with increasing exogenous cue predictability, the typically observed alpha-band power lateralisation over occipito-parietal regions should become even more pronounced. This experiment could also include replication of the effects reported here, and the EEG analysis could be directly informed by the current results. Crucial in this design variant would be how explicitly participants are informed about the cue predictability (see Gould et al. 2011 for a similar manipulation). A second interesting experiment would be to account for possible control mechanisms by simultaneously manipulating endogenous and exogenous processes, similar to the implementation in Chapter 2 and 3. This may allow for establishing exogenous neural correlates whilst avoiding endogenous confounds. A crucial aspect here would be the choice of physical stimuli, as the rhythmic apparent motion stimulation (moving and flashing from gray to white on a black background)implemented here would evoke strong evoked potentials in the EEG signal. These physically evoked responses are challenging to dissociate from ongoing oscillatory activity in the EEG.

In terms of neural substrates, it would be interesting to further probe the interactions between the dorsal and ventral parietal attention network nodes. For instance, one could specifically test the causal directional influence that exogenously drives the dorsal parietal network nodes (i.e., IPS), with direct interactions via visual cortex and/or indirectly interactions via TPJ being the candidate mechanisms. One approach to answering this question could be to employ combined fMRI-TMS. This idea is similar to a study conducted by Leitao et al. (2015), who investigated the influence of rIPS-TMS on rTPJ, yet the reverse effect remains to be tested (e.g., influence of rTPJ-TMS on rIPS).

Regarding the recently proposed ‘hybrid model’ of attention control (Duecker and Sack 2015), it would be of interest to investigate to what extent the dorsal parietal vs. frontal distinction also applies to the ventral fronto-parietal system (which has been omitted in this model), particularly when attention is exogenously driven.

Another interesting question would be to investigate how the implication of the dorsal fronto-parietal and ventral fronto-parietal systems evolve over time (e.g., Chambers et al. 2004). This may reveal that interactions occur at specific time points within certain nodes and would help us to better understand the temporal dynamics of endogenous and exogenous processing across both networks.

Furthermore, the posterior parietal cortex consists of different functionally and anatomically defined sub-regions (e.g., Sack 2009; Silver and Kastner 2009). such as superior parietal lobule (SPL), angular gyrus (AG), supramarginal gyrus (SMG), anterior intraparietal sulcus (aIPS) and posterior intraparietal sulcus (pIPS) which have been implicated in different aspects of attentional selection. For instance, SPL and SMG have been suggested to play a role in selecting relevant information by mediating attentional competition (Chambers et al. 2006). Moreover it appears that while the SMG (but not AG) is involved in strategic attentional deployment (Chambers, Stokes, et al. 2004; Schenkluhn et al. 2008), the AG (but not SMG) is crucial for reorienting of attention (Rushworth et al. 2001; Chambers, Payne, et al. 2004; see also a discussion by Chambers and Heinen 2010). Hence, it would be interesting to further probe the role of specific sub-regions and their interactions.

Note that in general, there appears to be a discrepancy/inconsistency in the literature on the validity of TMS targeting using functionally (e.g., based on fMRI) vs. anatomically defined TMS target locations. Each method may have advantages and disadvantages depending on the question. For instance, when TMS targets are based on functionally acquired activation maps (revealed by previous fMRI studies), (de-)normalization procedures of the target coordinates between native and common space are usually required (e.g., as implemented in Chapter 3). These transformation procedures may not reflect the optimal stimulation location in each individual participant, unless functional activation maps are acquired individually. While anatomically defined locations can be more precisely determined in every participant, this requires detailed neuroanatomical knowledge and is associated with difficulties in target selection as some anatomical regions may be relatively large (e.g., rTPJ comprises the inferior parietal lobule and parts of the superior temporal gyrus or IPS can be sub-divided in anterior and posterior parts).

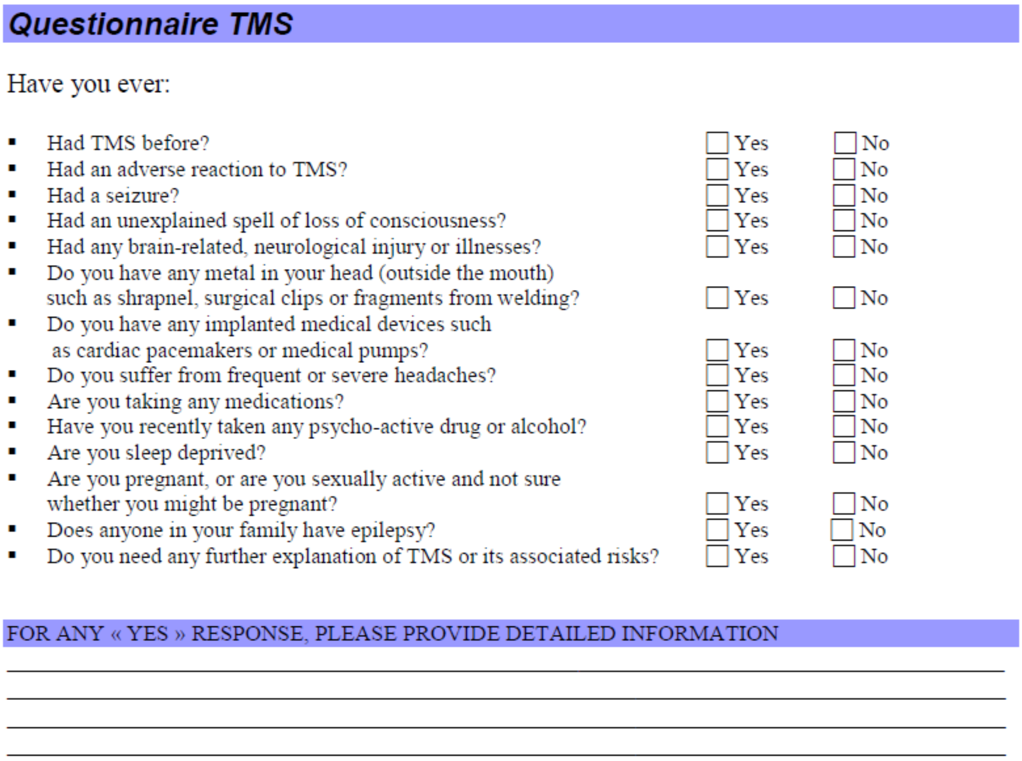
5.4 Conclusion

Previous studies have made a clear distinction between endogenous and exogenous attentional systems, usually also trying to separate them by experimental design. However even when tested in isolation, these two attention systems likely still influence each other and may not be as strictly dissociated as often assumed (and/or tested), in particular at the neural level. This is highlighted by the results in **Chapter 3**, showing that the dorsal and ventral attention networks are not as functionally dissociated as previously suggested; instead both parietal network nodes (i.e., rIPS and rTPJ) are implicated in exogenously driven attention. Moreover, the findings in **Chapter 4** have shown that even a classic design triggering exogenous attention shifts is influenced by cognitive control components. Hence, to effectively test the dynamic interplay of both systems, or when interested in the exogenous attention system in isolation, the classic experimental designs appear to be too simplistic and require modification to account for potential confounds (e.g., as implemented in **Chapter 2** and **3** and discussed in **5.2**). Overall, the findings of this thesis are of interest to inform future visuospatial attention, neuroimaging and TMS studies and may eventually facilitate improved understanding of spatial attention deficits such as those observed in hemispatial neglect.

Supplemental Material

Supplement 1: Link to Spreadsheet containing individual participant data of Chapter 2 (experiment 1). Sheet 1: Performance accuracy. Sheet 2: Reaction time. Available at: https://doi.org/10.1371/journal.pone.0144082.s001 (XLSX)

Supplement 2: Screening questionnaire for TMS safety



Questionnaire TMS

Have you ever:

▪ Had TMS before?	☐ Yes	☐ No
▪ Had an adverse reaction to TMS?	☐ Yes	☐ No
▪ Had a seizure?	☐ Yes	☐ No
▪ Had an unexplained spell of loss of consciousness?	☐ Yes	☐ No
▪ Had any brain-related, neurological injury or illnesses?	☐ Yes	☐ No
▪ Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips or fragments from welding?	☐ Yes	☐ No
▪ Do you have any implanted medical devices such as cardiac pacemakers or medical pumps?	☐ Yes	☐ No
▪ Do you suffer from frequent or severe headaches?	☐ Yes	☐ No
▪ Are you taking any medications?	☐ Yes	☐ No
▪ Have you recently taken any psycho-active drug or alcohol?	☐ Yes	☐ No
▪ Are you sleep deprived?	☐ Yes	☐ No
▪ Are you pregnant, or are you sexually active and not sure whether you might be pregnant?	☐ Yes	☐ No
▪ Does anyone in your family have epilepsy?	☐ Yes	☐ No
▪ Do you need any further explanation of TMS or its associated risks?	☐ Yes	☐ No

FOR ANY « YES » RESPONSE, PLEASE PROVIDE DETAILED INFORMATION

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