COMBINED TMS-EEG

STUDIES OF VISUAL ATTENTION

Submitted by

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I hereby declare:

That the PhD thesis: “Combined TMS-EEG studies of visual attention” authored by Francesca Bocca, and supervised by: Dr. Paul Taylor, Prof. Dr. Hermann Müller and Dr. Roger Kalla, in fulfillment for PhD requirements at the Graduate School of Systemic Neuroscience, was defended on February 3rd, 2015. The examination committee consisted of Dr. Paul Taylor, Prof. Dr. Hermann Müller, Prof. Dr. Stefan Glasauer and Prof. Dr. Paul Sauseng.

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“Thus the duty of the man, who investigates the writings of scientists, if learning the truth is his goal, is to make himself an enemy of all that he reads, and, applying his mind to the core and margins of its content, attack it from every side. He should also suspect himself as he performs his critical examination of it, so that he may avoid falling into either prejudice or leniency.”

Ibn al-Haytham

“Doubts Concerning Ptolemy”

SUMMARY

The simultaneous application of TMS and EEG combines the ability to draw causal inferences on the role of specific cortical areas with recording neural activity with a high temporal resolution. This thesis studies two aspects of visual attention employing TMS-EEG: the first part is concerned with how action and perception interact during visual search, and the second with the relationship between cortical excitability and spatial attention orienting.

Part 1: Combined TMS-EEG and Visual search

The first study was designed to investigate the role of the right angular gyrus (rAng) in intertrial effects in visual search. We employed a compound search task, which allowed us to dissociate between target- and response- defining stimulus characteristics and therefore assess whether the rAng would be causally involved in either, or in an interaction between them. rAng TMS made reaction times faster when trials contained a complete repetition of both target-defining feature and response. This effect was mirrored in the ERP, as we found that the N1 component's amplitude increased in the same type of trials. These results suggest that the rAng is involved in the formation and maintenance of combined expectancies, therefore linking perception and action, facilitating trial-by-trial adaptive performance.

Part 2: Spatial cueing and phosphene perception

The second project consists of two experiments exploring the relationship between cortical excitability and spatial attention orienting. On each trial, we presented an endogenous spatial cue, after which TMS was applied over a part of the right occipital cortex from which phosphenes could be evoked. On some trials, a visual stimulus was also presented at the time of the TMS pulse, on which the participants had to perform a discrimination task.

In the first experiment, we employed TMS below phosphene threshold; the lack of phosphene perception allowed us to investigate the interaction between spatial attention and cortical excitability through modulations in the TMS-evoked potential (TEP), without the potential confound of a visual stimulus being present. We observed that TMS over the right occipital cortex affected left- and right-cued trials differently as measured by the TEP (in the time bin 240-280 ms). This result suggests that attention modulates cortical excitability in the absence of perception, similarly to what has been described from other methods as a ‘baseline shift’.

In the second experiment, TMS was applied at phosphene threshold; participants could therefore perceive phosphenes on half of trials. We observed both early (70-140 ms) and later (180-240, 240-280 and 280-400 ms) differences between phosphene presence conditions, suggesting that phosphene perception is generated through recurrent waves of cortical processing. We also observed dissociable cueing effects for phosphene present versus absent trials, which are likely to be the result of baseline shifts during phosphene absent trials, and feedback processing or conscious perception of the stimulus for phosphene present trials.

Taken together, the studies in this thesis strongly agree with a view of the brain in which different processes (perception and action, or attention and consciousness) affect each other optimizing real-world performance.

LIST OF ABBREVIATIONS

ADAN	Anterior directing attention negativity
AG	Angular gyrus
BOLD	Blood oxygenation level dependent
dD	Different dimension
DTI	Diffusion tensor imaging
DWA	Dimension Weighting account
EDAN	Early directing attention negativity
EEG	Electroencephalography
ERP	Event-related potential
FEF	Frontal eye fields
FIT	Feature integration theory
fMRI	Functional magnetic resonance imaging
GS	Guided search
IOR	Inhibition of return
LDAP	Late directing attention positivity
LRP	Lateralized readiness potential
PCN / N2pc	Posterior contralateral negativity
PET	Positron emission tomography
PPC	Posterior parietal cortex
rAng	Right angular gyrus

rLRP	Response locked lateralized readiness potential
RT	Reaction times
rTMS	repetitive TMS protocol
sDdF	Same dimension, different feature
sDsF	Same dimension, same feature
sLRP	Stimulus locked lateralized readiness potential
TEP	TMS-evoked potential
TMS	Transcranial magnetic stimulation

Contents

GENERAL INTRODUCTION

NEUROPHYSIOLOGICAL TECHNIQUES

Cognitive functions are carried out by intricate networks of neurons that can be investigated at various levels of abstraction; therefore different neurophysiological techniques can provide a different understanding and highlight different processes. For example, single-neuron recordings have proven to be very useful in investigating the functional anatomy of the primary visual cortex (Hubel & Wiesel, 2005), while fMRI and DTI have been useful in revealing changes in connectivity between different areas or tackling higher-order processes like visual attention (Carrasco, 2011).

Comparing different neuroscientific methods is not simple: some are invasive, while others are not; some are best suited for animal studies, others can be applied on human participants; some require short experiments, others need a much larger number of trials. A useful way of synthetizing this is to compare them based on spatial and temporal resolution, pictured in Figure 1 (Grinvald & Hildesheim, 2004).

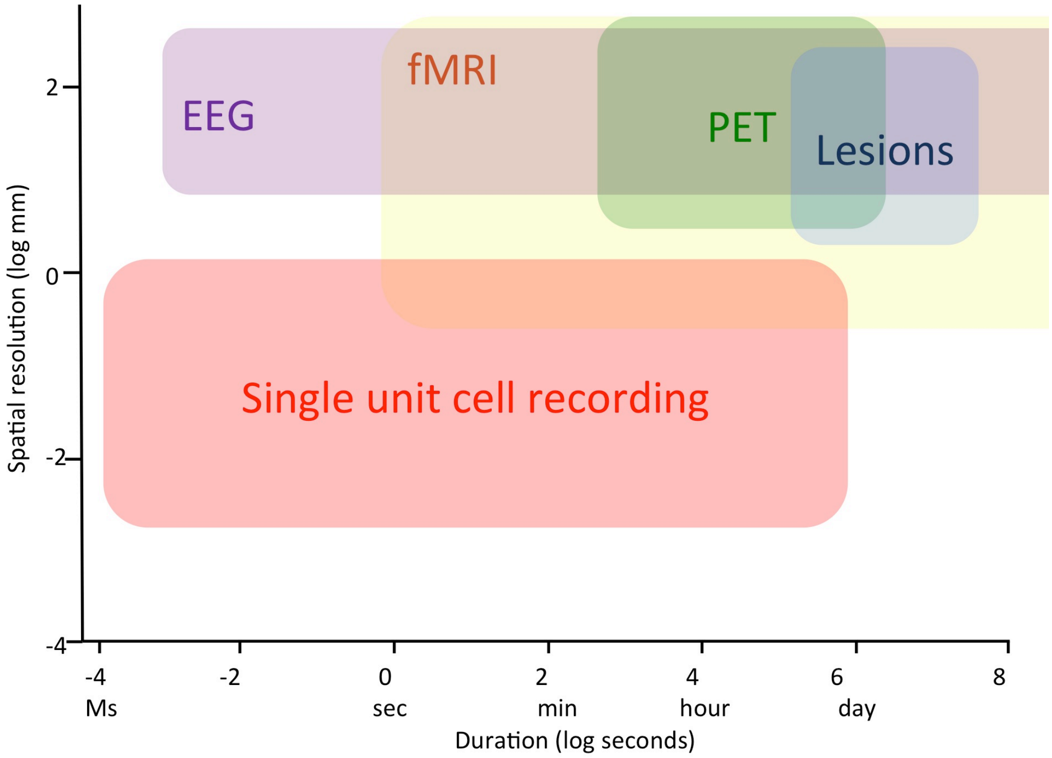

Figure 1: a comparison of different neuroimaging techniques depending on time resolution (x axis) and spatial resolution (y axis). Adapted from Ginvald & Hildersheim, 2004.

Such an illustration can prove very useful in determining which technique is more suitable for a certain research question. Interestingly, some techniques are more versatile than others, occupying a greater area in the spatio-temporal resolution coordinates in Figure 1, and therefore being useful in analysing different sizes of brain areas or different durations of brain processes.

CAUSALITY: THE CRUCIAL DIFFERENCE

However, there is one more dimension that should be considered to better compare different neurophysiological methods, which is causality, answering the question: can the neurophysiological technique of interest provide an answer about the correlation between behaviour and measurement, or can it give a hint about the causal role of a particular area?

For example, lesions on animal subjects (as observed in Figure 1) have a worse time resolution but comparable spatial resolution to PET. However, while imaging methods can only tell us which brain areas show activity that correlates with a certain behaviour or function, lesions can reveal that the ablated area is necessary for a certain task – by making the animal or the neurosurgical patient unable to perform the task anymore (Pascual-Leone, Bartres-Fazf, & Keenan, 1999).

Figure 2 shows a 3D space in which the different methods are represented, being categorised also on the basis of whether or not they allow causal inferences, in addition to temporal and spatial resolution (Walsh & Cowey, 2000). The causality dimension divides neurophysiological methods in two main categories; those that are correlational (like PET, MRI and EEG), and those that are causal (like TMS or microstimulation).

Causal techniques, in turn, differ in terms of safety, reversibility, and invasiveness. Importantly, lesions, one of the techniques used most to explore the functions of brain areas, are not reversible and therefore cannot be applied widely to human participants. Microstimulation, although often reversible, requires surgery to be fitted to the subject. Transcranial magnetic stimulation, on the other hand, is non-invasive, relatively painless, and safe if employed within the parameters contained in international guidelines (Rossi, Hallett, Rossini, Pascual-Leone, & Group, 2009; Wassermann, 1998). Screening questionnaires have been developed for the safe selection of participants to TMS studies, allowing researchers to minimize the rare occurrence of epileptic seizures caused by TMS pulses (Rossi, Hallett, Rossini, & Pascual-Leone, 2011).

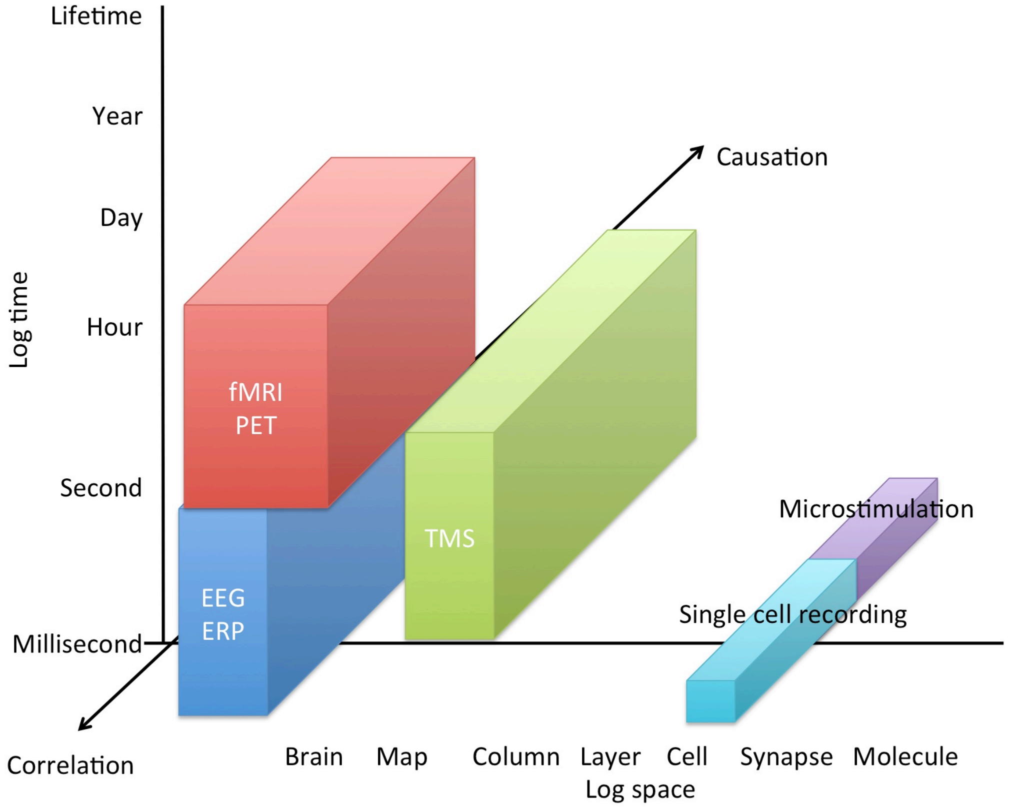

Figure 2: a comparison of different neuroimaging techniques depending on time resolution (x axis), spatial resolution (y axis), and causality (z axis). Adapted from Walsh & Cowey, 2000

TRANSCRANIAL MAGNETIC STIMULATION

PHYSICAL PRINCIPLES OF TMS

TMS employs Faraday's electromagnetic induction principle (Faraday, 1832) to induce a focal current in the brain that transiently affects the activity of the targeted neurons.

The first instance of application of TMS to humans was in 1985 (Barker, Jalinous, & Freeston, 1985). In this first study, Barker successfully obtained muscular twitches from TMS pulses to the motor cortex. The development of TMS was relatively late compared to other stimulation techniques, because of the technical challenges of creating a compact stimulator machine able to produce a 2 T magnetic field with a sufficiently short duration (rise of 100 µs and duration of 400 µs).

TMS achieves neuronal stimulation through a mechanism akin to the one of implanted electrodes; the magnetic field induces currents in the body in a manner proportional to the rate of change of the magnetic field (Barker & Freeston, 2007). It is important to remember that the stimulation is the strongest at the cortical surface, and that the maximum focus of the stimulation cannot reach deep brain areas with regular coils (L. Heller & van Hulsteyn, 1992).

Some researchers believe that the name 'magnetic' in TMS is not entirely appropriate, as it is in fact inducing electrical currents in the brain (Barker & Freeston, 2007). It has been suggested that a better name for TMS would be TMIES: transcranial magnetically induced electrical stimulation (Cowey, 2005).

Before discussing the effects that a TMS pulse has on the brain, it is beneficial to understand its technical principles. In the electric stimulator employed in TMS a capacitor needs to be charged before the machine is able to produce a pulse (this charging duration is the physical limit between two pulses if only one stimulator is employed) (Cowey, 2005). Then, the current is discharged through a coil in a very fast manner. The way the pulse is generated depends on the electrical circuitry of the machine: some produce monophasic electrical fields, while others can produce biphasic pulses, which are more physiologically effective (Cowey, 2005).

The way a TMS coil is shaped also influences the brain response. The simplest coil is circular in shape, and it the minimum field induced is under the centre of the circle, and the maximum is under the rim. The orientation of the coil is also very important (Cowey & Walsh, 2001), as neuronal fibres can only be depolarized by a change in electric field across membranes (Barker, 1998).

Nowadays, however, figure-of-eight coils (also called butterfly coils) are more commonly used. In such coils, the peak of the electric field is under the intersection of the two wire windings (Walsh & Cowey, 2000). Other designs able to focus the electric field even more have been developed, but are not used as commonly (Ren, Tarjan, & Popović, 1995). TMS machines have been developed that employ up to 100 multiple coils (called multichannel coil arrays); their individual currents can be changed to shape the stimulating fields and increase current focus even more (Ruohonen & Ilmoniemi, 1998).

The size of the coil is another important factor: the smaller the coil, the higher the spatial resolution of the stimulation. However, smaller coils overheat easily, and cannot produce the same electrical stimulation having weaker magnetic fields.

NEUROPHYSIOLOGICAL EFFECTS OF TMS

While the physical principles on which TMS is based are straightforward, there has been a debate about what exactly a TMS pulse does cause in the brain. One of the most common ways to define TMS on a neurophysiological level has been a “virtual lesion” (Pascual-Leone, Walsh, & Rothwell, 2000). This term has been very successful, as it provides a simple explanation of many of the early effects that TMS has been observed to cause on behaviour. For example, TMS has been observed to replicate attentional impairments associated with post-stroke neglect when applied to the right posterior parietal cortex (Hilgetag, Théoret, & Pascual-Leone, 2001). However, more recent studies have been able to manipulate behaviour with TMS is a way that is not compatible with the model of TMS simply creating a “virtual lesion”. TMS has been observed to enhance human cognitive performance in a variety of tasks; which has led researchers to develop alternative theories of the effect of TMS (Luber & Lisanby, 2014). Facilitatory effects of TMS on behaviour have been explained via two mechanisms: modulation of the activity in a certain area making processing more efficient, or disruption of competing processes (which is conceptually similar to removing an inhibition).

An early example of these two effects that TMS can have - disrupting or enhancing performance - comes from studies of masking. In one landmark study disrupting performance in paradigms of experimental psychology by using TMS (Amassian, Cracco, & Maccabee, 1989), researchers applied single-pulse TMS over the occipital cortex of the participants, while they were instructed to perform a letter identification task. They showed that TMS could be used to impair performance in a recognition task in a time-specific manner (Figure 3, left panel). This disruptive effect was particularly marked when the pulse happened between 80 and 120 ms after display onset. In a complementary experiment employing masking (Amassian, Cracco, Maccabee, & Cracco, 1993), it was shown that TMS could effectively “unmask” a visual stimulus, therefore enhancing task performance (Figure 3, right panel); in this experiment as well, the effect was time-specific.

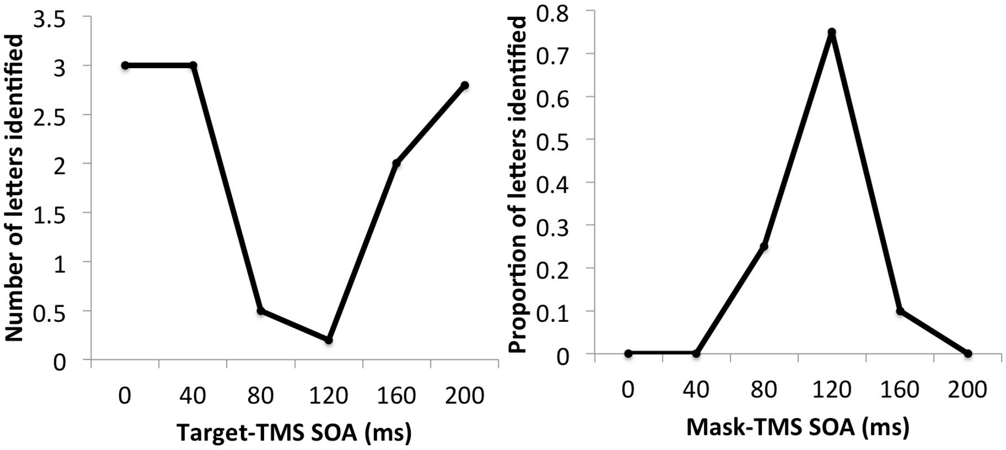

Figure 3: Left panel. Results of the experiment by Amassian et al., 1989. Number of letters identified depending on SOA. Right panel. Results of the experiment by Amassian et al., 1993. Proportion of letters identified depending on SOA.

These results have been described as a “watershed” (Walsh & Cowey, 1998), as they opened the road to TMS studies investigating the relevance of different areas to well-known psychological paradigms; they also illustrated the two main patterns of results found when TMS is applied during a cognitive task: facilitation or inhibition.

The term “modulation” is used very frequently when discussing the neuro-physiological effect of TMS, and its more general meaning is better suited to account for all the different effects that TMS has been shown to elicit on behaviour, from impairment to facilitation (McKinley, Bridges, Walters, & Nelson, 2012).

However, employing TMS alone, one can only observe changes in overt behaviour (like reaction times or error rates), while other important information (for example, the exact timing with which TMS affects an area) remains inaccessible. For this purpose, TMS has more recently been combined with other techniques, offering a deeper insight into its neurophysiological effects; for example combining TMS with fMRI can help understanding the link between structure and function (Sack, 2006; Sack & Linden, 2003). Among those particularly fruitful combinations is the one between TMS and electroencephalography (Thut & Miniussi, 2009).

COMBINED TMS - EEG

One of the reasons to combine TMS and EEG is to study the temporal dynamics of the effect of the pulse on neural activity, which can be achieved with the excellent time resolution of electroencephalography. It is also important to note that when a TMS pulse is delivered over a brain area there are also effects in the areas connected to it, and this temporal pattern can be showed in the EEG. In other words, while TMS is focal in its nature, its effects are modulated by the underlying neural connections (Taylor, Walsh, & Eimer, 2008). The development of TMS-compatible EEG electrodes, however, had to overcome many technical difficulties; the main problem was that, EEG electrodes being very sensitive, a huge artefact was created in the recording immediately following the very strong TMS pulse. Nowadays, most amplifiers can effectively stop recording (or record from an internal channel) around the time of the TMS pulse, minimizing the amplitude of the TMS artefact, and avoiding amplifier saturation (Ilmoniemi et al., 1997). Amplifiers are now very quick in recovering from TMS artefacts, and some recordings have been accomplished as short as 2 ms after TMS pulse (Ilmoniemi & Kičić, 2009), although there is no consensus as to when is the earliest time in which an artefact-free signal can be accomplished. Post-recording, furthermore, there are multiple ways to filter out or reduce the magnitude of the TMS artefact, the most common ones being ICA and excision (Ilmoniemi & Kičić, 2009).

Combined TMS-EEG studies can be further categorized by the variable of interest being analysed, and three main categories can be identified: the TMS-evoked potential (TEP), traditional ERPs, or brain rhythms either preceding or following the TMS pulse. TMS-EEG studies analysing traditional ERPs are perhaps the most straightforward; a TMS pulse is sent either in the inter-trial interval or preceding a stimulus, and the ERPs to the stimulus are then analysed. The experiment presented in the *Visual Search* chapter of the present thesis is an example of this type of study. Conversely, when the TEP is the variable of interest, the ERP immediately following the TMS pulse is analysed, typically divided in time bins; this type of experiment presents more technical difficulties caused by the closeness of the TMS artefact to the data of interest. The two experiments in the *Cueing and Visual Attention* chapter are an example. Finally, TMS-EEG studies could also be concerned with differences in brain oscillations, and how these might be affected by TMS. It has been found that TMS can cause both synchronization and desynchronisation (Komssi & Kähkönen, 2006), and can either trigger or perturb oscillatory activity (Rosanova et al., 2009).

It is important to note, however, that combined TMS-EEG still presents inherent problems, as does any other neuroscientific technique. In particular two of the limitations of EEG and TMS remain even when they are combined together; while the location of the TMS coil can be made more accurate through neuronavigation (Duecker et al., 2014), it is not possible to locate as precisely the effects of the pulse measured by the EEG. Such an aim would require additionally incorporating an imaging technique like fMRI, which has been proven to be technically difficult (Peters et al., 2013). Another limit of combined TMS-EEG is that only the surface of the cortex can be initially stimulated with TMS, limiting the investigation to the neural areas nearest the scalp surface (even though it should be kept in mind that the effects of a TMS pulse spread to other interconnected areas).

The interpretation of combined TMS-EEG data can also be potentially ambiguous; in a combined TMS-EEG study where the measured variable is the amplitude of the TEP and the experimental paradigm manipulates a psychological variable like attention or awareness, a difference in the measured TEP could mean one of two things; it is possible that the TMS pulse caused a difference in the psychological process measured (for example enhancing the processing of a stimulus), or that the psychological variable affected excitability or activation of the cortex under the TMS coil (measured by the TEP), therefore changing the responsiveness to the TMS pulse.

In the studies included in the present thesis, we interfered with cortical activation of selected areas and drew inferences about the underlying relationship between perception and action (see Chapter: *Visual search*), and the one between attention and consciousness (see Chapter: *Cueing and Visual Attention*), respectively. We will now present the two paradigms employed in our experiments; visual search and endogenous spatial cueing.

VISUAL SEARCH

The concept of attention is something very familiar to everybody, yet psychologists have struggled to find a common definition of it. William James, in his seminal work “Principles of Psychology”, wrote:

> *"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization and concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others." (James, 1890)*

Much of the attentional research has been conducted in the field of vision, because of the early advances in the understanding of its physiology, and its dominance on the other senses (Posner, Nissen, & Klein, 1976). One early distinction concerning attention has been its ability to be directed to different aspects, like visual objects (Duncan, 1985), features (Treisman & Gelade, 1980) or spatial locations (Posner et al., 1976).

While the understanding of vision from a physiological point of view was gaining in completeness, two simple observations paved the way for the development of the study of visual attention as we know it today. Firstly, the neural circuitry in our brain is by no means sufficient to process the whole amount of visual information present in the complex visual scenes that constitute our world (Desimone & Duncan, 1995). Secondly, the change in an observer’s awareness – or attentional state – while keeping the retinal image equal, causes a change in perception (Carrasco, 2011). The focus of attention can be actively changed by the individual (Helmholtz, 1867) in an overt (through a movement of the eyes) or covert (with eyes remaining stationary, but attentional focus actively shifting) manner. These changes in focus improve the ability of humans to interact with the external world (Donald, 1958).

THEORIES OF VISUAL SEARCH

We perform visual search almost continuously in our everyday life, while looking in the street for somebody we know, or scanning our cluttered desks to find our keys (Nakayama & Martini, 2011).

This very naturalistic behaviour has been adapted to be suitable as an experimental paradigm. In a typical visual search experiment, participants are seated in front of a computer screen where visual stimuli are flashed on the screen. One would find in visual search experiments a target (an item that is different from the others and on some characteristics of which the response is based) as well as distractors (that can share some attributes with the target).

Two variables are analysed in visual search experiments: error rates and reaction times. Error rates are known to vary with the difficulty of the task (Chen, Navalpakkam, & Perona, 2011) and as such are a good indicator of amount of processing going on in the brain. Reaction times (RTs) are the amount of time between the presentation of the stimulus and the behavioural response of the participant and are also known to correlate with task difficulty (Chen et al., 2011). Another important differentiation in visual search is the one between dimension and feature; a dimension is a range of variations which is processed by a specific brain subsystem (for example colour, orientation or shape), while a feature is a value within a dimension (for example red and green within the colour dimension) (Treisman & Gelade, 1980).

Visual search has been divided into two main categories: feature search and conjunction search. Figure 4 shows an example of both: In the left panel, the target (the horizontal black bar) is different from the distractor in one feature within a dimension, which is orientation. Distractors are homogenous, making this type of search easier. In the right panel, the target (the horizontal red bar) is different from the distractor in a conjunction of features, from two different dimensions: colour and orientation. It is easy to notice how feature search is generally easier and faster to perform than conjunction search.

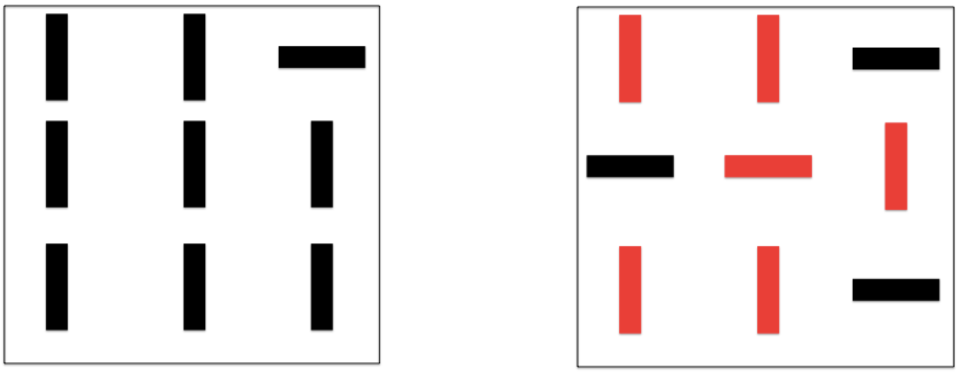

Figure 4: Typical experimental displays employed in visual search. Left panel: to find the target (horizontal bar) a feature search is required. Right panel: to find the target (horizontal red bar) a conjunction search is required.

FEATURE INTEGRATION THEORY (FIT)

The qualitative difference between feature and conjunction search has been experimentally shown by Anne Treisman (Treisman & Gelade, 1980); in her experiment she manipulated search type (feature vs. conjunction) as well as set size (number of distractor items in the display). Participants were required to detect the presence of a target. She observed that feature and conjunction search show radically different behaviours with the increase of set size; while in feature search the slope describing the correlation between number of elements and reaction time is essentially flat (the item “pops out”), in conjunction search this slope increases steeply. It has been estimated that the slope increase per item is about 15 ms/item when the target is present, and 30 ms/item when the target is absent (Wolfe, 1998).

To explain their findings, Treisman proposed a feature integration theory (FIT) of visual attention (Treisman, 1977; Treisman & Gelade, 1980). In this theory, incoming visual information is first broken down into several primitive visual features, represented within feature maps (that can be imagined as two-dimensional arrays of detectors). The feature maps are then processed and integrated to form a single saliency map, which measures the perceptual vividness making certain regions of a visual scene immediately catch our attention. Treisman argues that this second stage represents attention, which is the “glue” that binds together features creating the perception of a coherent object in our perception. In other words, for Treisman the attentional focus mode (be it narrow on a single object, or more distributed on the whole scene) determines what and how we see (Treisman, 2006).

The elaboration of the concept of saliency map has been a milestone in visual attention research, generating abundant experimental and modelling results. (Itti & Koch, 2001; Nakayama & Martini, 2011) Despite its seminal role in visual attentional research, FIT has received much criticism; for example, it has been observed that FIT cannot account for the detection of targets not known beforehand, like in paradigms when participants are instructed to perform an “odd-one-out” discrimination (Wolfe, 1994). Furthermore, many conjunction searches are more efficient than what the model would predict, and the pattern of processes like texture segmentation is incorrectly predicted by FIT. (Cohen, 1993; Wolfe, 1992). Finally, the concept of distinct feature maps – although useful computationally and for modelling – might not reflect the underlying neural architecture; studies have shown the existence of neurons responding to a conjunction of two or more features, therefore being situated in the intermediate stages between feature maps and the saliency map (Rangelov & Zeki, 2014).

GUIDED SEARCH (GS)

To address the shortcoming of the Feature Integration Theory, while keeping the useful concept of a general saliency map, the Guided Search (GS) model was developed. (Wolfe, 1994; Wolfe, Cave, & Franzel, 1989).

GS postulates a continuum between feature and conjunction search, and proposes that attention is required to perform any type of search. In the GS model, the first stage of processing occurs in parallel throughout the visual field, and is carried out by separate feature maps. The number of maps was roughly one per independent dimension (i.e. colour, size, motion, etc.) in the early models of GS, while the number of features that can guide visual search has been object of discussion more recently (Wolfe & Horowitz, 2004).

The second stage of processing is shaped by both bottom-up and top-down components: the former will be stronger the greater the dissimilarity between one item and the surrounding locations in the activation map. This top-down influence is crucial when the target items are unusual in the search display, and for this type of search to be successful, focused attention is necessary. Finally, top-down and bottom-up feature maps are summed together in a saliency map, in which the location of the most attention-grabbing item can be computed.

A very important consequence of the architecture of GS, is that the only information that can be extrapolated from the final saliency map is the location of the item which produces the biggest saliency signal. The features that have made it salient become indistinguishable, and cannot be retrieved from the overall saliency map, whose purpose is exclusively to direct attention (Wolfe, 1994).

THE DIMENSION WEIGHTING ACCOUNT (DWA)

The Dimension Weighting Account (DWA) started from early observations of Treisman (Treisman, 1988); she found a difference in reaction time performance between conditions in which the target dimension was known beforehand and those in which the target was unknown. While the slopes of both were flat, there was a difference in the intercept for the cross-dimension trials. Müller (Müller, Heller, &

Ziegler, 1995) further examined this effect in a series of experiments: he instructed participants to discriminate whether the items in the display where homogenous or heterogeneous, limiting the amount of task-related processing (like discrimination or recognition) to be performed on the target. Despite the change in task, the difference in intercept between known and unknown target dimensions remained.

This dimensional switch cost was additionally found to be modulable by interference (presence of ‘response-irrelevant’ items in the display) and by top-down control (knowledge of the target feature reduced the cost).

Importantly, these findings cannot be explained by either FIT or GS: both models assume that saliency signals from the separate feature maps are summed together in the master map and weighted equally, giving rise to a saliency signal which is not dimension-sensitive. Clearly, when the dimension defining the target is uncertain, the results are inconsistent with this assumption (Müller & Krummenacher, 2006a).

The DWA also incorporates findings observing a difference between dimension and feature switch cost (Found & Müller, 1996). This phenomenon was first observed by employing feature search for odd-one-out items, which could vary along two different dimensions (colour or orientation), and each dimension contained two feature levels (e.g. red or blue for the colour dimension). In this way, three possible “switch” conditions were created. In the first scenario, the same item was presented twice in two consecutive trials: this condition is a repetition of dimension and feature (usually abbreviated with “sDsF”, meaning “same dimension, same feature). Another possible combination is when the target differs in feature but not in dimension from the previous target; for example, a red item is presented after a blue one (usually abbreviated with “sDdF” meaning “same dimension, different feature”). The third possible trial type is when the target differs in dimension from the previous target; for example, a triangle is presented after a blue item (usually abbreviated with “dD”, meaning: “different dimension”).

The difference between the intertrial conditions has been observed by Müller and colleagues (1995), in an experiment that required participants to identify the target (which was present in every trial) in a visual search display. The results are summarized in Figure 5.

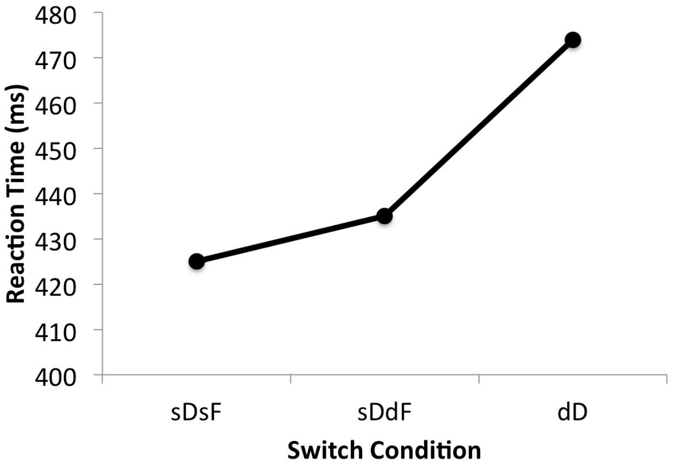

Figure 5: Reaction times for visual search depending on switch condition. Switch conditions are: sDsF (same dimension same feature), sDdF (same dimension, different feature), and dD (different dimension). (Adapted from Found and Müller, 1996)

The results clearly show a difference in RTs among the different conditions, with target repeats being the fastest. Feature switches generated a cost as well, although smaller than dimension switches. The explanation for this pattern of results postulates the existence of a mechanism that “weights” saliency maps differently and that produces a carryover effect on subsequent trials. The concept of weight is necessary, since the processing capabilities of the human visual and attentional system are limited, and a complete analysis of all feature maps would be overwhelming. (Duncan & Humphreys, 1989)

Once the existence of the dimension weighting effect was observed, the most important questions to answer is: is it susceptible to top-down processes? The answer to this question can provide important insights about the neural architecture of the attentional system. The third experiment of the paper addressed this topic (Müller et al., 1995). The stimuli were preceded by a cue in the shape of a word appearing on the experimental monitor, indicating the most likely source of variation of the target. This design was formulated in order to bias one dimension over the other, and prioritize which dimension would be checked first. The results showed that top-down priming of a dimension is possible.

Overall, the DWA has been the first attentional model to account for inter-trial dimensional effects, which are created by weighting mechanisms in the attentional system. Weights are not a purely bottom-up phenomenon, as they can be modulated by top-down influences in the form of cueing (Müller, Reimann, & Krummenacher, 2003).

TASK EFFECTS

Visual search performance and dimensional effects, however, are not only influenced by stimulus characteristics; the task that participants are instructed to perform also has an effect. This aspect of visual search was not contemplated in early attentional models (Itti & Koch, 2001; Wolfe, 1994), while it is included in the current formulation of the DWA, called the “Multiple Weighting Systems Hypothesis” (Rangelov, Müller, & Zehetleitner, 2012).

One way in which different tasks can differ is in the amount of perceptual analysis they require (Rangelov et al., 2012). For example detection tasks (requiring participants to discern presence vs. absence of a target) necessitate less perceptual analysis of the target than a discrimination task (requiring performing a judgment on some property of the target).

There are several different paradigm properties that can have an effect of visual search task. Stimuli, response criteria and response modalities have an impact on the overall participant performance, and each of them corresponds to a different cognitive process, namely stimulus selection, perceptual analysis and response selection (Rangelov et al., 2012).

There are occasions in which a certain paradigm will create an interactive pattern of reaction times; this is the case of the compound task (Duncan, 1985), in which the target-defining feature is different from the response-defining feature. In this task, reaction times in trials in which both response and target repeat are the fastest, and trials where one of the two properties switches are the slowest, giving rise to partial-repetition costs (Zehetleitner, Rangelov, & Müller, 2012).

CUEING

ATTENTIONAL CUEING

ATTENTIONAL ORIENTING

The focus of the second part of this thesis will be the reorienting of spatial attention. The focus of attention can be dynamically changed (Nobre, 2001); most commonly the location of our attentional focus could be oriented through movements of the eyes, or saccades (Henderson, 1993); this type of attentional allocation is defined as overt. Attentional focus can also be allocated in a different manner, without requiring eye movements; this is called covert attentional allocation. It was first observed by von Helmoltz (Helmholtz, 1867). He performed an experiment on himself, in which he briefly presented groups of letters in various parts of his visual field, while keeping his eyes stable on the centre of the display. He was able to discriminate the letters on attended areas falling outside his fixation point, therefore showing that eye movements and attention can be dissociated.

Spatial attention movements, whether overt or covert, can be influenced by a variety of factors, both top-down and bottom-up. Cueing is a widely employed experimental paradigm to investigate the spatial allocation of visual attention. Perhaps the most famous version of this task was introduced by Posner (Posner, 1980). He presented participants with a central fixation point that could be neutral (in the shape of a plus sign) or directional (in the shape of an arrow). After an interval, a target was presented on either side of the cue, and the participants’ task was to detect the target. This experimental design gave rise to three possible conditions: *neutral* trials, in which the neutral cue was presented; *valid* trials, in which the arrow cue pointed at the side of the target; and *invalid* trials, in which the arrow cue pointed at the opposite side of the target. Posner observed a very stable pattern of results: valid trials elicited the fastest reaction times, followed by neutral trials, while invalid trials gave rise to the slowest reaction times; he also observed that this pattern of results was very robust and persistent among different tasks.

His results confirmed the observation of von Helmoltz (Helmholtz, 1867), while adding a new way to influence covert attentional orienting. The dissociation between foveal fixation and attentional allocation, although rarely found in ecological situations, proves that attentional orienting can be studied without the need of eye movements, and that the two processes are indeed at least partially independent.

FACTORS INFLUENCING CUED BEHAVIOUR

As the basic cueing paradigm has proven to be a simple and versatile tool to study spatial attention, many factors influencing participants' performance in the task have been identified; the most important being the type of cue (endogenous or exogenous), cue validity, and stimulus prevalence.

TYPE OF CUES: ENDOGENOUS VS. EXOGENOUS

First, cues have been divided into two main categories: endogenous and exogenous. An endogenous – or central cue, is a symbolic stimulus presented at fixation location, like an arrow. An exogenous – or peripheral cue is a salient change (for example, in terms of luminance) directly at the indicated location. These two types of cues have been shown to behave in different ways (Müller & Rabbitt, 1989): while endogenous orienting is in its nature voluntary and its activation lasts relatively long (more than 500 ms), exogenous orienting is reflexive, and the activation it produces is transient (less than 200 ms).

The two cues have been shown to differ not only in the timing of their effect, but in the way they affect ERP waveforms. It has been observed that endogenous cues affect a variety of early ERP components, like P1 and N1 (Mangun & Hillyard, 1991). Endogenous cues, in the shape of arrows, affected the N2 component in a Go-no-Go task (Eimer, 1993). The effects of visual orienting employing exogenous cueing resulted in very different results (Eimer, 1994); targets appearing at the cued side elicited an increased negativity than targets on the uncued side. This effect has been explained as enhanced processing of the attended location. These experiments show that the effects on the ERPs generated by the two types of cues are quite different, and reflect the differences that have been observed in behavioural experiments.

These results were a very important step in characterizing the specific ERP components affected by cueing, as well as in opening the way to study the different brain responses and excitability changes elicited by the two different types of cues.

fMRI has also been used to investigate the intrinsic differences between endogenous and exogenous cues. Early studies failed to show qualitative differences between the two types of cues; both were shown to activate a largely overlapping network composed of dorsal and parietal regions (Rosen et al., 1999). A later study has proposed that the bad temporal resolution of blocked-designed fMRI experiments was the cause of the lack of effects, and employing an event-related fMRI protocol, they were able to observe different BOLD signal distributions for the two types of cues; endogenous cueing elicited the activation of a larger cortical network compared to exogenous (Mayer, Dorflinger, Rao, & Seidenberg, 2004).

Taken together, the results suggest that endogenous orienting is a more effortful process than the exogenous one, reflecting top-down components and an increased load on working memory. In the present experiments, we will employ endogenous cues, as we are interested in the covert allocation and maintenance of effortful attention to a predetermined location in space.

CUE VALIDITY

Cue validity (i.e. the proportion of validly cued trials) is also an important factor in modulating attentional orienting; targets appearing at cued locations elicit faster reaction times than those appearing at uncued ones. It has been suggested that the magnitude of the validity effect is directly correlated to overall cue validity (Jonides, 1981). Behavioural and electrophysiological experiments have also showed that even when cues are not informative, they still induce an attentional shift; however, non-informative peripheral cues elicit greater reflexive orienting than central ones (Eimer, 1997).

EEG experiments have shown that targets appearing at validly cued locations generate an enhanced negativity in their ERP waveform (Eimer, 1993). Interestingly, uninformative cues have also been shown to generate both a behavioural effect and a similar negativity in the ERP (Eimer, 1994). In a study comparing informative (with a 75% validity) with uninformative (with a 50% validity) cues, it was observed that the ERP effect for valid cues was bigger. The fact that even uninformative cues do elicit a cueing effect has been explained as involuntary attentional biasing.

An fMRI study (Vossel, Thiel, & Fink, 2006) investigated the effect of cue validity. By designing blocks with different cue validity (90% and 60%), they observed how it affects components of the fronto-parietal attentional network (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). They showed that attentional shifting mechanisms are sensitive to cue validity information. In the present thesis, we chose to employ highly valid cues (80%), in order to elicit a strong activation of the attentional network.

PROBABILITY OF STIMULUS OCCURRENCE

Another factor affecting the effect of cues in visual performance is the probability of stimulus occurrence; as in some experiments ‘catch trials’ are employed (i.e. trials not containing a stimulus). It has been shown that presenting the target on most trials increases participants’ performance in stimulus detection (Näätänen, 1972).

Although the practice of inserting catch trials has been developed in order to minimize the frequency of anticipatory responses (Correa, Lupiáñez, & Tudela, 2006), the role of rare (30%) visual stimuli in our experiment will be to compel participants to perform the cueing task, while the trials of interest will be target absent trials, where a TMS pulse will be administered.

After having reviewed the technical advantages of employing combined TMS-EEG and the classical findings pertaining to visual search and attentional cueing, the present thesis will include three experiments; one employing TMS-EEG to study the function of the rAng in the creation of intertrial effects in visual search, and two investigating the relationship between attention (elicited by cueing) and visual cortical excitability.

VISUAL SEARCH

“My experience is what I agree to attend to. Only those items which I notice shape my mind.”

William James in The Principles of Psychology, Vol.1

INTRODUCTION[1]

The Visual Search section of the General Introduction chapter has reviewed the basics of visual search, as well as classical theories of its mechanisms and more recent neurophysiological studies involved in its functioning. This section will discuss the nature of intertrial effect and the role of the Posterior Parietal Cortex in their formation.

THE NATURE OF INTERTRIAL EFFECTS

The study of intertrial effects allows the investigation of different aspects of stimulus processing, and to draw conclusions about the relationship between perception and action.

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[1] Francesca Bocca, Paul Taylor and Thomas Töllner designed the study, based on experimental procedures formerly designed by Thomas Töllner. Francesca Bocca programmed and conducted the experiment, analysed the data, and wrote the paper. Paul Taylor, Hermann Müller and Thomas Töllner commented and revised the manuscript. The manuscript was submitted to the journal “Brain Stimulation” on 20/10/2014.

Perhaps one of the earliest findings is that when orthogonal stimulus-defining dimensions repeat across trials, reaction times are facilitated; while when one of the dimensions changes, reactions times show a cost higher than if both dimensions changed. To explain his findings, Kingstone (1992) suggested that different encoding systems in the brain are not independent, but are constantly engaged in a type of crosstalk, creating the bias for regularity that is normally observed in real life stimuli.

The compound task (Duncan, 1985) is an ideal paradigm to investigate the interaction between orthogonal dimensions, whether they are stimulus- or response- defining.

In particular, the existence of a connection between stimulus and response processes suggests that perception and action are not completely separate modules, but rather interact dynamically. Recently (Clark, 2013; Friston, 2010), several comprehensive theories of the relationship between perception and action have been proposed; although the mechanisms thought which this connection is implemented vary, they all agree on the intrinsic connection between perception and action.

THE RIGHT POSTERIOR PARIETAL CORTEX (RPPC)

The right Posterior Parietal Cortex (rPPC) is a cortical area that has been suggested to be important in the connection between stimulus and response, as well as in spatial cognition (Sack, 2009). Ellison and colleagues (Ellison, Rushworth, & Walsh, 2003) suggested that the rPPC has the ideal location and connectivity to perform stimulus-to-response mapping, formulating the “visuomotor hypothesis” of the rPPC, contrasting with earlier theories that identified the PPC as an area exclusively involved in visual aspects of search tasks. This idea was supported by an rTMS experiment, in which stimulation over the rPPC disrupted performance during visual search in conditions requiring the association of visual and motor information (i.e. changing stimulus-response mapping), not simple visual binding.

Later studies have also strengthened the view of the PPC as an area involved in coding and employing spatial information during search (A. R. Lane, Smith, Schenk, & Ellison, 2011), observing an effect of right PPC TMS during visual search when a visuomotor transformation (i.e. pointing at the target as opposed to detecting it) was required to perform the task.

Other studies employing rTMS in combination with fMRI (Sack et al., 2002) have confirmed the causal role of the parietal cortex in the performance of visuospatial tasks; rTMS was applied at an inhibitory frequency (1 Hz) over the parietal cortex and resulted in an impairment of spatial judgments on previously presented visual information.

In the present thesis, the application of TMS-EEG to study the inter trial effect of stimulus- and response- defining features could potentially help identifying the neural areas and the exact timing in which different types of inter trial effects happen, and contribute to the nature of the connection between perception and action.

THE NEURAL CORRELATES OF DWA

The behavioural experiments investigating the effect of cues and priming on the dimension weighting effects were aimed at creating a model of the neural circuitry involved in the dimension weighting process (Müller & Krummenacher, 2006b). More recently, other techniques have been employed to investigate the DWA, mainly fMRI and EEG. These techniques have been able to add strength to the neural plausibility of the DWA.

FMRI STUDIES

fMRI provides an ideal tool to investigate the correlation between behaviour and functional neuroanatomy, even though its poor temporal resolution (Kim, Richter, & Ugurbil, 1997) makes it difficult to separate different processes occurring simultaneously or to investigate fast-occurring intertrial effects , therefore requiring ad-hoc experimental designs to be created in which the variable of interest is blocked, or trials are particularly long (Haller & Bartsch, 2009).

The first fMRI study directly investigating the DWA compared brain activation of participants performing an odd-one-out task in two conditions of pop-out search: dimensional certainty (only switches of features) and dimensional uncertainty (both dimension and feature could switch). Changes in BOLD signal correlating with dimensional changes were observed in a network of areas including the posterior parietal cortex (PPC), already known to correlate with spatial (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991) as well as non-spatial (Dove, Pollmann, Schubert, & Wiggins, 2000) shifts of attention.

In another study, the same authors investigated dimension switches in conjunction search (Weidner, Pollmann, Müller, & Cramon, 2002); they observed activations in different areas, the most prominent of which was the intra-parietal sulcus (IPS). The IPS was strongly activated in dimension changes, and more weakly activated in feature changes. Some areas showed a selective activation for dimension changes in feature (left frontopolar cortex) or conjunction search (frontomedial cortex).

A third study from the same authors (Pollmann, Weidner, Müller, Maertens, & Cramon, 2006b), employing a compound task, dissociated between response-related and dimension-related activity in the BOLD signal. Once again, an involvement of the parietal cortex was observed in trials characterised by dimensional changes.

In a review of their series of studies, Pollman and colleagues (Pollmann, Weidner, Müller, & Cramon, 2006a) made some hypotheses about the underlying architecture of dimension weighting. They observed how many of the areas involved with attentional shifts would also be activated during dimensional switches; and that areas traditionally involved in executive control, like the prefrontal cortex, also showed an activation in dimension switches, even when the dimensional value of the target was response-irrelevant (odd-one-out task). Furthermore, an involvement of the PPC in dimension switches was observed as a main effect in both singleton and conjunction search.

The parietal cortex is involved not only in the classical dimensional switches effects in visual search, but also in priming of pop-out; an fMRI study found a correlation between PPC activity (among other areas like FEF and medial frontal cortex) and intertrial priming of feature pop-out (Kristjansson, Vuilleumier, Schwartz, Macaluso, & Driver, 2007).

ELECTROPHYSIOLOGY

Another method employed to investigate attentional mechanisms, and that confirmed the DWA's predictions, is electroencephalography (EEG). This technique has very good temporal resolution, but bad spatial resolution, allowing a different but complementary type of investigation compared to fMRI (Luck, 2005).

RELEVANT EVENT-RELATED POTENTIALS

Event-related potentials (ERPs) are electrical potentials evoked by a stimulus, and are obtained through averaging various waveforms time-locked to the stimulus of interest.

There are many visual components, related to different processing of visual stimuli. The most relevant for the present thesis are summarized in the following table (Luck, 2005):

ERP component	Process
P1	Stimulus perception. Influenced by attention and stimulus saliency.
N1 (posterior)	Intermediate stimulus processing. Influenced by task and spatial attention.
PCN (N2pc)	Spatial attention to lateralized visual stimuli
sLRP	Selection of motor response
rLRP	Execution of motor response

Most of the ERP components mentioned above are sensitive to attentional allocation, and therefore their modulation has been studied in relationship with dimensional effects in a visual search task.

EXPERIMENTAL RESULTS

One of the DWA-related experimental topics that have been investigated with EEG is the origin of intertrial facilitation. The main distinction that can be made is between perception-based and response-based intertrial facilitation effects. Proponents of the perceptual origin explain intertrial facilitation as a pre-attentive and early sensory facilitation of the most important attributes for the task (Leonard & Egeth, 2008; Müller et al., 1995; Wolfe, Butcher, Lee, & Hyle, 2003). Proponents of the response-based origin argue that after perception and visual processing of the target have been accomplished, facilitation arises in concomitance with response preparation (Theeuwes, Atchley, & Kramer, 2000).

As response and dimension switches are tied together in the traditional visual search discrimination task, other paradigms have been developed to separate between response and dimension related switches and repeats. One such paradigm is the "compound task" (Duncan, 1985), that is defined as a dissociation between response-determining and target-defining features. Even though dimension weighting effects are smaller in compound task experiment (Krummenacher, Müller, & Heller, 2001), it is an ideal tool to dissociate between response-related and stimulus-related variations in behaviour.

Employing the compound task, Töllner and colleagues (Töllner, Gramann, Müller, Kiss, & Eimer, 2008) have addressed the question of perceptual vs. response-related dimension effects by observing event-related potentials (ERPs) directly correlated to attentional shifts and attentional allocation.

The experiment focused on two ERP components known to correlate with the early (perceptual) and late (response) processing of visual stimuli; the first was the N2pc; a component which is calculated as the double subtraction between the voltage of parietal electrodes over the two hemispheres (ipsilater or contralateral to the hemifield in which the target appeared); the maximum voltage being observed on visual areas contralateral to the attended stimulus (Eimer, 1996). Its average onset time is 200 ms after stimulus presentation, even though it can vary from between 175 and 300 ms after stimulus. Because of its variable timing, it has been suggested a better name would be PCN instead of N2pc. The other component of interest in the study was the response-locked LRP (rLRP), calculated as the double subtraction of electrodes C3/C4 from -100 to -20 pre-response.

The averaged difference waves (between ipsi-and contralateral to singleton) at electrode position PO7/PO8 showed a significant main effect of dimension change, but no effect of response change or interaction in the time bin traditionally associated with the PCN (190-270 ms post-stimulus). The same analysis was performed for the rLRP, and it showed a mirrored effect: response change, but not dimension change, affected the amplitude of the ERP.

These results have shown how at least part of the intertrial effects can be interpreted as a more efficient and faster attentional allocation to the repeated target, independently of response repetitions.

TMS STUDIES OF VISUAL SEARCH

The first TMS study of visual search employed both feature and conjunction search, and applied single TMS pulses over the posterior parietal cortex (PPC) (Ashbridge, Walsh, & Cowey, 1997). No effect of TMS was observed on reaction times in feature search, while the reaction times were affected in conjunction search.

After revealing this pattern, further studies have enlightened the contributions of different areas in visual search. A double dissociation between the PPC and the superior temporal gyrus (STG) has been observed, when participants were asked to perform either conjunction or difficult feature tasks (Ellison, Schindler, Pattison, & Milner, 2004). Using a similar paradigm, a role of the Frontal Eye Fields (FEF) has been highlighted in conjunction search as well as feature search with a high degree of uncertainty (Muggleton et al., 2003).

Some models of areas involved in visual search, in particular PPC, have been developed following those important TMS studies. For example, some authors suggested that the primary role of the PPC is to update information (Rushworth & Taylor, 2006).

Despite the important results found employing TMS during visual search, it is impossible to use this method alone to investigate the temporal dynamics of brain activity following the TMS pulse. To do so, TMS has to be applied together with other techniques, like EEG (See the Combined TMS - EEG section of the *General Introduction* chapter).

COMBINED TMS-EEG STUDIES OF VISUAL SEARCH

Being the combination of TMS-EEG such a recent achievement, the number of TMS-EEG studies of visual search is relatively small compared to the wealth of publications employing behavioural paradigms.

The first combined TMS-EEG study of visual search (Fuggetta, 2006) employed conjunction search. TMS was applied 100 ms after visual stimulus onset, causing a delay in response times already observed in the literature (Ashbridge et al., 1997). The examination of visual stimulus locked ERPs showed a difference in the N2pc in the corresponding condition in which reaction times were made slower. Although this study was the first to show ERP correlates of classical TMS effects in visual search, and to be therefore able to relate them to the underlying psychological mechanism, the paradigm itself did not allowed to investigate inter-trial attentional effects.

Another study investigated a phenomenon called “priming of pop-out” (Taylor, Muggleton, Kalla, Walsh, & Eimer, 2011). In this study, the right angular gyrus (rAng) or the frontal eye fields (FEF) of participants were stimulated with TMS (online paradigm, 5 pulses at 10Hz), while they were performing a visual search task. The displays were constituted of four elements (pentagons), one of which differed in colour from the distractors (either the distractors were red and the target green, or the other way around). Participants had to determine whether the different pentagon had a cut on the upper or lower part. TMS had an effect on both behaviour and EEG; improving RTs for rAng TMS in the switch condition, as well as decreasing positivity in the ERP for the same condition. This study showed that the rAng is causally involved in priming components in feature visual search, generating effects in both behaviour and ERPs.

THE RIGHT-ANGULAR GYRUS (RANG)

ANATOMY

The rAng is a substructure of the posterior parietal cortex; it is located on the posterior part of the inferior parietal lobule, and it roughly corresponds to Brodmann area (BA) 39. Figure 6 shows a lateral view of the rAng and the most important surrounding anatomical landmarks.

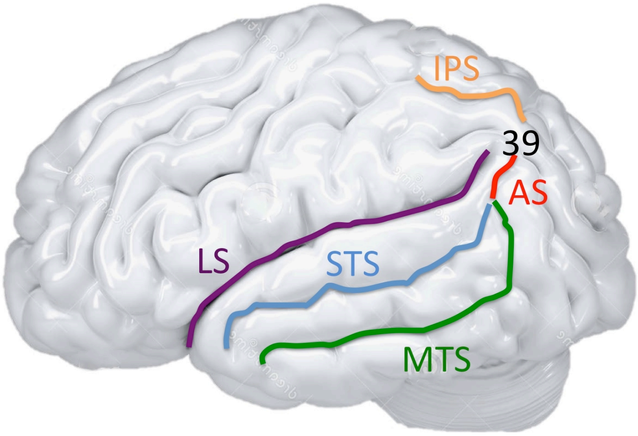

Figure 6. Lateral view of a 3D rendered brain. The rANG is shown in correspondence of the number 39 (Brodmann's area number), Other anatomical landmarks include: the lateral sulcus (**LS**), the superior temporal sulcus (**STS**), the middle temporal sulcus (**MTS**) and the intraparietal sulcus (**IPS**).

The first important feature of the rAng is its position: it is found at the junction between the parietal, occipital and temporal lobes. It has therefore been suggested that the role of the rAng might be a multisensory integration hub (Seghier, 2012).

CONNECTIVITY

Currently, there is a lack of consensus concerning which area in the monkey brain would be the ideal homologue of the human rAng; therefore the most reliable method to study the connectivity of the rAng is to employ non-invasive neuroimaging methods on humans (Seghier, 2012).

DTI studies have shown that the rAng has indeed a rich connectivity to many close and distant regions (Mars et al., 2011). The left and right AG are interconnected through the corpus callosum. The AG connects to the ipsilateral frontal and opercular areas via the longitudinal fasciculus. It also connects to the caudal posterior temporal regions through the middle longitudinal fasciculus. The occipitofrontal fasciculus connects the AG to the precuneus and the superior frontal gyrus, while the inferior longitudinal fascicle connects them to the parahippocampal gyrus and hippocampus. The AG also connects to the supramarginal gyrus through local connections. Importantly, the AG receives no direct input from primary sensory areas (Seghier, 2012).

FUNCTION

The rAng has been shown to correlate to a variety of tasks in fMRI studies; from speech, to memory, to visual attention (Seghier, 2012). TMS studies have also shown the role of the rAng in different tasks, like cognitive control or visual search (A. R. Lane et al., 2011; Sack, 2009; Soutschek, Taylor, Müller, & Schubert, 2013; Taylor et al., 2008). In the present experiment, we will apply TMS over the rAng to investigate the role of this area in intertrial effects related to response and target components. We believe the connectivity of the rAng makes it the ideal candidate to be involved such processes.

EXPERIMENT AIMS

We designed the present study in order to investigate the causal role of the rAng in feature visual search, using a combined TMS-EEG setup. We employed a compound task in order to be able to dissociate between target- and response- related components. The effect of TMS on the rAng was compared to two controls: one consisting of no-TMS blocks, and another consisting of TMS over a task-irrelevant area.

The rAng was the chosen area of our TMS stimulation, as it has been shown to be involved in intertrial effects in feature search, and its extensive connectivity make it the ideal candidate to be involved in inter-trial effects in a compound task.

In this study, we chose to employ a repeated-TMS (rTMS) protocol. We employed a frequency of 10Hz, which has been typically linked to a temporary excitatory outcome (Thut & Miniussi, 2009).

Our interest was to observe a change in behaviour caused by rAng TMS, and to explore the EEG correlates of the effect in order to discriminate the underlying psychological process affected by TMS.

The right angular gyrus combines perceptual and response-related expectancies in visual search: TMS-EEG evidence [2]

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ABSTRACT

Background: Visual search performance is sensitive to changes in the environment. Attention is sensitive to trial history, in terms of both perception and response. Although the bases of these sensorimotor interactions remain unclear, both behaviourally and neurally, converging evidence from a variety of methods indicates that the right angular gyrus (rANG) may be important.

Objective/Hypothesis: The present study tests whether the rANG plays a causal role in generating these intertrial effects.

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[2] Manuscript submitted to the journal "Brain Stimulation" on 20/11/2014

Methods: Participants performed a compound task for feature singleton targets. We applied rTMS over the rANG (or a control site, or no TMS) during the intertrial interval and measured effects both on behaviour and on neural activity using psychophysics and event-related potential (ERP) recording.

Results: rANG TMS during the intertrial interval improved performance to the upcoming stimuli only when the target-defining dimension and the response-defining feature both repeated across successive trials. rANG TMS also increased the amplitude of the visual N1 component evoked by the upcoming stimuli. These effects did not occur after control TMS.

Conclusion: rANG plays a causal role in the formation of combined expectancies binding together stimulus- and response- characteristics of the previous trial to optimize visual search performance. This supports a visuomotor theory of parietal cortex and the dimension weighting account of attention. We suggest current models of intertrial effects in visual search need to be expanded to include an interactive component representing both perceptual and motoric intertrial expectancies, affecting the early analysis of stimulus features in the upcoming trial.

Keywords: TMS, EEG, visual search, attention, N1, dimensional weighting

INTRODUCTION

Visual search performance is sensitive to changes in the environment. Despite the seeming automaticity of these processes, recent research suggests that they can be modulated by other factors seemingly unrelated to immediate perception, such as task history or even the response context (Rangelov, Töllner, Müller, & Zehetleitner, 2013; Töllner, Rangelov, & Müller, 2012). This has been particularly evident in inter-trial effects in visual search performance (Kristjánsson & Campana, 2010; Maljkovic & Nakayama, 1994). During search for a simple feature ('pop-out') target, participants respond faster when the targets on consecutive trials are characterized by the same dimension (e.g., colour or shape) (Found & Müller, 1996). When the precise target features repeat (rather than just the dimension), a benefit in reaction times is also evident, although this smaller than that observed for dimension repeats (Found & Müller, 1996) – suggesting that this effect of task history on attention is organized at the level of dimensions, rather than features within dimensions (Zehetleitner et al., 2012). Search performance is faster when there is a complete repetition of target- and response-defining features, and is slower if one or the other switches (Müller & Krummenacher, 2006a; Töllner et al., 2008). The interaction between target- and response-defining features can be generalized to measure the relationship between perception and action: there may be an intrinsic relationship between the two processes, as assumed, for example, by forward models of action control, ideomotor theories, and common coding frameworks (Memelink & Hommel, 2013).

Imaging and TMS studies have shed some light on the neural bases of these effects of perceptual and response history on search performance. Activations in the posterior parietal cortex (PPC) correlate with dimensional manipulations in visual search (Pollmann, Weidner, Müller, & Cramon, 2000) and lesions here affect dimensional carry-over effects (Utz, Humphreys, & Chechlacz, 2013). Event-related potential (ERP) studies using compound-search tasks support the notion that response selection during similar tasks is not independent of demands on attentional selection (Töllner et al., 2008; Töllner, Zehetleitner, Gramann, & Müller, 2010; Wiegand, Finke, Müller, & Töllner, 2013) and that early perceptual processing can be modulated by action intention (Wykowska & Schubö, 2012). TMS studies stimulating the right angular gyrus (rANG) within PPC during conjunction visual search have disrupted performance at target detection (Ashbridge et al., 1997), but without an effect observed in feature search. If response context is manipulated, however, a critical role of rANG has been demonstrated even for feature search (A. Lane, Smith, Schenk, & Ellison, 2012).

Employing a combination of TMS-EEG, it is possible to causally determine the functional role of a cortical area and assess the timing of its contribution to network neural activity (Komssi & Kähkönen, 2006; Miniussi & Thut, 2009). A previous combined TMS-EEG study (Taylor et al., 2011) has shown that rANG stimulation affects priming of pop-out, but did not explore changes in the dimension of the target-defining feature, nor changes in the response-defining feature. The aim of the current experiment was to test for a causal role of the rANG in creating the interactive pattern of response (action)- and target (perception)-defining dimension on performance and neural activity in visual search.

METHODS

PARTICIPANTS

Nineteen healthy right-handed volunteers (mean age 26±0.93 years, 12 women) participated in the study. All had normal or corrected-to-normal vision, gave written, informed consent, and were paid 10 Euros per hour. The protocol was approved by the ethics commission of the German Psychological Association (DGPs).

PROCEDURE

Participants sat in a dark room, their eyes 57 cm away from the computer monitor, with viewing distance controlled using a chin-rest. Visual stimuli were presented on a liquid crystal display computer monitor (SyncMaster 2233RZ, Samsung) at a refresh rate of 100 Hz. Figure 7 shows the timeline of two successive sample trials.

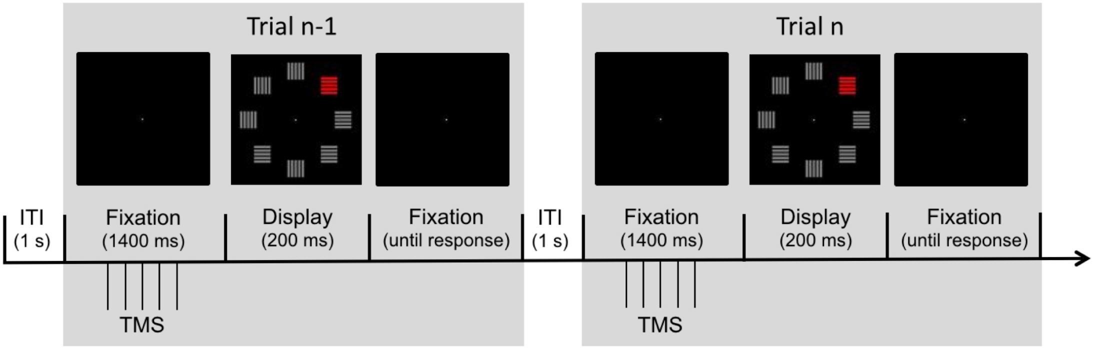

Figure 7: Timeline of two consecutive trials. The compound task required participants to respond to the orientation of the grating within the element that differed from the others in the display. In this example, both the response-defining (i.e., horizontal orientation) and target-defining (i.e., red colour) features repeat. In TMS blocks, 5 pulses of TMS were applied at 10 Hz to either the right angular gyrus (rANG, in posterior parietal cortex) or a control site during the period before display presentation, in order to affect anticipatory priming processes.

At the start of each trial, a grey fixation point (0.05° of visual angle, RGB value: 125, 125, 125, luminance: 11 cd/m^2) was presented centrally on a black screen (RGB value: 0, 0, 0, luminance: 0.1 cd/m^2) for 1400 ms. TMS was applied block-wise; on TMS trials, 5 TMS pulses were applied at 10 Hz starting 500 ms after fixation point onset (TMS trains lasting 400 ms), followed by an additional 500 ms of fixation. A visual search display was then presented for 200 ms, comprising an array of eight items arranged in a virtual circle, centred on the fixation point and with a radius of 3.0° of visual angle. Seven of the items were grey squares (each side 1.2° long) and one item was the target, which differed in either shape or colour from the distractors ("pop-out" item). Target and distractors were isoluminant (25 cd/m^2). Targets defined by colour could be either red (RGB value: 160, 0, 0) or blue (RGB value: 10, 10, 255), while those defined by shape could be either triangles (height 2.4°) or circles (diameter 2.4°); i.e., there were two levels of the target-defining feature value within each of the two dimensions. This yielded three possible types of intertrial target-defining feature sequence: same dimension same feature (sDsF, or complete target repeat), same dimension different feature (sDdF), and different dimension (dD). The fixation point remained on screen from the beginning of the trial until a response key was pressed.

Each display item, whether target or distractor, comprised a grating composed of four bars, oriented either horizontally or vertically (bar thickness 0.4°). The task was to report the orientation of the grating inside the target item, giving two possible response-defining feature sequences: same response (sR) or different response (dR). The use of such a "compound task" (Duncan, 1985) allowed us to dissociate between potential effects of TMS on priming of the target-defining feature, priming of the response-defining features, or a combination of the two. Participants responded with the index fingers of each hand placed on two vertically adjacent keyboard keys (B and G on a German keyboard). Response keys and block order were counterbalanced across participants. Participants were instructed to keep central eye fixation and avoid unnecessary movements during blocks.

Before the main experiment, participants completed two training blocks in which error feedback was given onscreen after each trial. During the main experiment, participants were informed after each block about their error rate and mean reaction time. Participants were asked to perform as fast and accurately as possible, and to keep the error rate below 10%. The experiment consisted of 9 blocks of 82 trials each.

TMS

We applied TMS to the right hemisphere using a PowerMag Research machine (Brain Products, Munich, Germany) and a figure-of-eight coil (outer winding diameter 95 mm). TMS pulses were delivered with a frequency of 10 Hz in trains of five pulses lasting 400 ms at 110% active motor threshold, with the handle pointing downwards. The minimum inter-train interval was 3200 ms. There were three types of blocks: rANG TMS, Control TMS, and noTMS. TMS sites were marked on each participant’s 3T structural MRI scan using infrared stereotactic registration (Brainsight, Rogue Research, Montreal), and converted into MNI space using FLIRT (Andersson & Jenkinson, 2007). The location of the TMS sites is shown in Figure 8.

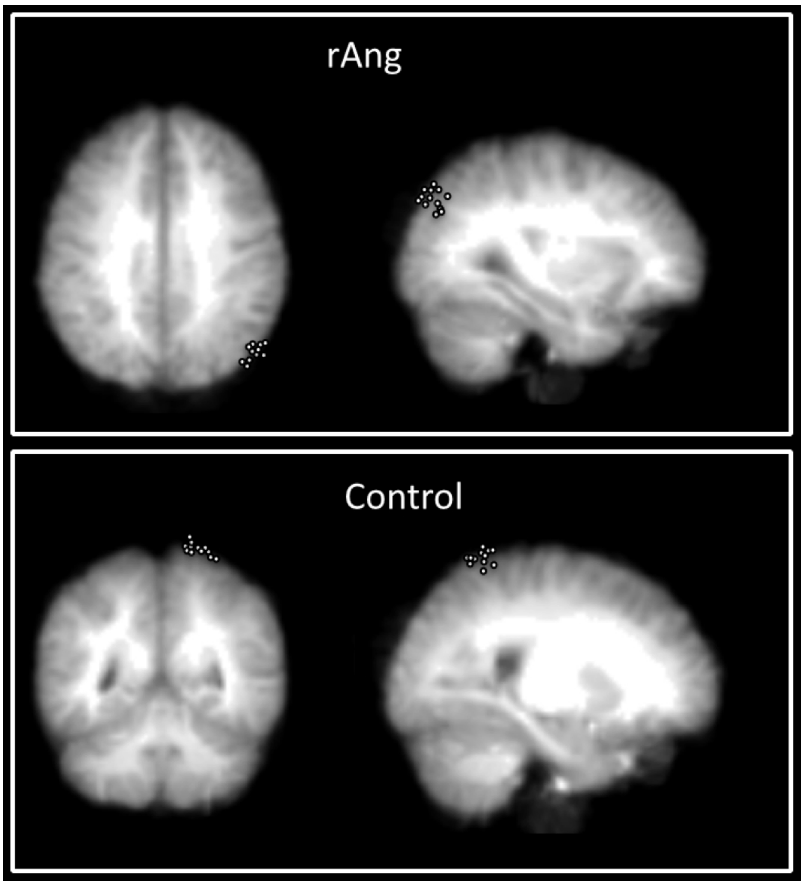

Figure 8*:* Location of the rANG (top panel) and control site (bottom panel) for all participants, overlaid on the average of their structural images.

The rANG site for each participant was defined as the mid-point of the virtual line that starts at the medial end of the ascending limb of the superior temporal sulcus, continues in the trajectory of that sulcus across the angular gyrus, and ends at the intraparietal sulcus. MNI coordinates (mean, x = 32; y = -66; z = 38) were consistent with those previously reported for the rANG (Seghier, 2012). In Control TMS blocks, the coil was placed with the same orientation and lateral distance from the midline as the rANG site, but 1.5 cm caudal to the primary motor representation of the first dorsal interosseus (mean MNI coordinates: x = 24, y = -51, z = 62).

EEG RECORDING

EEG was recorded continuously with a BrainAmp DC amplifier (Brain Products, Munich, Germany), with all online filters deactivated and a digitization rate of 5000 Hz. Recording used 28 Ag-AgCl electrodes mounted on an elastic cap (EasyCap, Brain Products, Munich) placed at positions FP1, FPz, FP2, F3, F4, FC5, FC6, C3, Cz, C4, CP5, CP6, P7, P3, Pz, CPz, P8, PO7, POz, PO8, O1, Oz, O2, FC1, F9, F10, FC2. For vEOG recording, an additional electrode was placed under the left eye. Electrode impedances were kept below 5 kΩ. The ground electrode was at AFz with the active reference on the left earlobe.

DATA ANALYSIS

The first trial of each block and trials with reaction times longer than 1000 ms or shorter than 200 ms were removed from both behavioural and ERP analyses. Participants were additionally excluded from the analyses if overall reaction times were more than two standard deviations slower than the population mean (1 participant excluded) or if excessive eye movements in the EEG recording led to less than 40 trials per condition (5 participants excluded). 13 participants (mean age 26 years, 9 women) passed these criteria.

EEG data was analysed using BrainVision Analyser (version 2.0, Brain Products, Munich, Germany). Prior to epoching the EEG, we performed an independent component analysis (ICA), as implemented in the BrainVision Analyser software, to eliminate blinks and horizontal eye movements from the EEG. Additionally, after epoching, trials with signals exceeding ±60 µV on any channel were excluded. Data were filtered with a low-pass filter (40 Hz, 24 dB), a high-pass filter (0.01 Hz, 24 dB), and a notch 50-Hz filter. The EEG was averaged starting 200 ms before the onset of the visual display, until 500 ms after visual display offset. As we were particularly interested in alterations of early sensory processing, we focused our analyses on the P1 and N1 components (Luck, Woodman, & Vogel, 2000). These components were analysed at electrode position PO8, where the waveforms were most prominent. The baseline was corrected based on the 200-ms prestimulus time window. The amplitude of the P1 component was calculated as the most positive voltage in the time window 80–140 ms post stimulus onset. The amplitude of the N1 component was calculated as the most negative voltage in the time window 110–170 ms post stimulus onset. We then analysed the mean amplitude of the time bin ±10 ms around the peak of the P1 component (i.e., 95–115 ms, with the P1 peaking 105 ms after stimulus onset) and the N1 component (i.e., 140–160 ms, with the N1 peaking 150 ms post stimulus onset).

RESULTS

BEHAVIOURAL RESULTS

For reaction time (RT) analysis, we conducted a repeated-measures ANOVA with factors: *Dimension Sequence* (i.e., repetition or switch of the dimension of the target-defining feature: either same Dimension and same Feature (sDsF) as on the previous trial, same Dimension but different Feature (sDdF), or different Dimension (dD); *Response Sequence* (i.e., repetition or switch of the response-defining feature: same

Response or different Response (sR, dR), and *TMS* (rANG, Control, no-TMS). Repeats of dimension and, respectively, response expedited RTs (main effects: F's$\geq$12.5, p's$\leq$0.003; t-tests: p's$\leq$0.006), and response repetition improved RTs only when the dimension repeated, independently of whether the target-defining feature repeated or switched (Dimension x Response Sequence interaction F(2,24)=26.6, p<0.003, paired sR vs. dR t-tests: within sDsF, t(12)=5.0, p<0.001, within sDdF, t(12)=3.75, p=0.003, within dD: p=0.7).

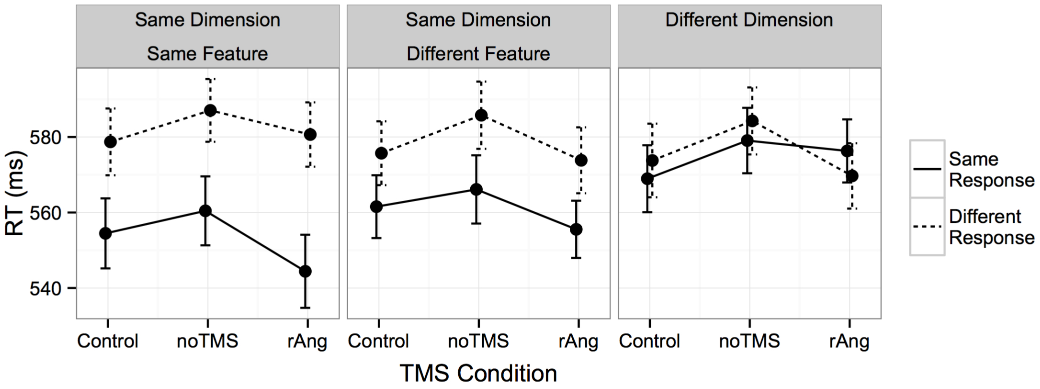

Figure 9. Behavioural data. rANG-TMS made performance faster, but only when both the target-defining dimension and the response-defining feature repeated across consecutive trials. In addition, performance was faster overall for same-response (thick line) than for different-response (dashed line) trials, though this effect was not evident when the target-defining dimension switched. Error bars represent the SEM.

From Figure 9, it can be seen that inter-trial rANG-TMS acted to boost the normal performance benefit that arises when both the target-defining and the response-relevant feature of the target repeat. This observation was substantiated by the three-way interaction being significant (F(4,48)=3.02, p=0.027). Follow-up ANOVAs, with the factors *Response Sequence* and *TMS*, revealed the three-way interaction to be due to interactions of TMS with Response Sequence for sDsF and, respectively, dD trials (all Fs>4, all ps<0.03), but not for sDdF trials (p=0.68).

For sDsF trials, the TMS x Response Sequence interaction was due to TMS affecting behaviour only when the response repeated (F(2,24)=4.56, p=0.029), i.e.: rANG-TMS expedited RTs relative to both the no-TMS (t(12)=3.03, p=0.01) and the Control condition (t(12)=2.32, p=0.039); there were no significant comparisons for different-response trials (all p's>0.1). Thus, the effect on behaviour was specific to rANG-TMS speeding performance only when both the target-defining and the response-defining feature repeated.

For dD trials, by contrast, the TMS x Response Sequence interaction was due to TMS affecting performance only on different-response trials (F(2,24)=5.2, p=0.014), with rANG-TMS giving rise to slightly (10 ms) faster RTs compared to no-TMS (t(12)=3.5, p=0.004); no other comparisons were significant (all p'*s*>0.14).

The lack of an interaction between TMS and Response Sequence for sDdF trials does not necessarily mean that the behavioural pattern is different from sDsF trials (Nieuwenhuis, Forstmann, & Wagenmakers, 2011). In fact, the original three-way interaction vanishes when only sDsF and sDdF (but not dD) trials are included in the ANOVA (F(2,24)=2.165, p=0.137). This suggests that feature switches (within a repeated dimension) did not significantly affect the behavioural pattern. Furthermore, when looking only at the rANG condition, and including only same-response trials, RTs on both sDsF and sDdF trials differed from those on dD trials (sDsF: (t(12)=-2.45, p=0.017; sDdF: t(12)=-4.12, p<0.001), while sDsF and sDdF did not differ (t(12)=-0.85, p=0.17). This pattern is consistent with the dimension-weighting account, in that rANG-TMS influenced behaviour when the critical dimension repeated, independently of whether the target-defining feature within that dimension repeated or switched.

As expected from participant training, accuracy was high (>95% for all participants and all conditions), and analyses on error rates revealed no significant main effects or interactions (all p*s*>0.1).

ERPS

The visual stimulus array evoked the classical set of P1 and N1 components, which were maximal at electrode position PO8 (Figure 10 shows the topography for the N1 component). This electrode was therefore selected for further analysis. To identify the neural correlate of the speeding of behaviour by rANG-TMS, the mean P1 and N1 amplitudes were analysed as a function of the target-defining feature, the response-defining feature, and TMS condition (as in the behavioural analysis).

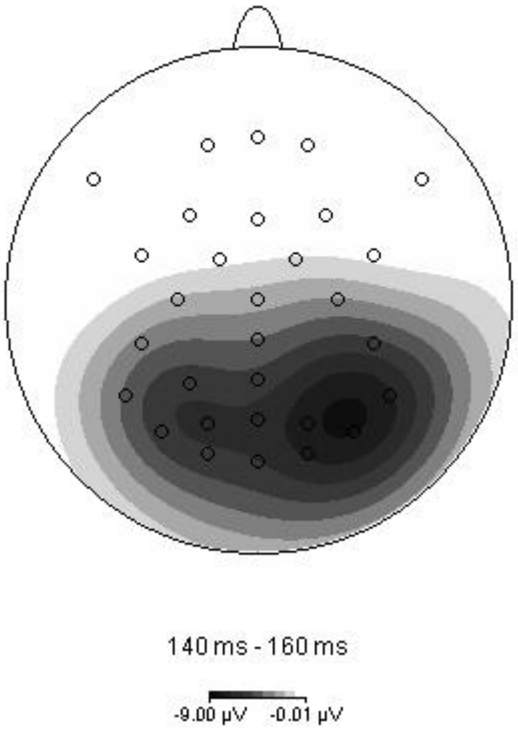

Figure 10: Topography map of the subtraction of the ERP between rANG-TMS and no-TMS in the sDsF-sR condition, for the N1 component in the time bin 140–160 ms post stimulus onset, showing a posterior negativity that was enhanced by rANG-TMS.

P1

An ANOVA of the P1 amplitudes, with the factors *TMS* (rANG, Control, no TMS), *Dimension Sequence* (sDsF, sDdF, dD), and *Response Sequence* (sR, dR) revealed only the main effect of Dimension Sequence to be significant ($F(1,12)=3.9$, $p<0.034$), largely due to the P1 amplitude being marginally smaller for sDsF relative to dD trials ($t(12)=-2.7$, $p=0.06$, Mean difference: 0.7 µV). Other comparisons were not significant (all $ts<1.4$, all $ps>0.18$).

N1

In contrast, the N1 ANOVA revealed the main effects of Dimension Sequence to be significant (F(2,24)=49.78, p<0.001) and TMS (F(2,24)=27.02, p<0.001), as well as the interactions between TMS and Dimension Sequence (F(4,48)=11.63, p<0.001), TMS and Response Sequence (F(2,24)=5.8, p=0.009), Dimension Sequence and Response Sequence (F(2,24)=15.43, p<0.001), and the critical interaction between TMS, Dimension Sequence, and Response Sequence (F(4,48)=28.81, p<0.001). The latter interaction was followed up by two-way, *TMS* (rANG, Control, no-TMS) x *Response Sequence* (sR, dR) ANOVAs conducted separately for sDsF, sDdF, and dD trials.

For sDsF trials, this ANOVA revealed the TMS x Response Sequence interaction to be significant (F(2,24)=34, p<0.001), driven primarily by an effect of TMS on same-response trials (F(2,24)=9.23, p=0.001), on which rANG-TMS led to a larger N1 compared to both the Control (t(12)=-2.72, p=0.018; mean difference: -0.81 µV) and the no-TMS condition (t(12)=-5.69, p=<0.001; mean difference: -1.23 µV). Of note, this enhancement of the N1 occurred in the very same condition in which rANG-TMS facilitated behavioural performance (Figure 11, Figure 12). Although there was also an effect of TMS on different-response trials (F(2,24)=38, p<0.001), separate t-tests showed that this was due to the N1 having a larger amplitude following Control-TMS compared to either rANG-TMS (t(12)=-10.4, p<0.001; mean difference: 2.5 µV) or no-TMS conditions (t(12)=-6.57, p<0.001; mean difference: 2.4 µV) (all other p's>0.2). As this does not correlate with any behavioural effect, it is hard to interpret the functional significance of this pattern.

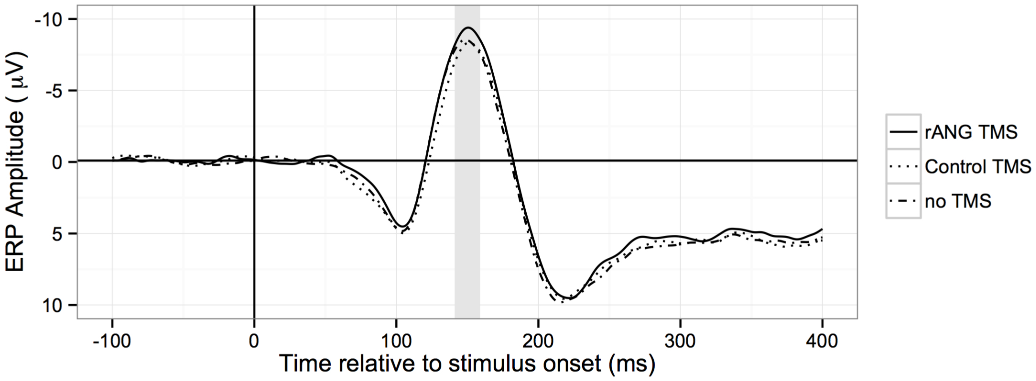

Figure 11*:* Stimulus-locked ERP for sDsF (same dimension same feature) sR (same response) trials. The shading (in the time bin 140-160 ms) represents the area of interest for the N1 analyses, in which rANG-TMS elicited a more negative N1 compared to the other two conditions, suggesting a boost in early sensory stages of stimulus processing in the sDsF-sR condition.

For sDdF trials, there was also a significant TMS x Response Sequence interaction (F(2,24)=20.1, p<0.001). This was due to an effect of TMS in the same-response condition (main effect: F(2,24)=51.4, p<0.001), in which the N1 was larger after Control-TMS than no-TMS (t(12)=4.7, p=0.001; mean difference: 1.6 µV); as well as an effect in the different-response condition (main effect: F(2,24)=7.72, p=0.003), caused by rANG TMS reducing the N1 amplitude compared to no-TMS (t(12)=3.6, p=0.005; mean difference: 0.7 µV). Again, this complex pattern did not reflect any effects of TMS on behaviour and is thus hard to interpret.

Finally, for dD trials, the TMS x Response Sequence (F(2,24)=12, p=0.005) was also significant, due to a main effect of TMS on same-response trials (F(2,24)=21.14, p<0.001), with rANG-TMS reducing the N1 amplitude compared to the Control (t(12)=-4.66, p=0.001, mean difference: -0.29 µV) and no-TMS conditions (t(12)=-3.167, p=0.004, mean difference: -0.21 µV). (No other tests reached significance; all p’s>0.05). This pattern, opposite to the one reported for sDsF trials, does not reflect an effect observed on behaviour.

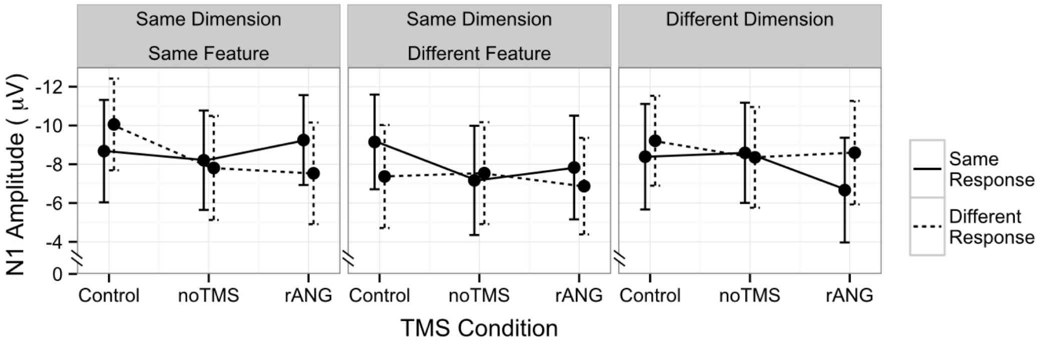

Figure 12: Effects of TMS on the N1component across conditions. rANG TMS increased N1 amplitude on trials where the target-defining feature and instructed response were the same on successive trials (same dimension, same feature, same response). Error bars represent the SEM.

DISCUSSION

TMS over the right angular gyrus (rANG) modulated inter-trial effects in a compound-search task, by facilitating performance and increasing N1 amplitudes on trials characterized by a complete repeat of target- and response-defining features. These results can be interpreted within a theoretical framework in which perceptual selection is not independent of response selection, where the rANG plays a causal role in combining sensorimotor expectancies that facilitate early stages of visual processing on the subsequent trial.

Behaviourally, rANG-TMS improved task performance when the dimension of the target-defining features repeated across trials, in either the presence or the absence of a feature switch within that dimension. This supports the dimension weighting account (Müller & Krummenacher, 2006a), according to which attentional selection operates on and from dimension-specific, rather than feature-specific, salience maps. Furthermore, the TMS effect was specific to the response context, speeding reaction times only when the required response also repeated from one trial to the next. This contributes to a long-standing debate: it has been proposed that attentional modulation (as assessed by inter-trial effects) originates at the visual selection stage (Maljkovic & Nakayama, 2010) – but that account cannot explain the effects of response sequence that are observed in the compound task (Figure 9, (Müller & Krummenacher, 2006a; Töllner et al., 2008)). An opposing view interprets inter-trial effects as originating only at the response selection stage (Cohen & Magen, 1999), but this view is also incomplete by not explaining how the target-defining dimension can play a role. A theoretical reconciliation of the two views (Müller & Krummenacher, 2006a) suggests that considering attentional selection and response selection as completely separate processes is not viable, and that the system implicitly assumes a correlation between response and target-defining characteristics. Earlier, preattentive target selection and later, postselective response selection may not be independent, but rather, based on the current stimulus-response association, the processing system generates an expectancy for the subsequent association (of the form "if the target repeats, the response will also repeat"), and any partial departure from that expectation creates costs. These so-called partial repetition costs have been explained within various theoretical frameworks, notably, that of 'combined expectancies' (Kingstone, 1992) and, respectively, the (common-coding) Theory of Event Coding (Memelink & Hommel, 2013), which describe the priming by action representations of task-relevant features on successive trials. These are compatible with our finding that TMS affects stimulus processing only on trials characterized by a combination of stimulus- (perception) and response- (action) defining properties.

Recent work has started to explore the mechanism by which action intentions may modulate perceptual processing (Memelink & Hommel, 2013), with some recent ERP evidence for modulation of pre-selective processes (Wykowska & Schubö, 2012). By combining TMS online with ERP recording, we were able to measure the neural activity evoked by the visual stimulus arrays and to test for a neural correlate of the behavioural effect of TMS. rANG-TMS increased the amplitude of the N1 component on the very same trials on which reaction time performance was modulated. The N1 component is thought to reflect preattentive analysis of stimulus features (Luck et al., 2000), is modulated by spatial attention, showing a larger amplitude for attended stimuli (Luck, Heinze, Mangun, & Hillyard, 1990), and is sensitive to action-related information, being larger for appropriately versus inappropriately grasped objects (Humphreys et al., 2010). Here, the N1 amplitude was larger when performance was enhanced through rANG-TMS. This suggests one potential route through which the brain creates predictions (combined expectancies) of upcoming stimuli based on perceptual and response history, with the rANG representing the combined expectancies which then take effect on early preattentive visual processing. Our results, showing a causal role of the rANG in facilitating performance in a reference frame defined not only by the perceptual but also response-related aspects of the target stimulus, supports the visuomotor hypothesis of rANG (Ellison et al., 2003). We propose that stimulating the rANG in the inter-stimulus interval affected the formation of a combined expectancy, or prediction, (in terms of an implicit memory trace) of a linkage between previously encountered stimulus and response attributes, which affects performance on subsequent trials by influencing early, preselective stages in the analysis of stimulus features.

Our pattern of results fits well the growing literature of cognitive enhancement effects of TMS (Luber & Lisanby, 2014; McKinley et al., 2012). Although TMS has been compared to a “virtual lesion”, it is increasingly used as a tool to modulate cortical dynamics (Ruff, Driver, & Bestmann, 2009). Stimulation of the same area can facilitate, inhibit, or have no effect on behaviour, depending on the task that participants are required to perform (Alford, van Donkelaar, Dassonville, & Marrocco, 2007). Demonstrating facilitatory effects of rANG-TMS in feature search may require using a task such as a *compound* search where response- and target-defining features can be varied independently. In a flanker task dissociating between perceptual and response conflict, parietal TMS increased perceptual conflict but also reduced response conflict (Soutschek et al., 2013) in a manner consistent with models according to which perceptual and response selection processes can be performed in parallel (Hübner, Steinhauser, & Lehle, 2010). Additionally, the timing of the TMS pulses and the type of search employed may be critical: while PPC-TMS applied shortly after visual stimulus onset disrupts performance on conjunction search (Ashbridge et al., 1997), TMS applied in the inter-stimulus interval of pop-out search can result in facilitatory effects (Taylor et al., 2011).

To conclude, our results indicate that the rANG is a key structure in the representation of combined expectancies, and that TMS applied to this area can bias the attentional system according to both perceptual and response-relevant prior history, resulting in facilitation through an enhancement of early stimulus processing. We believe our findings should be incorporated into current models of intertrial effects in visual search, expanding them with an interactive component representing the combination of perceptual and motor intertrial expectancies.

ADDITIONAL EEG ANALYSES

The analyses reported in this section did not interact with the TMS manipulation, and were therefore not included in the manuscript. They include lateralized components; the PCN, sLRP and rLRP, which have been found to vary depending on different dimensional and response priming conditions in visual search in previous studies (Töllner et al., 2008).

METHODS

Preprocessing of the EEG data was identical to the one reported in the Methods section of the manuscript.

For the PCN analyses, the EEG was averaged starting 200 ms before the onset of the visual display, until 600 ms after visual display onset. The baseline was corrected relying on the 200 ms pre stimulus. A 30 Hz low-pass filter was applied on the averaged data. The PCN was calculated as a double subtraction of contralateral (in respect to the visual stimulus position) and ipsilateral signal of the electrodes PO7/PO8. The amplitude of the PCN component was calculated as the minimum voltage in the time window 150-350 ms post-stimulus onset. For all the ANOVAs calculated on the PCN component, we used repeated measures, full factorial and type-III error model. All the p-values are calculated using the Huynh-Feldt method.

For the stimulus-locked LRP (sLRP), the EEG was averaged starting 200 ms before the onset of the visual display, until 800 ms after visual display onset. The baseline was corrected relying on the 200 ms pre stimulus. The sLRP was calculated as a double subtraction of contralateral (in respect to the manual hand response) and ipsilateral signal of the electrodes C3/C4. Before calculating latencies and amplitudes, we filtered the data with a 4Hz low-pass filter. The amplitude of the sLRP component was calculated as the minimum voltage in the time window 250-700 ms post-stimulus onset. To calculate the onset latencies of the sLRP, we employed the jackknifing method (Ulrich & Miller, 2001), in which the LRP latency is considered as the point in which the signal reaches a certain percentage of the maximum amplitude. Before calculating latencies, we filtered the data with a 4Hz low-pass filter. For sLRPs, we used the point in time in which the double-subtracted average reaches 50% of the maximum amplitude as the latency value. As the jackknifing method reduces the variance in the data, we also corrected the F-value of the ANOVAs accordingly, with the formula $F_{corrected}=F/(n-1)^2$ (Ulrich & Miller, 2001)

For the response-locked LRP (rLRP), the EEG was averaged starting 800 ms before to 200 ms after response onset. The baseline was corrected relying on the 200 ms pre stimulus. The rLRP was calculated as a double subtraction of contralateral (in respect to the manual hand response) and ipsilateral signal of the electrodes C3/C4. Before calculating latencies and amplitudes, we filtered the data with a 4Hz low-pass filter. The amplitude of the sLRP component was calculated as the minimum voltage from 200 ms pre-stimulus to stimulus onset. To calculate the onset latencies of the sLRP, we employed the jackknifing method and filtering in a manner identical to the sLRP, except that latencies were calculated when the filtered data reaches 90% of the maximum deflection. The same F-value correction of sLRPs was also applied.

PCN

PCN AMPLITUDE

Before conducting PCN analyses, we made sure that a PCN was present in all conditions for all participants.

Figure 13 shows the absolute value of the PCN voltage (being the PCN negative for all subjects and all conditions).

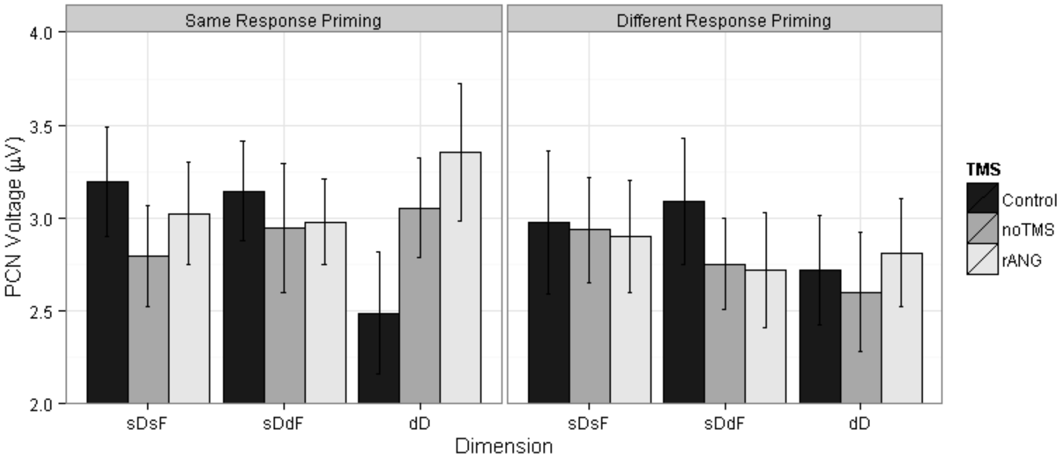

Figure 13: PCN (posterior contralateral negativity) voltage depending on experimental conditions. Panels represent response priming, while the dimension is represented on the x axis (sDsF = same Dimension, same Feature; sDdF = same Dimension, different Feature; dD = different Dimension). Different shades of grey represent the TMS condition. Error bars represent the standard error of the mean (SEM)

We run a repeated-measures 3-way ANOVA on the data, with factors being Dimension (sDsF, sDdF, dD), TMS (noTMS, Control and rANG) and Response Priming (same, different). We observed no significant main effects or interactions (all Fs<1.5, all ps>0.2)

NO-TMS AMPLITUDE

We also analysed only noTMS data, in order to investigate dimensional- and response- effects independent of TMS stimulation. The two-way ANOVA with factors Dimension (sDsF, sDdF, dD) and Response Priming (same, different) showed no significant main effects or interactions (All Fs<1.5, all ps>0.25).

SLRP

Before conducting sLRP analyses, we made sure that the sLRP was present in all conditions for all participants.

AMPLITUDE

Figure 14 shows the absolute value of the sLRP voltage (being the sLRP negative for all subjects and all conditions).

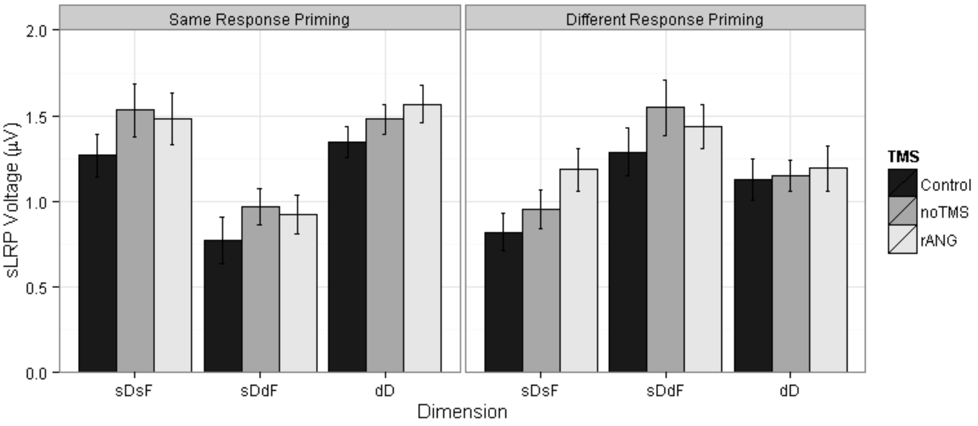

Figure 14: sLRP (stimulus-locked response potential) latency depending on experimental conditions. Panels represent response priming, while the dimension is represented on the x axis. Different shades of grey represent the TMS condition. Error bars represent the SEM.

We run a repeated-measures 3-way ANOVA on the data, with factors being Dimension (including 3 levels: sDsF, sDdF, dD), TMS (including 3 levels: noTMS, Control and rANG) and Response Priming (including 2 levels: same response or different response).

We observed a main effect of Response Priming (F(1,12)=17, p<0.001), a marginal main effect of Dimension (F(2,24)=3,28, p=0.055), while the effect of TMS was not significant (F(2,24)=2.6, p=0.1). No two-way or three-way interaction reached significance (All F*s*<1.6, all p*s*>0.23).

We then investigated the main effect of Response Priming; Figure 15 shows the difference between same and different response sLRP amplitude. A t-test showed that the difference was significant, with same response sLRPs having a smaller amplitude than different response sLRPs (t(12)=-4.656, p=0.0005. Mean of the differences: 0.44 µV).

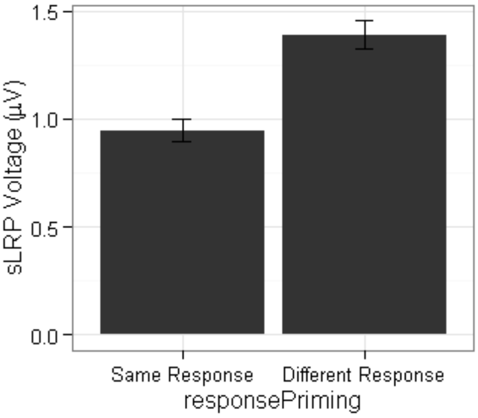

Figure 15: sLRP (stimulus-locked response potential) voltage (on the y-axis) depending on response priming(on the x-axis). Error bars represent the standard error of the mean (SEM)

We then investigated the main effect of Dimension; Figure 16 shows the difference in amplitudes between sDsF, sDdF and dD.

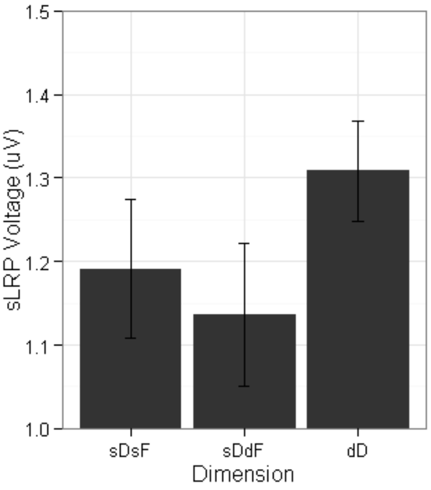

Figure 16: sLRP (stimulus-locked response potential) voltage (on the y-axis) depending on Dimension (on the x-axis). Error bars represent the standard error of the mean (SEM)

Separate t-tests were run between the different conditions, showing that the effect was driven by a marginal difference between sDdF and dD (t(12)=1.94, p=0.076, mean difference -0.172 μV), while the difference between sDsF and sDdF (t(12)=0.64, p=0.64, mean difference 0.056 μV) and the difference between sDsF and dD (t(12)=-1.14, p=0.28, mean difference -0.116 μV) did not reach significance.

NO-TMS AMPLITUDE

Including only the noTMS data, we ran a two-way ANOVA with factors Dimension (sDsF, sDdF, dD) and Response Priming (same, different). We observed only a significant main effect of Response Priming (F(1,12)=12.5, p=0.004), and not a main effect of Dimension nor an interaction. (All F*s*<0.5, All p*s*>0.5)

The main effect of Response Priming was caused by Same Response trials eliciting a smaller LRP voltage than Different Response (t(12)=-1.59, p=0.014, mean difference: =0.36 μV).

LATENCY (JACKKNIFING)

Figure 17 shows the latency of the sLRP component (using the jackknifing method, at 50% maximum amplitude).

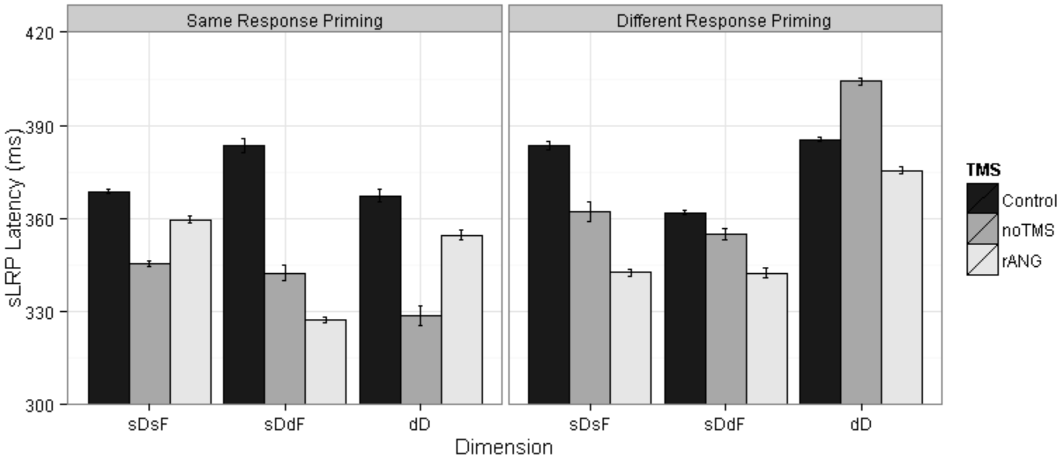

Figure 17: sLRP (stimulus-locked response potential) latency depending on experimental conditions. Panels represent response priming, while the dimension is represented on the x axis (sDsF = same Dimension, same Feature; sDdF = same Dimension, different Feature; dD = different Dimension). Different shades of grey represent the TMS condition. Error bars represent the standard error of the mean (SEM)

We run a repeated-measures 3-way ANOVA on the data, with factors being Dimension (including 3 levels: sDsF, sDdF, dD), TMS (including 3 levels: noTMS, Control and rANG) and Response Priming (including 2 levels: same response or different response).

F values were corrected; as jackknifing reduces variance in the data (Ulrich & Miller, 2001). We observed neither significant main effects nor interactions (All Fs<1, all ps>0.35).

RLRP

Before conducting rLRP analyses, we made sure that a rLRP was present in all conditions for all participants.

AMPLITUDE

Figure 18 shows the absolute value of the rLRP voltage (being the rLRP negative for all subjects and all conditions).

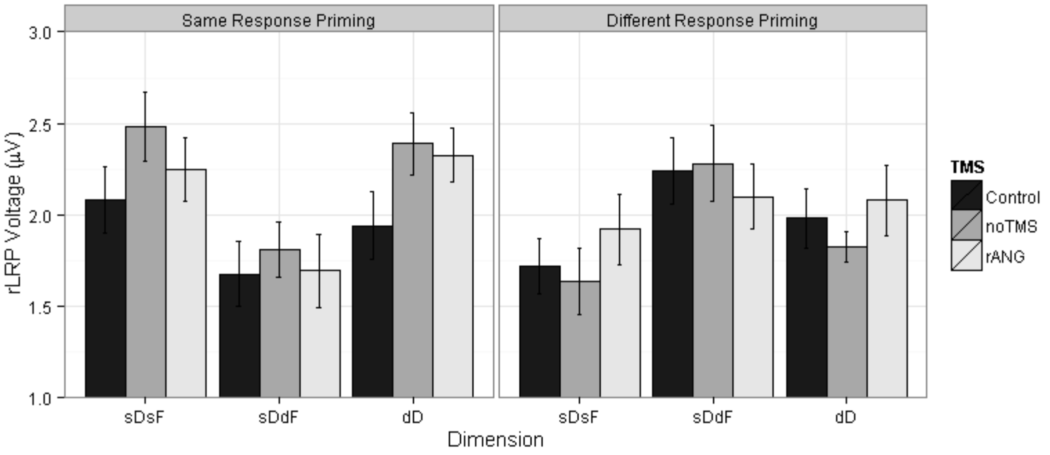

Figure 18: rLRP (response-locked response potential) amplitude depending on conditions. Panels represent response priming, while the dimension is represented on the x axis (sDsF = same Dimension, same Feature; sDdF = same Dimension, different Feature; dD = different Dimension). Different shades of grey represent the TMS condition. Error bars represent the standard error of the mean (SEM)

We ran a repeated-measures 3-way ANOVA on the data, with factors being Dimension (sDsF, sDdF, dD), TMS (noTMS, Control and rANG) and Response Priming (same response or different response).

We observed a main effect of Response Priming (F(1,12)=26, p<0.001), while no other main effect nor interaction reached significance (All Fs<2.5, all ps>0.1)

We investigated the main effect of Response Priming further;

Figure 19 shows the difference between same and different response rLRP amplitude. A t-test showed that the difference was significant, with same response priming voltage being smaller than different response priming (t(12)=-4.5298, p=0.0001. Mean of the differences: 0.41 µV).

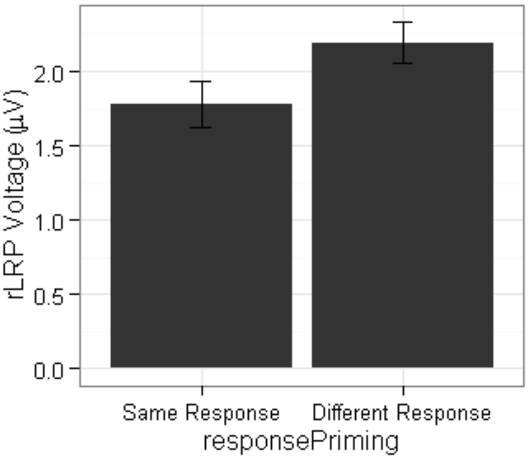

Figure 19: rLRP (response-locked response potential) voltage depending on response priming. Error bars represent the standard error of the mean (SEM)

NO-TMS AMPLITUDE

We then ran a two-way ANOVA with factors Dimension (sDsF, sDdF, dD) and Response Priming (same, different), including only data from noTMS; which highlighted a main effect of Response Priming (F(1,12)=18.5, p=0.001); no other main effect or interaction was significant (All F*s*<0.6, all p*s*>0.5).

The main effect of Response Priming was caused by Same Response trials generating a smaller amplitude rLRP than Different Response (t(12)=-3.12, p=0.009, mean difference: -0.58 µV).

LATENCY (JACKKNIFING)

Figure 20 shows the latency of the rLRP component (using the jackknifing method, at 90% maximum amplitude).

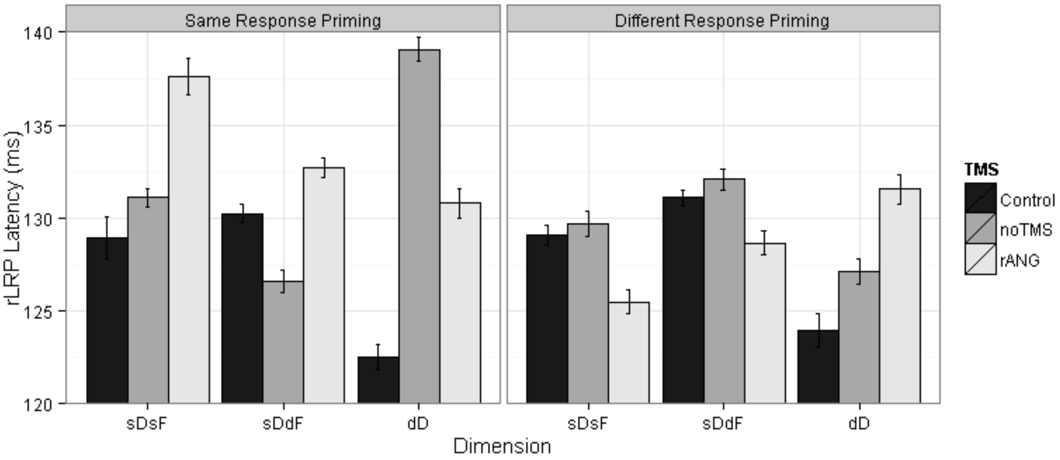

Figure 20: rLRP (response-locked response potential) latency depending on experimental conditions. Panels represent response priming, while the dimension is represented on the x axis (sDsF = same Dimension, same Feature; sDdF = same Dimension, different Feature; dD = different Dimension). Different shades of grey represent the TMS condition. Error bars represent the standard error of the mean (SEM)

We run a repeated-measures 3-way ANOVA on the data, with factors being Dimension (sDsF, sDdF, dD), TMS (noTMS, Control and rANG) and Response Priming (same response or different response).

After correcting F values, we observed neither significant main effects nor interactions (All Fs<1, all ps>0.5).

DISCUSSION

The additional analyses included lateralized components known to be affected by dimensional or response manipulations in visual search (Töllner et al., 2008); PCN, sLRP, and rLRP.

We did not observe any dimensional or response effect on the PCN, while it has been reported that PCNs for Different Dimension trials elicit smaller amplitude PCN than those for Same Dimension (Töllner et al., 2008). Perhaps, this different finding is caused by differences in the experimental design between the two experiments; the one by Töllner and colleagues (2008) included only sDsF and dD trials, while we also included sDdF trials in the experiment.

Conversely, we observed that Different Response rLRPs had an increased amplitude compared to Same Response; an effect that has been already been reported (Töllner et al., 2008). The same effect was observed in the stimulus-locked lateralized readiness potential; which again is reported in the literature (Töllner et al., 2008).

Overall, our results are compatible with response priming effects already reported in the literature; while the lack of dimensional effects could be explained as a difference in the experimental design in our experiment.

Our data also showed a lack of interaction between lateralized response potentials and TMS; in particular the lack of TMS effect in the PCN, a component traditionally associated with visual attention, might seem surprising. However, we believe the explanation for this result is simple; our behavioural results, showing a facilitation in trials in which both stimulus- and response- defining characteristics remained the same, was location-independent. Therefore, a lateralized component subtracting contralateral and ipsilateral responses to a visual stimulus is not the ideal tool to reflect a location-independent effect. As a matter of fact, the only component affected by TMS as well as by response- and stimulus- defining characteristics was the N1, at electrode position PO8 regardless of stimulus position in the visual display.

Taken together, the results shown in the manuscript and the additional lateralized components analyses reported in the present chapter suggest that stimulus or response lateralization was not a key factor in explaining the TMS effects reported in the behavioural results. However, we replicated LRP effects already observed in the literature, both while including TMS blocks and while excluding them.

CUEING AND VISUAL ATTENTION

> “Attention is an intentional, unapologetic discriminator, it asks what is relevant right now, and gears us up to notice only that.”
>
> (A. Horowitz, 2013)

INTRODUCTION

CUEING AND EEG

Electroencephalography allows researchers to investigate cueing in several ways; for example, the amplitude or latency of specific visual ERP components might be affected by cueing, or lateralized components can be calculated to reflect the difference between cued and not cued side.

The list of ERP components affected by cueing has been expanding through the years, including the most well-studied visual ERPs: P1, N1, and P2 (Luck, 2005). In general, it has been observed that stimuli appearing at attended location generate higher-amplitude ERPs than stimuli appearing at unattended location (Hillyard & Anllo-Vento, 1998). The time-course of attentional shifting has been investigated with EEG, employing a variety of behavioural paradigms (Luck et al., 2000).

Although traditional ERP studies can be helpful to study reorienting of attention elicited by cues, specific cue-related potentials have been developed; the most common are the ADAN and the LDAP. The Anterior Directing Attention Negativity (ADAN) is present 300-500 ms post cue onset, and is calculated as a lateralized potential from electrode position FC5 and FC6 (Eimer, Velzen, & Driver, 2002). This component is thought to reflect frontal attentional control activity. Recently (McDonald & Green, 2008), it has been suggested that the Late Directing Attention Positivity (LDAP) component might provide researchers with a clearer way to contrast attended and unattended space in a cueing paradigm. The LDAP is a later component than the ADAN; it peaks at 500-700 ms post cue onset, and is calculated at electrode position PO7 and PO8.

Each of these components is sensitive to different manipulations in the experimental paradigm, and is thought to reflect a specific attentional sub-process.

BRAIN NETWORKS OF VISUAL ORIENTING

The idea that attention is generated by a network of cortical and subcortical brain areas owes much to studies of neglect: patients with lesions disconnecting the parietal from the frontal cortex exhibit neglect in the absence of visual field defects (Doricchi & Tomaiuolo, 2003).

Cue-induced attentional orienting has been employed as a paradigm in combination with various methods (fMRI, PET, and cell recording) to investigate the neural mechanisms of attentional. Different aspects of spatial attention have been investigated: its transient allocation through cues, its sustained maintenance, or the act of attentional shifting itself (Carrasco, 2011).

MONKEY STUDIES

The anatomy of the monkey's visual system seems to already suggests the presence of top-down influences: all connections between progressively higher-order areas in the ventral stream are paired with feedback connections from parietal and prefrontal cortex (Ungerleider, Gaffan, & Pelak, 1989).

Indeed, single cell recordings on monkeys have shown that when attention is directed covertly towards a cell's receptive field, its response will increase compared to when it is not attended, referred to as a *baseline shift*. This has been observed in many visual areas (V1, V2, V4) as well as motion perception areas (MT) (Kastner & Ungerleider, 2000). It has also been observed that attention increase synchrony in neuronal firing rate for attended areas; that this increase in synchrony might represent a facilitation of communication between attentionally-relevant areas (Peelen & Kastner, 2014).

Concerning the distinction between endogenous and exogenous attention, electrophysiological studies in macaque monkeys supported the behavioural and EEG findings, distinguishing between a faster (exogenous) and a slower (endogenous) attentional system. While monkeys were performing a double-cueing task (with a first endogenous cue and a second exogenous cue), neurons in area MT showed temporally dissociable effects of the two cues (Busse, Katzner, & Treue, 2008).

Covert attention (generated endogenously) has been shown to “shrink” the size of receptive fields of neurons, therefore increasing resolution at the attended side (Anton-Erxleben, Stephan, & Treue, 2009).

Taken together, monkey studies have provided researchers with a clearer understanding of the neuronal basis for the known behavioural effects of attention. These results have opened the way for human neuroimaging studies reviewed in the next chapter, and facilitated their interpretation.

NEUROIMAGING

Neuroimaging studies have shown a variety of areas to be involved in attentional tasks, including frontal, parietal and occipital regions (Green & McDonald, 2008).

One of the earliest PET studies of attention (Corbetta, Miezin, Shulman, & Petersen, 1993) employed a variety of tasks requiring attention (endogenous cueing and discrimination tasks) and observed activations of a network of areas including substructures in the PPC, the FEF and MFC. Interestingly, these are the same areas that are damaged in neglect patients (Mesulam, 1999).

Frontal, parietal and occipital areas all take part in the allocation of attention. Interestingly, attention has been shown to also affect areas that have been considered purely sensory in the past, like V1 (Desimone & Duncan, 1995). Frontal and parietal areas in particular, have been shown to be active in attentional tasks in a variety of studies (Corbetta et al., 2000).

In summary, the fMRI studies have shown a variety of areas to be involved in spatial attention tasks, from sensory to associative, and models have been proposed to explain attentional control through these area. Experimentally, the timing of the activation of all the various areas has also been studied (Green & McDonald, 2008). Using beamforming analyses, the sources of low-frequency brain waves associated with attention have been reconstructed, and it has been observed that the parietal cortex is the first structure to be activated after a cue is presented; the frontal cortex gets activated only afterwards. Therefore, instead of models where top-down attentional control is initiated by the frontal cortex, the parietal cortex is the structure initiating the attentional shift.

ATTENTION AND CONSCIOUSNESS

As attention affects a variety of sensory as well as higher order areas both before and after a stimulus is perceived, it is relevant to question at which stage does consciousness emerge.

It is difficult to conclusively say that a brain area or a process measured with EEG represents a correlate of consciousness; there are in fact other mechanisms that occur in close proximity to consciousness, even though they do not reflect consciousness itself. These distinct functions are, for example, neural prerequisites and neural consequences of consciousness (de Graaf & Sack, 2014). As in one of the experiments in the present thesis (Experiment 2) we will manipulate spatial attention while generating illusory visual stimuli, it is important to be aware that any effect correlating with their perception does not necessarily reflect consciousness.

Recent studies employing masking and EEG have attempted to determine which brain events correlate the most with conscious reports (Del Cul, Baillet, & Dehaene, 2007). Even though they observed early, subliminal effects reflecting stimulus processing, they suggested that consciousness “happens” later (around 270 ms post stimulus).

This view of consciousness as the fruit of several subliminal steps of stimulus processing, and arising through recurrent activity of higher order areas has been proposed by Lamme on the basis of several visual neurosciences experiments employing paradigms like figure-ground discrimination (Lamme, 2006); he argued that consciousness is generated through localized recurrent processing in higher order areas.

TMS AND CUEING

INDICES OF CORTICAL EXCITABILITY

Several studies have suggested that endogenous cueing changes the excitability of the visual cortices through top-down modulation. TMS is the ideal technique to investigate such a claim, as it provides various ways of measuring cortical excitability. We will describe the most common three indices of cortical excitability employed in TMS experiments: motor threshold, TMS-evoked potential, and phosphenes.

The earliest TMS study (Barker et al., 1985) showed that, by applying stimulation on the primary motor area, a movement in the corresponding contralateral part of the body could be observed The minimum TMS intensity necessary to observe a detectable movement (or electromyogram) has been called motor threshold.

When TMS is not applied to the occipital or motor cortex, and therefore no behavioural output or inner report can be produced, it still induces effects e.g. a differential EEG response when ipsilateral and contralateral electrodes are compared (Komssi, Aronen, Huttunen, & Kesäniemi, 2002). The EEG response to the TMS pulse is called a TMS-evoked potential (TEP), and it reflects the spread of activation from the particular site of stimulation to the interconnected regions, and is an important index of cortex activation. This spreading from the TMS active site to other areas has been investigated also for sub-threshold motor and visual areas (Ilmoniemi & Kičić, 2009), and is therefore considered an index that can be used for cortical excitability of any area in the cortex.

By applying TMS over the visual cortex, visual perception can be suppressed, stimuli can be unmasked, and phosphenes can be elicited (Thut, Ives, Kampmann, Pastor, & Pascual-Leone, 2005). A phosphene is an illusory perceived flash of light (Walsh & Cowey, 1998). The position of the reported phosphenes changes proportionately with the location of the coil on the participant's scalp in a manner compatible with the cortical magnification factor (Kammer, 1998).

It has been observed that motor threshold and phosphene threshold are not correlated within subject (Gerwig, Kastrup, Meyer, & Niehaus, 2003; Stewart, Walsh,

& Rothwell, 2001); hence phosphene threshold is a better index of visual cortex excitability, and should be employed in studies concerned with the visual areas.

PROPERTIES OF PHOSPHENES

The nature and origin of phosphenes has been debated: it has been argued that they are generated in V1, in extrastriate areas (Kammer, Puls, Erb, & Grodd, 2005), or even in the optic radiation (Marg & Rudiak, 1994).

The perceived phosphene changes accordingly to the stimulated area; stimulation on areas like MT/V5, can generate the perception of moving phosphenes (Stewart, Battelli, & Walsh, 1999). Earlier studies (Marg & Rudiak, 1994) investigated the more phenomenological aspects of phosphene perception, showing a wide variety of shapes and locations described by participants (see also the section Phosphene perception in the *Methods* of *Experiment 1* and *Experiment 2*) .

One issue that may have prevented phosphene thresholds from becoming as widespread as motor thresholds in the past is that their measurement relies on participant's reports, meaning they are an indirect measure of cortical excitability. Recently, the combination of TMS and EEG has allowed the ERP-characterization of the phosphene evoked potential (Taylor, Walsh, & Eimer, 2010). By applying TMS to the occipital cortex, and instructing participants to report the presence or absence of a phosphene, it was possible to characterize the different waveforms for the perception of phosphene compared to no perception (Figure 21).

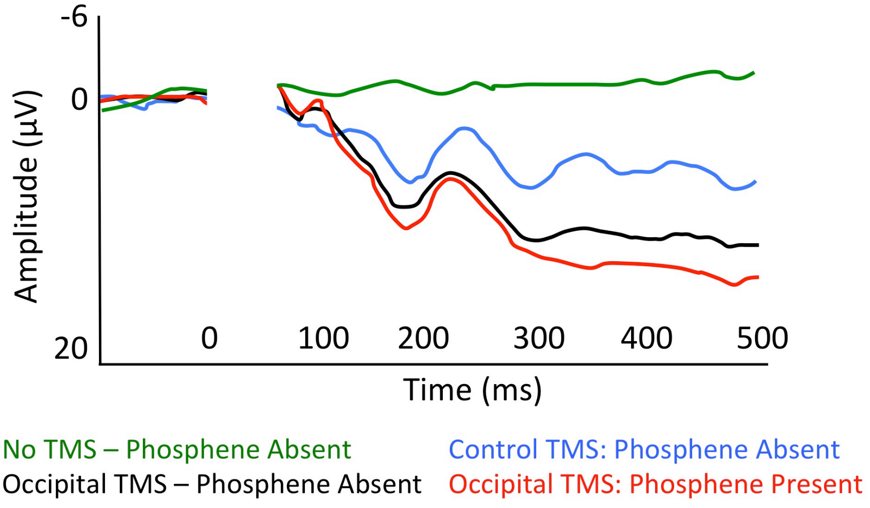

Figure 21: TMS-locked waveforms comparing different perceptual and TMS conditions, from electrode position Poz. (Adapted from Taylor et al., 2010)

The results showed that the same stimulation condition (occipital TMS) generated different TMS-evoked brain potentials depending on reported phosphene perception. More specifically, this effect was observed first at 160-200 ms after TMS pulse.

The time bin in which the effect of phosphene was observable, as well as the general topography of the effect were also very relevant to an underlying debate concerning the nature of phosphenes, about their early or late nature. The early hypothesis suggests that phosphenes are generated through a mechanism akin to the one of TMS over the primary motor cortex (Hess, Mills, & Murray, 1987); accordingly their effect on the EEG should be very early and topographically localized. The late hypothesis instead starts from the observation that recurrent processing is a necessary prerequisite for visual perception, and that consequently such processes must be present for phosphenes to be perceived (Pascual-Leone & Walsh, 2001). It would therefore predict a late effect on the EEG, and a more distributed activation across different cortical regions. The effects observed by Taylor et al. (2010) are compatible with the late hypothesis.

The identification of a phosphene-evoked potential opened the possibility for researchers to observe the effects of experimental manipulation on phosphene perception directly, without having to rely on participants' reports.

Phosphenes also interact with visual stimuli presented at the same time and location. The more precise topographic location of phosphenes and their relationship with the visual scotomas induced by TMS over the occipital lobe has been investigated (Kammer, 1998): it was observed that when a phosphene is perceived, detection threshold for stimuli presented at the same location is also increased. The study of visual stimuli masking with TMS has shown that many different effects can be generated at different times, contributing in understanding the timeline of visual perception (de Graaf, Koivisto, Jacobs, & Sack, 2014). Phosphenes can also be used to "unmask" visual stimuli; when the TMS pulse is administered shortly after a visual stimulus followed by a mask, the mask is suppressed hence enhancing the stimulus detection (Amassian et al., 1993). The interaction between visual stimuli and phosphenes has been investigated with a combination of TMS and EEG; it has been shown that TMS affects the visual evoked potentials of visual stimuli in a manner which is dependent on the intensity of the pulse (Reichenbach, Whittingstall, & Thielscher, 2011); a possible explanation is that although stimulus perception is robust to a certain amount of disruption, strong disturbances might cause saturation and therefore impairment.

TMS, ATTENTION AND EXCITABILITY

Covert attention through endogenous cueing has been investigated with TMS (Bestmann, Ruff, Blakemore, Driver, & Thilo, 2007). Participants were required to perform a visual detection task on a visual stimulus that was present only on part of the total amount of trials. In the remaining trials, participants had to move their attention, and a TMS pulse over the occipital cortex was administered instead, at varying intensity. Participants had to respond verbally whether they saw a phosphene or not.

Thus, it was possible to compare the TMS intensity for attended and non-attended locations and, given that phosphenes are an index of visual cortical excitability (Stewart et al., 2001), it was possible to critically assess the hypothesis that excitability increases for attended vs. non attended stimuli. Indeed, they observed a lower phosphene threshold for attended stimuli. In a control experiment, the same was observed for sustained attention throughout a block.

This experiment, however, could only prove that spatial attention affects cortical excitability indirectly, through participants' verbal reports. Combining TMS and EEG can allow researchers to identify the crucial timing in which the facilitation is observed, and the phosphene-evoked potential could be used as a better measurement of cortical excitability.

THE PRESENT EXPERIMENT

In the present studies, we aim at studying cortical excitability changes caused by endogenous cueing employing a combination of TMS and EEG.

The aim of the first study is to investigate whether covert endogenous visual attention can modulate the excitability of early visual cortical areas. We utilised central cues in the shape of arrows, with a validity of 80%, pointing to lateralised visual stimuli, appearing on only 33% of the trials. This paradigm allowed us to manipulate participant’s spatial attention, while probing their right occipital cortex with TMS and observing the ERP caused by sub-threshold stimulation. In this experiment, we employed a short cue-visual stimulus interval, suitable for the analysis of ERPs; the TMS pulse was sent at the time of visual stimulus onset, with a jitter. We employed three TMS conditions; Occipital (in which the coil was placed over the right phosphene-generating occipital cortex, see Figure 25), Control (in which the coil was placed over a non-phosphene generating area, see Figure 25), and Orthogonal (in which the coil was placed over the phosphene generating area but flipped of 90 degrees and with the handle pointing downward so that only the side rim of the coil would touch the head of the participant, and the magnetic field created by the TMS pulse would flow parallel to the head). The presence of three separate TMS conditions was necessary given the variety of neural as well as non-neural effects elicited by TMS (Duecker, de Graaf, Jacobs, & Sack, 2013); in particular the Orthogonal (sham) condition would help in dissociating which aspects of the TEP are due to somatosensory stimulation from the TMS.

The aim of the second study is to investigate the interaction between covert endogenous visual attention and cortical excitability while employing TMS at phosphene threshold intensity. This allowed us to investigate allocation of attention and phosphene perception both separately and together, thus being able to investigate the effects of attention and perception on the TMS-evoked potential. Furthermore, in this study, we employed a longer cue-TMS interval: this allowed us to investigate the cue-locked potential in a bigger time frame, and to perform frequency analyses in the cue-stimulus interval. We expected to observe a main effect (or multiple main effects) of phosphene, replicating published results (Taylor et al., 2008), as well as interactions between phosphene perception and cueing, whose timing and location would reflect different influences of attention on consciousness.

EXPERIMENT 1: ATTENTION AND EXCITABILITY[3]

METHODS

PARTICIPANTS

Fifteen healthy right-handed paid volunteers (mean age 28±0.67 years, 12 females) with normal or corrected to normal vision participated in the present experiment. Participants gave informed consent in accordance with the Ludwig-Maximilians University Ethics Advisory Committee. Participant selection complied with current guidelines for repetitive TMS research (Rossi et al., 2009).

PROCEDURE

Participants were seated in a dark room, with their eyes 57 cm away from a computer monitor. A chinrest was employed to restrict movements; participants were instructed to perform unnecessary movements only between blocks, and to blink only in the inter-trial interval. Visual stimuli were presented on a cathode ray tube

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[3] Francesca Bocca, Hermann Müller and Paul Taylor designed the study. Francesca Bocca programmed the experiment, which was conducted by Francesca Bocca and Paul Taylor. Francesca Bocca analysed the data.

computer monitor at 1,024 x 768 pixels resolution with a refresh rate of 75Hz (monitor model 21P4, made by Fujitsu Siemens).

Before beginning the experiment, participants' motor and phosphene thresholds were measured. Only participants that were able to reliably perceive phosphenes were included in the experiment. A sigmoidal function was fitted to the measured responses, and the stimulator output intensity of 50% 'yes' responses was taken as the motor threshold. At least 30 trials or 8 reversals were considered sufficient to terminate the thresholding algorithm. Phosphene thresholds were measured with the participant fixating on a central point on the blank screen (with same luminance of the one used in the experiment). TMS pulses were applied to the right hemisphere, to the site that elicited the strongest visual phosphene in the left hemifield (with lateralization compatible to the position of the placeholders on the screen). The phosphene threshold was identified with the same algorithm as the motor threshold.

After the phosphene threshold was identified, participants were asked to draw the shape of the phosphene they saw using an image processing software (Paint for Windows). They were also asked to fill a brief questionnaire regarding the shape, colour, texture and other characteristics of the phosphene. The qualitative data regarding phosphenes is presented in the next section.

Participants then performed a training block (without TMS), for a total of 60 trials. The training block consisted solely "visual stimulus present" trials: the timeline is illustrated in Figure 22, top panel.

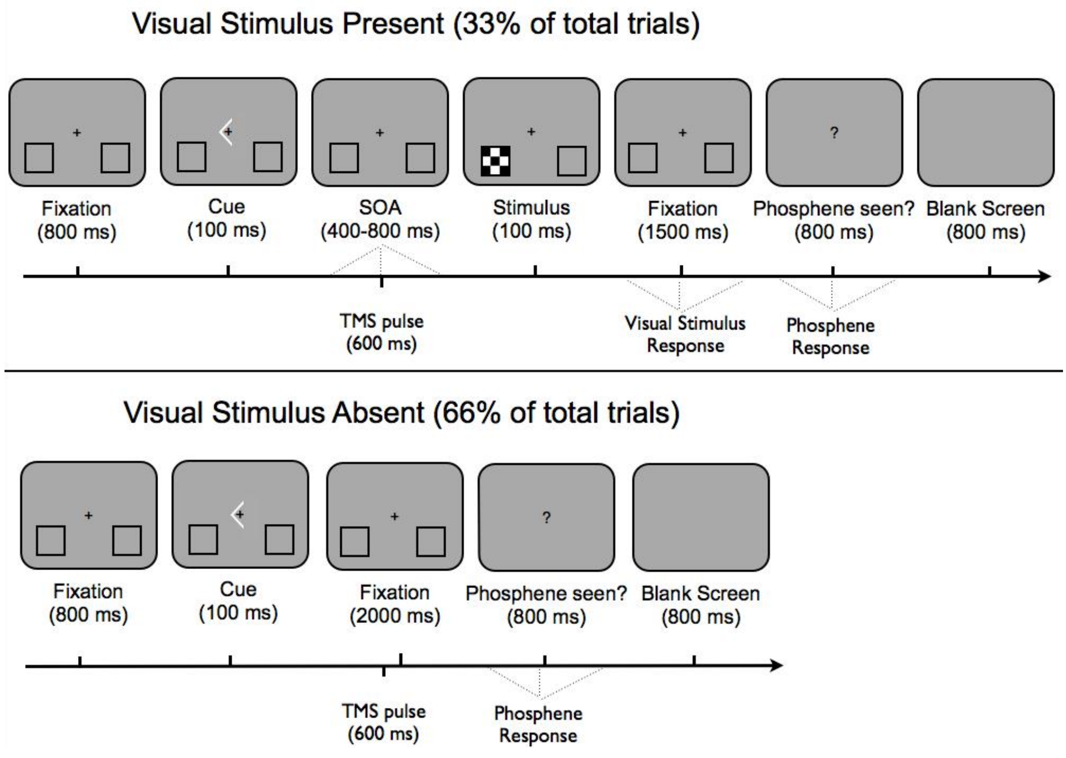


Figure 22. Timeline of a sample trial. Trial duration was identical in no-TMS and TMS trials; in no-TMS trials the fixation lasted for 1400 ms, uninterrupted.

Each training trial was preceded by a central black fixation cross (0.05° of visual angle) on a grey screen (23 cd/m^2). The fixation cross was presented along with two placeholders in the shape of symmetrically lateralised square frames, whose coordinates were matched on the position of the perceived phosphene, so that the left placeholder overlapped with the position of the phosphene when the participant fixated in the centre. After 800 ms, a cue in the shape of a white arrow was presented on the screen for 100 ms. Participants were instructed to move their attention - but not their eyes - to the placeholder on the side indicated by the cue. The cue was congruent on 80% of the trials, and incongruent on 20%. Then, after a variable interval between 400 and 800 ms, a visual stimulus appeared, in the shape of a 3x3 checkerboard, remaining onscreen 100 ms. Participants were instructed to respond as fast and as accurate as possible discriminating whether the checkerboard had a black centre or a white one. Response keys were adjacent on the keyboard (keys M and N on a German keyboard), and subjects were instructed to press them with the index and middle finger of their right hand. The stimulus-response key combination was counterbalanced across subjects. After 1500ms from stimulus onset, whether or not subjects responded, error feedback was given in the shape of written text in the centre of the screen. Afterwards, a question mark was presented in the centre the screen, prompting participants to report whether or not they perceived a phosphene. Response keys were adjacent on the keyboard (keys Y and X on a German keyboard), and participants were instructed to press them with the index and middle finger of their left hand. The phosphene-response key combination was counterbalanced across subjects. During the training block participants were instructed to always respond with the "no" key for phosphenes, as no TMS stimulation took place.

After the end of the training block, participants' performance was showed on the monitor in the form of text feedback. Training was considered complete when participants could perform with an average reaction time faster than 1000 ms and an error rate smaller than 20%.

During the experiment, TMS was applied block-wise; In TMS blocks, after 600 ms of the cue dot onset, a TMS pulse at 90% intensity of phosphene threshold was delivered. In each block, 33% of the trials contained a visual stimulus (see Figure 22, top panel), while 66% had no visual stimulus (see Figure 22, bottom panel). In visual stimulus absent trials, after cue onset, fixation lasted 2000 ms, after which the phosphene question mark was directly presented. Throughout the experiment, cue direction, visual stimuli positions and visual stimuli colour were balanced within each block. The block type was balanced across participants using a Latin square technique. The total experiment consisted of 15 blocks of 60 trials each.

PHOSPHENE PERCEPTION

Figure 23 summarizes the phosphene characteristics reported by participants concerning colour (left panel) and shape (right panel).

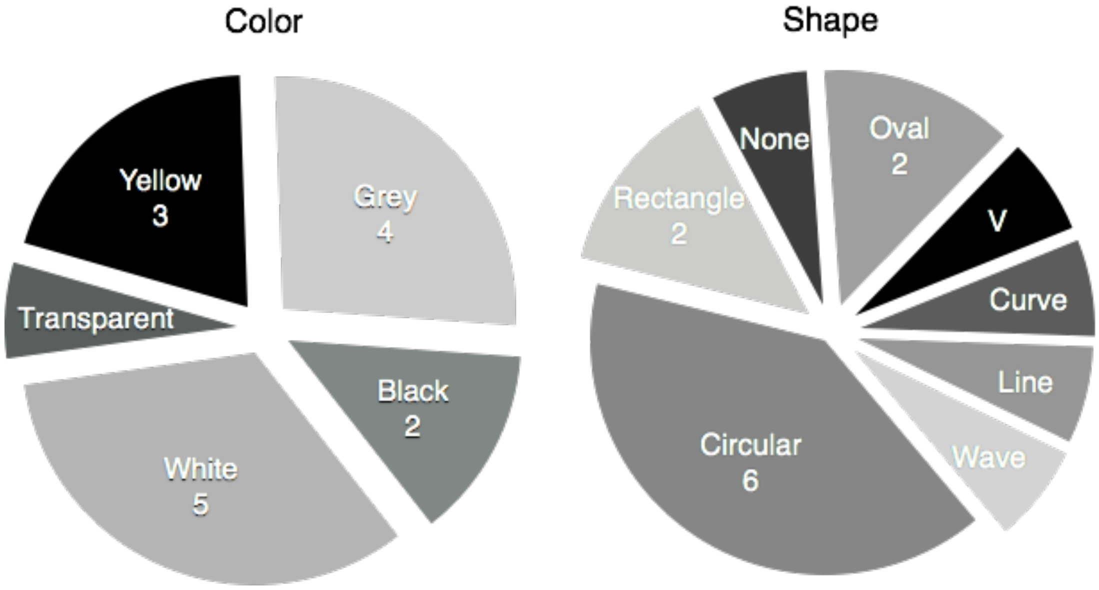


Figure 23. Pie charts summarizing the colour (left panel) and shape (right panel) characteristics reported by participants to describe their phosphene experience. The numbers inside the wedges represent the number of participants choosing the option; wedges without numbers represent categories chosen by only one participant.

Concerning colour, most phosphenes did not have one, but were just described in terms of changes in luminance; black, grey and white phosphenes made up 73% of the total (11 participants). Three participants described their phosphenes as being yellow, in a manner similar to artificial light. One participant could not point out the exact colour of the phosphenes, and described it to be transparent. Concerning shape, participants reported a lot of diverse experiences. Circular and oval shapes constituted 53% of the total (8 participants); while other participants reported more uncommon shapes, like rectangles and V-shaped “slices”. For one participant, phosphenes were not characterised by colour, but only by a change in luminance in one part of the visual field. Figure 24 summarizes the phosphene characteristics reported by participants concerning motion (left panel) and texture (right panel).

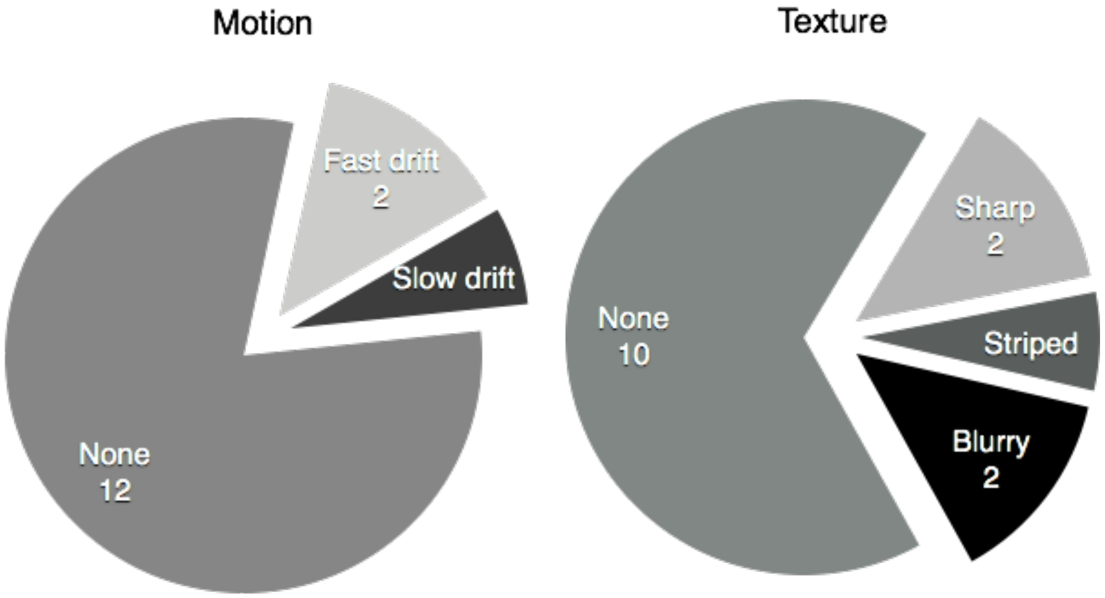


Figure 24. Pie charts summarizing the motion (left panel) and texture (right panel) characteristics reported by participants to describe their phosphene experience. The numbers inside the wedges represent the number of participants choosing the option; wedges without numbers represent categories chosen by only one participant.

The vast majority of participants (12) did not experience moving phosphenes, while all those who did described their movement as a drift; either fast or slow.

The presence of surface texture was not reported by most participants (10); those who did described their phosphenes to be blurry or sharp; while only one participant described them as striped.

TMS

We applied transcranial magnetic stimulation using a ‘PowerMag Research’ TMS machine (Mag & More, GmbH) with a figure-of-eight coil at 90% of the participant’s phosphene threshold.

9 out of 15 participants took part in a preliminary structural MRI scan. We employed the scan to perform coregistration of the stimulated areas through the Brainsight software (Rogue Research Inc.)

The images were processed with FSL (FMRI Software Library, Version 2.7.6) using the Brain Extraction Tool (BET) and an automated tool for linear intra- and inter-modal brain image registration (FLIRT).

The present experiment contained three types of block, called: Occipital, Control, and Orthogonal. In Occipital blocks, the coil was placed with the handle pointing towards the right (Kammer et al., 2001), and with the centre of the coil over the phosphene-eliciting area (mean MNI coordinates: x: 6; y: -106; z: -2). Figure 25, top panel, shows the average location of the phosphene eliciting area on a custom structural-MRI template, obtained as the average of the participants’ scans normalised into MNI space.

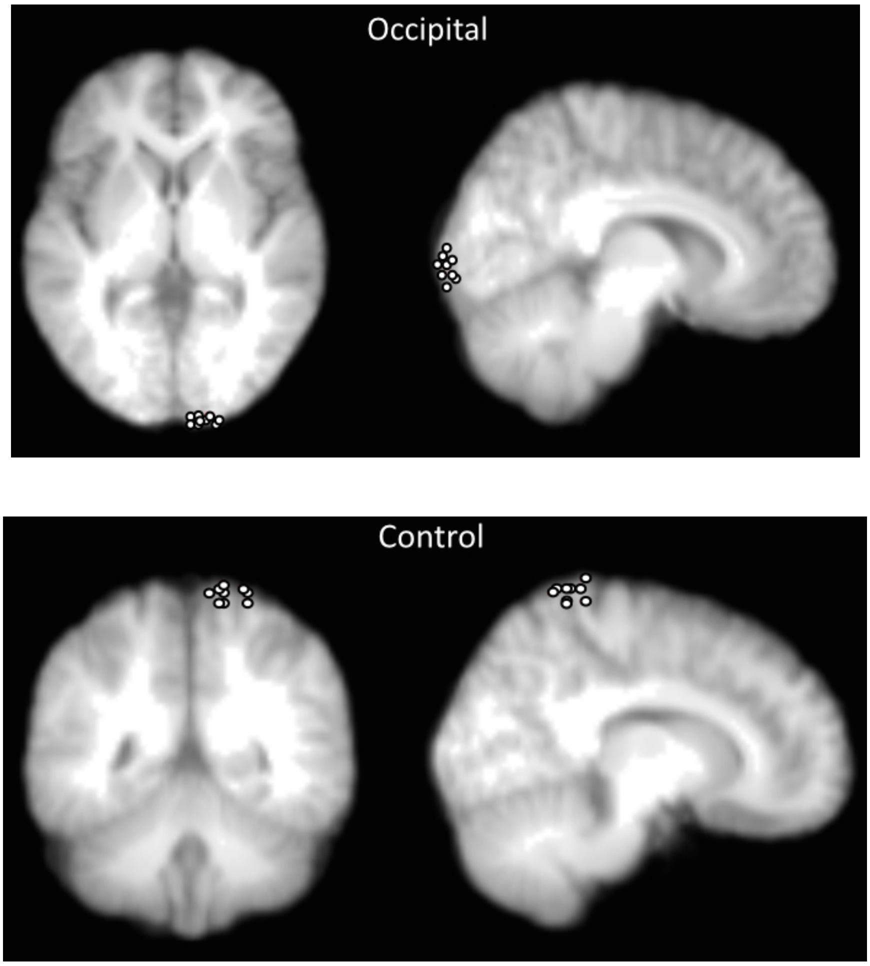


Figure 25. Top panel: Location of TMS for the Occipital condition, overlaid on their average structural (mean MNI coordinates: x: 6; y: -106; z: -2). Bottom panel: Control condition (mean MNI coordinates: x: 12; y: -47; z: 78).

In Control blocks, the coil was placed with an identical orientation and laterality to Occipital blocks, but the location was 5 cm caudal to the hand area, stimulating therefore the right parietal cortex (mean MNI coordinates: x: 12; y: -47; z: 78). This was chosen as a control site, to control for the somatosensory stimulation accompanying the TMS pulse. Participants received training with TMS to this area prior to the beginning of the experiment, to make sure no phosphenes nor motor twitches were elicited. Figure 25, bottom panel, shows the average location of the control site.

In Orthogonal blocks, the lateral coil rim was placed on the phosphene-eliciting area, but the coil itself was oriented perpendicularly in respect to the head (i.e. with the handle pointing down and only the rim of the coil touching the head). This type of stimulation does not induce phosphenes, as the magnetic field points perpendicularly to the head, but still it provides control for the auditory components of the TMS pulse (Duecker et al., 2013).

EEG RECORDING

EEG was recorded from 29 Ag-AgCl electrodes mounted on an elastic cap (EasyCap, Brain Products, Munich) referenced to the earlobes. Electrode positions were a subset of the international 10-20 system (American Electroencephalographic Society, 1994): C3, C4, Cp5, Cp6, Cz, F3, F4, F7, F8, Fc5, Fc6, Fcz, Fz, Fpz P3, P4, P7, P8, PO3, PO4, PO7, PO8, POz, Pz, T7, T8. The online reference was set to the left earlobe, and the ground at AFz. EEG was recorded with a BrainAmp DC amplifier (Brain Products, Munich, Germany) with all online filters turned off and a digitization rate of 5000 Hz. All electrodes impedances were kept below 5 kΩ, were checked at the end of each block and readjusted if necessary.

DATA ANALYSIS

For each subject, trials with a reaction time (RT) less than 100 ms or greater than 1500 ms, as well as trials containing an error, were removed from the reaction times analyses. In ANOVAs, the Huynh-Feldt correction was applied.

EEG data was re-referenced offline to the mean of the left and right earlobe electrodes. Prior to epoching the EEG, 1ms before and 39 ms after the TMS pulse were removed through linear interpolation, in order to delete the TMS artefact from the data. Once the artefact was removed, the EEG was down sampled to 1000 Hz, a sampling rate more commonly used in ERP analyses. After epoching the EEG, artefact rejection was applied - Trials with signals exceeding ± 80 μV on any recording channel, ± 30 μV on electrodes F9 and F10 (eye movements) or ± 60 μV on electrode Fpz (blinks) were excluded from further analyses before ERPs were averaged. Once the artefacts were removed, the data was filtered with a low-pass filter (40 Hz, 24 dB), a high-pass filter (0.01 Hz, 24 dB), and a notch filter (50 Hz). In all epochs, the baseline was corrected based on the 100 ms before the relevant event

For the cue-related ERP analyses, the EEG was averaged starting 100 ms before the cue onset until 800 ms after. In TMS-evoked potential (TEP) analyses, we analysed the EEG between 100 ms before the TMS pulse and 400 ms after, correcting the baseline 100 ms before the EEG was averaged starting 100 ms before the TMS pulse until 400 ms after.

The data was also pooled into two electrode groups: a right parietal (including electrodes P4, PO8), and a left parietal group (P3, PO7). Figure 26 shows the positions of the electrodes divided by group; the electrodes were chosen as they are commonly involved in attentional effects.

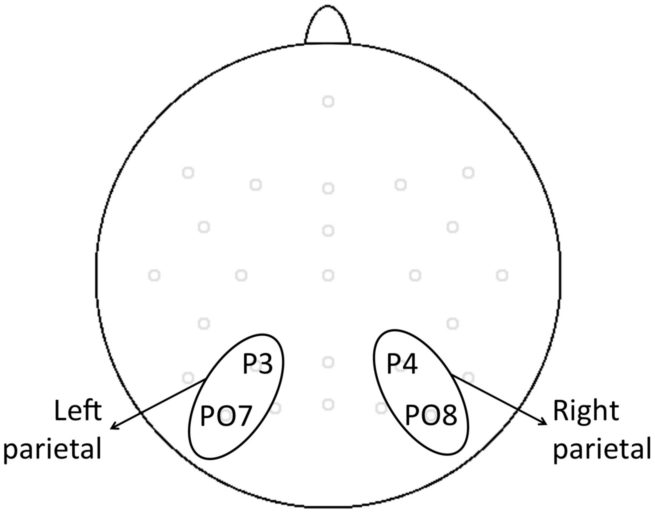


Figure 26. Electrode groups employed in the TEP analyses. The left parietal group was constituted by electrodes P3 and PO7, while the right parietal group was constituted by electrode P4 and PO8.

For all EEG analyses (cue- and TMS- locked) we made sure that each condition for each individual participant contained at least 40 trials after outlier rejection, in order to include only meaningful and stable data. Note that for this reason, it was not possible to look at visual stimulus present data, in which more than half of the participants (10 out of 15) did not pass the criterion.

The TEP data was divided into different time bins; 70-140 ms, 180-240 ms, 240-280 ms and 280-400 ms, replicating previously published data (Taylor et al., 2010). For each bin, the mean amplitude was analysed by means of a 2*3*2 repeated-measures ANOVA with factors Electrode Group (Parietal Left, Parietal Right), TMS (Occipital, Orthogonal, Control) and Cue (Left, Right).

RESULTS

ERRORS

We performed a three way ANOVA with factors Cue Direction (Left, Right), Cue Validity (Valid, Invalid), and TMS (Occipital, Control, Orthogonal). We observed a significant main effect of *TMS* (F(2,28)=6.29, p=0.006), and a marginal interaction between *Cue Validity and Cue Side* (F(1,14)=3.83, p=0.07). No other main effect or interaction reached significance (All F'*s*<2.6, all p'*s*>0.13).

The main effect of *TMS*, shown in Figure 27, was given by the Occipital condition bearing more errors than both Control (t(14)=2.82, p=0.014, mean difference: 4%) and Orthogonal (t(14)=4.13, p=0.001, mean difference: 8%). Control TMS also produced marginally more errors than Orthogonal (t(14)=1.82, p=0.08, mean difference: 4%). This effect is likely caused by Occipital TMS disrupting stimulus perception (Amassian et al., 1989).

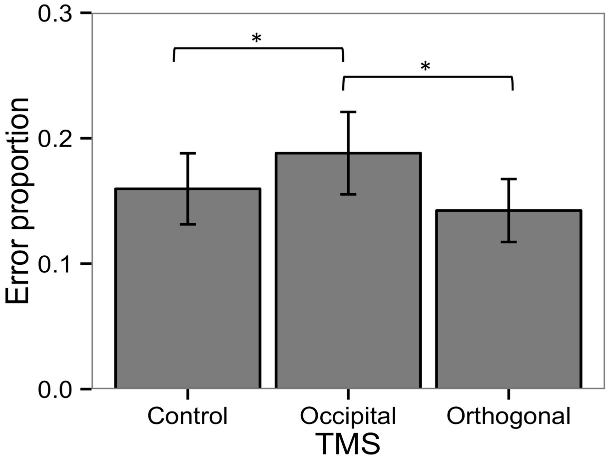


Figure 27. Error proportion depending on TMS condition. Error bars represent the SEM.

REACTION TIMES

For RTs, we analysed the data identically to error rates. We observed a significant main effect of *Cue Validity* (F(1,14)=9.18, p=0.009), a significant main effect of *TMS* (F(2,28)=14.4, p<0.001) and a significant interaction between *Cue Validity and TMS* (F(2,28)=6.1, p=0.006). All other main effects and interactions did not reach significance (All Fs<2, all ps>0.18).

The main effect of *Cue Validity*, shown in Figure 28, left panel, was due to valid cues generating a faster RTs than invalid cues, (t(14)=-3.292, p=0.002, mean difference: 41 ms), indicating that attention was allocated to the cued side (Posner, 1980).

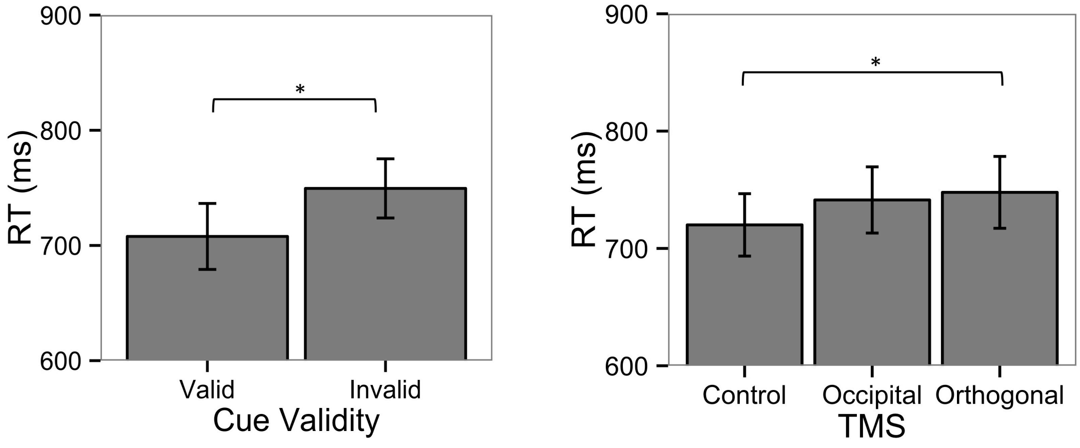


Figure 28. Left panel: effect of validity on RTs. Right panel: TMS effect on RTs. Error bars represent the SEM.

The main effect of *TMS* (Figure 28, right panel) was a result of the Control condition being significantly faster than Orthogonal (t(14)=-3.44, p=0.004, mean difference: 45 ms) and marginally faster than Occipital (t(14)=2.05, p=0.06, mean difference: 33 ms). Orthogonal and Occipital did not differ significantly (t(14)=0.25, p=0.8, mean difference: 12 ms). This facilitatory effect of Control TMS could be a result of it affecting higher order motor planning or execution due to its location.

Figure 29 shows the interaction between *TMS and Cue Validity*. This effect was given by the Control condition not showing a significant validity effect (t(14)=-1.67, p=0.11, mean difference: 28 ms), while both Orthogonal (t(14)=-2.06, p=0.05, mean difference: 26 ms) and Occipital (t(14)=-4.93, p<0.001, mean difference: 60 ms) showed validity effects. A possible explanation could be that Control TMS speeds RTs, thereby reducing the validity effect by decreasing the difference between valid and invalid cues.

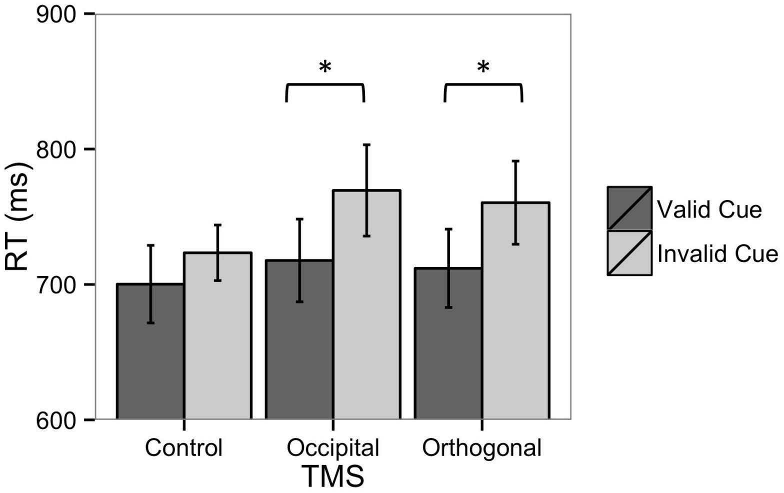


Figure 29. The interaction between TMS and cue validity in the RTs. Bars represent the SEM.

In sum, the behavioural analyses showed that participants were orienting their attention as instructed (shown by the presence of a validity effect in the RTs). We also observed that Occipital TMS decreased accuracy, while Control TMS decreased RTs. The fall in accuracy after Occipital TMS can be explained by the interference that visual stimulation might create on visual stimuli perception; while the effect of TMS making participants faster is well documented in the literature (Luber & Lisanby, 2014).

CUE-EVOKED POTENTIALS

In order to demonstrate that participants were allocating their attention to the cue, and to investigate the interaction between cueing and TMS, we derived lateralized cueing related components.

ANTERIOR-DIRECTING ATTENTION NEGATIVITY (ADAN)

To analyse the ADAN, we considered the mean ERP signal in the time bin 300-500 ms post cue onset, and calculated a lateralized potential for electrodes FC5/FC6. Figure 30 shows the waveform of the ADAN.

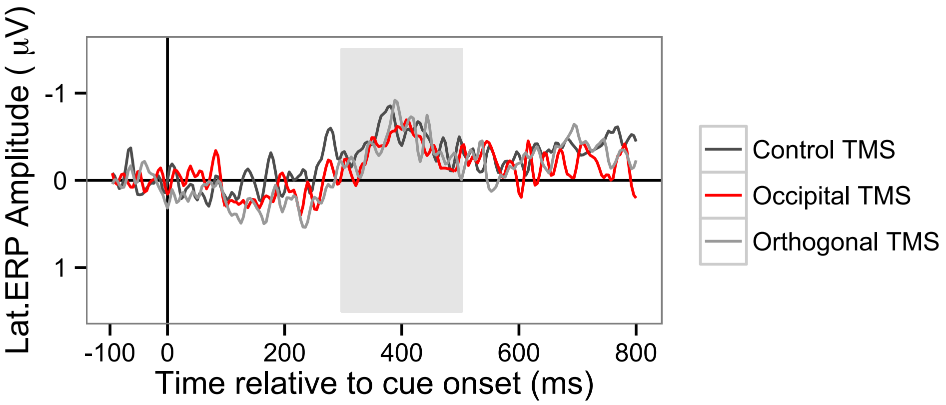


Figure 30. ADAN. The shaded area represents the time bin 300-500 ms post cue in which the ADAN was derived.

To test whether the ADAN values differed from zero (i.e. whether the ADAN was present), we ran one-sample t-tests for each TMS condition (Figure 31). The ADAN was observable for Control (t(14)=2.6, p=0.02) and Orthogonal (t(14)=2.51, p=0.025) and marginally for Occipital (t(14)=1. 8, p=0.07).

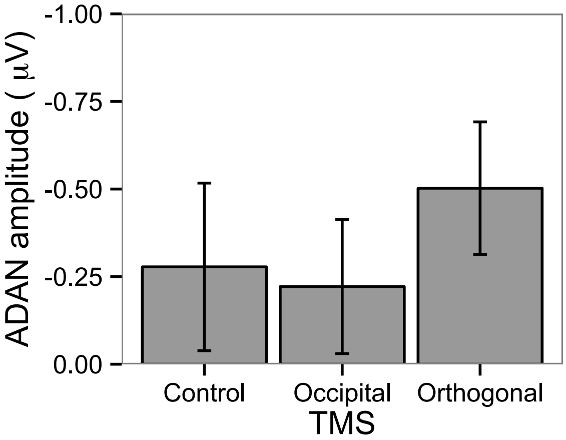


Figure 31. Mean amplitude of the ADAN, divided by TMS condition. Error bars represent the SEM

We also tested whether TMS would affect the ADAN, and we found that it did not. (F(2,28)=0.157, p=0.85).

LATE-DIRECTING ATTENTION POSITIVITY (LDAP)

To analyse the LDAP, we considered the lateralised subtraction of the average ERP activity in the time bin 500-700 ms post cue onset for electrodes PO7/PO8.

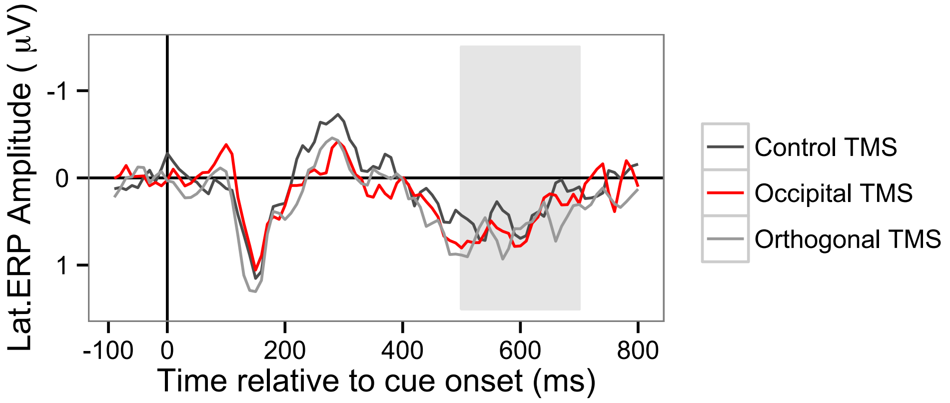


Figure 32. Waveform of the lateralized ERP at electrode position PO7/PO8 divided by TMS condition. The shading represents the area 500-700 ms, in which the LDAP was significantly different from zero in all three TMS conditions.

The LDAP was present in the Occipital (t(14)=2.68, p=0.018) and Orthogonal Conditions (t(14)=2.16, p=0.048), but not in Control (t(14)=1.13, p=0.232).

TMS however did no affect the LDAP amplitude significantly (F(2,28)=1.48, p=0.24).

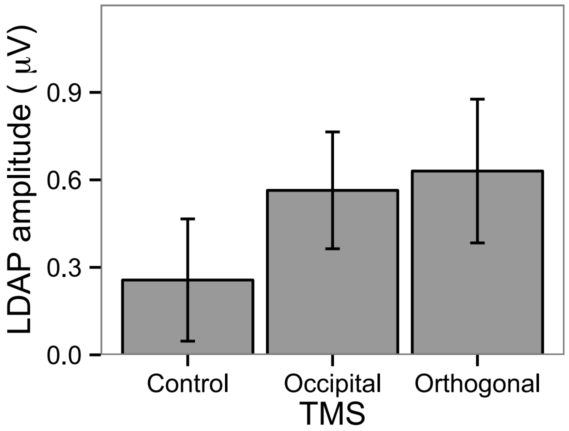


Figure 33. Mean amplitude of the LDAP (Late Directing Attention Positivity) 500-700 ms post cue onset. Bars represent the SEM.

The cue-locked analyses show that the type of cues employed in the present experiment cued attention, as shown by the presence of the attentional related cueing components. Furthermore, TMS did not affect this cueing process, as measured by the lack of a difference between different conditions in the paired t-tests.

TMS-EVOKED POTENTIALS

Figure 34 shows the TMS-evoked potential waveforms for different cueing conditions, divided by electrode group and TMS.

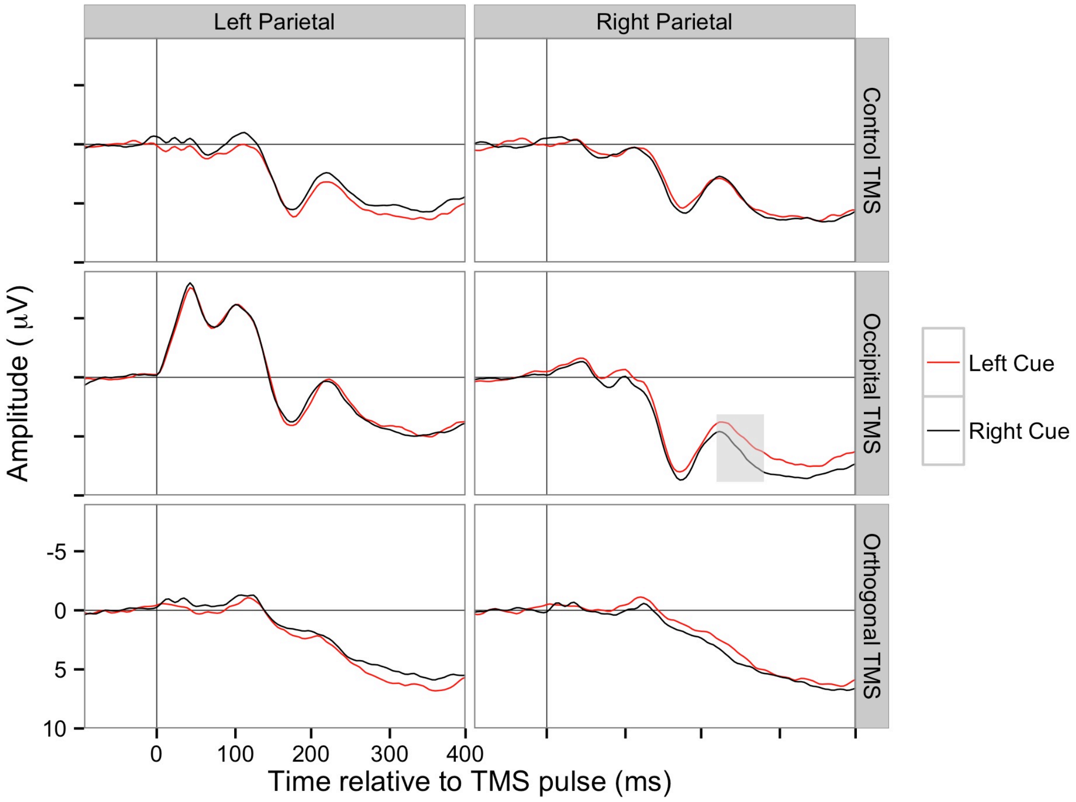
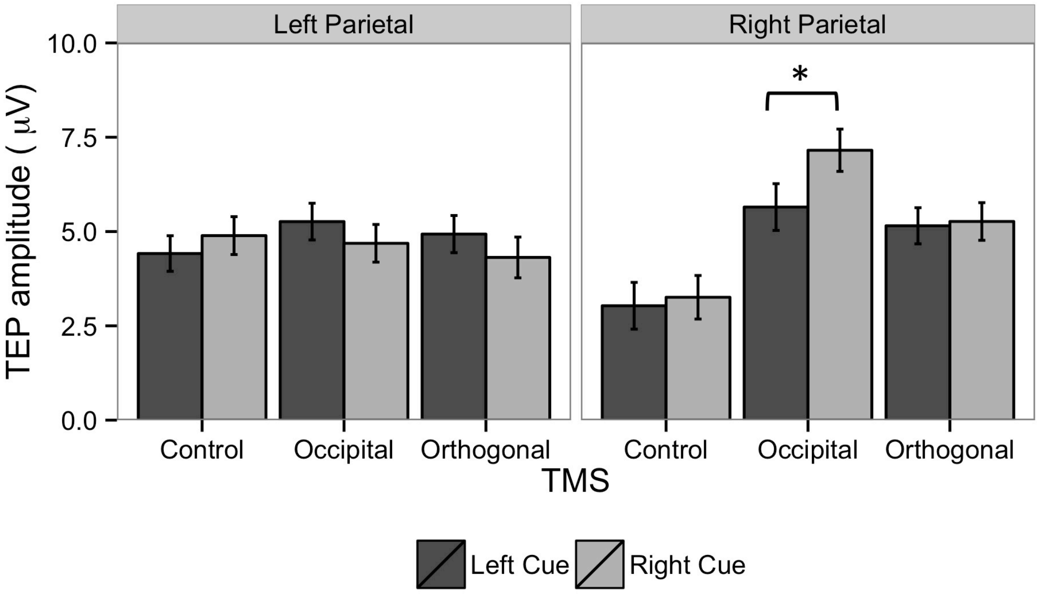


Figure 34. The TMS-evoked potential for different TMS conditions (rows) divided by Electrode group (columns). Colours represent cueing direction. The shading in the Right Parietal panel for the Occipital TMS condition represents the time bin 240-280 ms, in which the interaction between TMS and cueing was significant.

To test for effects of attention on excitability, our analyses focused on any interaction including both TMS and Cue (additional interactions are reported below); we observed a marginal interaction between *TMS and Cue* (F(2,28)=3.3, p=0.055) as well as a significant three way interaction between *Electrode Group, TMS and Cue* only in the time bin 240-280 ms (F(2,28)=3.8, p=0.034).

The interaction between *Electrode Group, TMS and Cue* in the time bin 240-280 was further investigated by separate 2*2 repeated measures ANOVAs with factors TMS (Occipital, Orthogonal, Control) and Cue (Left, Right) for each electrode group. The interaction between *TMS and Cue* was only significant for the Parietal Right electrode group (F(2,28)=4.3, p=0.023), which also showed a main effect of *Cue* (F(1,14)=8.4, p=0.012), and a main effect of *TMS* (F(2,28)=4.9, p=0.02). The Parietal Left group showed only a main effect of *TMS* (F(2,28)=4.8, p<0.021), with no other effects or interactions reaching significance (All F's<2, all p's>0.15).

The interaction between *TMS and Cue* within the Parietal Right electrode group (Figure 35, top panel) was investigated with separate paired-samples t-tests within TMS; we observed a significant cueing effect within the Occipital condition (t(14)=3.6, p=0.003, mean difference: 1.5 µV), while the cueing effect did not reach significance in either the Control (t(14)=0.27, p=0.79, mean difference: 0.11 µV) or the Orthogonal (t(14)=1.02, p=0.49, mean difference: 0.49 µV) conditions. Figure 35, bottom panel, shows the topography of the cueing effect for the Occipital condition; a negativity is most prominent over right parietal electrodes.



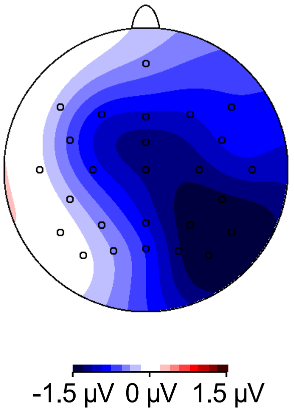


Figure 35. Left panel: TEP amplitude depending on TMS condition and cue direction for the time bin 240-280 ms divided by electrode group. Right panel: Topography map of the cueing effect (left-right) for the Occipital TMS condition in the time bin 240-280 ms.

Additional effects included a main effect of Electrode Group for the time bins 70-140, 180-240, 240-280 and 280-400 (All F's>15, all p's<0.001), an interaction between *Electrode Group and TMS* for the time bins 70-140, 180-240 and 240-280 (All F's>30, all p's<0.001) and *a Electrode Group by Cue* interaction for time bins70-140 and 240-280 (All F's>20, all p's<0.001). The latter two effects suggest that that the two electrode groups are performing different tasks in response to the TMS pulse and the cue, respectively. This is consistent with the fact that cues affect the two hemifields differently, and that TMS would not affect all electrodes at once but instead start as a focal phenomenon and then spread to other regions. No other effects or interactions reached significance (All F's<2.5, all p's>0.15).

DISCUSSION

We applied sub-threshold TMS to the right occipital cortex, while participants performed a discrimination task on rare lateralized stimuli. We observed that TMS modulated the excitability of the underlying cortex differently depending on cueing in the time bin 240-280 ms post pulse, suggesting that attention affects visual excitability.

Behavioural results confirmed that the participants were using the cues to orient their attention to the instructed target, as shown in the RTs (with validly cued trials being faster than invalidly cued ones). We observed that TMS had an effect on error rates; the fact that Occipital TMS was increasing error rates could be interpreted as disruption of visual stimulus perception. This finding agrees with previous studies reporting that TMS applied over phosphene-generating occipital areas decreases performance (Kammer, 1998).

TMS affected reaction times as well; the control condition elicited faster reaction times. This effect might be due to the location of our control area being close to higher order motor areas, or to arousal effects caused by TMS (Marzi, Mancini, & Savazzi, 2008). The speeding effect observed after Control TMS could also explain why the validity effect did not reach significance for this condition; the validity effect became smaller and therefore would have required a higher amount of trials to be detected.

The presence of a cueing effect was also demonstrated by cue-related lateralized components; ADAN and LDAP were measurable for all conditions. The absence of an effect of TMS on either cueing potentials indicates that the orienting processes they reflect (frontal attentional control for the EDAN and processing of the non-attended location for the LDAP) did not affect later cortical excitability.

Within the Occipital condition, cue left trials generated a less positive signal than cue right in the time-window 240-280 ms post TMS pulse, measurable only over right parietal electrodes. This finding strongly suggests that attention affects the TEP and hence cortical excitability. It is important to note that TMS intensity was kept below phosphene threshold and that, consequently, participants were not experiencing any visual percept when the TMS pulse was delivered. This enables attributing our effect solely to top-down attentional modulations over the visual cortex, avoiding confounds attributable to exogenous effects of visual perception, or to different levels of percept vividness.

The presence of a cueing effect in the absence of a percept has been interpreted as a “baseline shift” in cortical activity (Kastner & Ungerleider, 2000). It has been observed that, after a cue is presented, neurons containing the cued area in their receptive field fire at a higher intensity than neurons with receptive fields outside the cued area (Kastner & Ungerleider, 2000). It has also been found using neuroimaging, that baseline shifts are present at all stages of visual processing, from the striate cortex to higher order visual areas (Serences & Kastner, 2014). While fMRI can measure activity-dependent BOLD signal, the TEP can provide a measure of cortical excitability and allows for causal inferences as to the role of the stimulated area. We can therefore conclude that the TEP resulting from stimulation over the occipital cortex (on a phosphene-generating area) is affected by baseline shifting processes, even though EEG results do not permit inferences about the location of the effect due to the inverse problem (Luck et al., 2000).

As TMS provides a measure of cortical excitability (Taylor & Thut, 2012), our results speak to the effects of cueing on excitability. The effect of spatial attention on the excitability of the visual cortex has been investigated with TMS (Bestmann et al., 2007); the TMS intensity needed to elicit a phosphene was lower when the location of the phosphene was cued, hence suggesting that endogenous cueing exerts top-down influences over the visual cortex, changing its excitability. In Bestmann's (2007) study, however, the measure of cortical excitability was relying on participant's verbal report; thus it was not possible to look at sub-threshold modulations of excitability. In our study, instead, the use of the TMS-evoked potential allowed us to measure excitability changes that are completely unknown to the participant (not subject to the confound of perception), as well as pinpointing the specific time in which this change of excitability becomes measurable. Our results agree with the conclusion of Bestmann (2007), that spatial attention and excitability of the visual cortex are interrelated, although we cannot make a direct causal claim that spatial attention changes excitability; we can also add that this effect is relatively late in time (starting 240 ms after the TMS pulse), is measurable over the parietal right electrodes (adjacent to the stimulated area), and is present when no percept is reported.

Our results converge with data from studies investigating the relationship between α-band EEG oscillations and visual cortical excitability (Berger, Minarik, Liuzzi, Hummel, & Sauseng, 2014). Also, employing combined TMS-EEG, it has been observed that spontaneous trial-by-trial changes in α-band power predict whether participants would later perceive a phosphene when a TMS pulse was applied (Romei et al., 2008); it has also been shown that TMS can disrupt this anticipatory pattern of α-activity (Sauseng, 2011). α-band power can be modulated by endogenous cueing (Foxe & Snyder, 2011). These findings point towards a relationship between cortical excitability (measured by α-band oscillations and probed by TMS) and attention (elicited by cueing). Our results strengthen this link, providing another measure of cortical excitability (the TMS-evoked potential) that is sensitive to cueing; this measure can be observed after the TMS pulse and its timing is relevant to the underlying processes being affected.

One key issue in interpreting the current results is; does TMS modulate cueing processes, or do cueing processes modulate the TMS-evoked potential? Our results show that different patterns of disruption caused by TMS occur depending on cueing state, meaning that attention affects cortical excitability. Because TMS is not a passive probe of brain activity but changes it, this could equivalently be interpreted as TMS modulating the cueing effect caused by attention. These two different cause-effect relationships in the data set also correspond to two equivalent interpretations of TMS effects; either as a transient disruptor, causing a “virtual lesion”, or as a probe of brain connectivity (Pascual-Leone et al., 2000).

To conclude, the results of Experiment 1 showed that TMS over the occipital cortex interacts with cueing processes in the absence of a percept; we observed a difference in the EEG in the time window 240-280 ms post TMS pulse between left and right cues for right parietal electrodes. This pattern of results agrees with previous studies finding an effect of attention on neural activity even in the absence of a visual stimulus, and show that attention affects cortical excitability.

EXPERIMENT 2. ATTENTION AND CONSCIOUSNESS [4]

In Experiment 2, we manipulated participants' covert attention through endogenous cueing, and investigated its interaction with phosphene perception. The main difference with Experiment 1 was TMS intensity; while in Experiment 1 TMS was kept at below-threshold level, hence not resulting in phosphene perception, in Experiment 2 TMS was employed at phosphene threshold intensity, resulting in the perception of a phosphene in half of the trials.

This difference in design allowed us to investigate the TEP differences in the case of presence of absence of a percept, as well as the interaction between phosphene perception and attentional processes caused by cueing.

METHODS

PARTICIPANTS

Fifteen healthy right-handed paid volunteers (mean age 25.1±3.7, 7 females) with normal or corrected to normal vision participated in the present experiment. Participants gave informed consent in accordance with the Ludwig-Maximilians

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[4] Francesca Bocca and Paul Taylor designed the study. Francesca Bocca programmed the experiment, which was conducted by Francesca Bocca and Aleya Flechsenhar. Francesca Bocca analysed the data. A subset of the analyses has been reported in the Master Thesis of Aleya Flechsenhar titled "Effects of Spatial Attention and Excitability: Combined TMS-ERP Data", submitted as a fulfillment for her Master in Neuro-Cognitive Psychology (NCP), Ludwig-Maximilians University, in August 2014.

University Ethics Advisory Committee. Participant selection complied with current guidelines for repetitive TMS research (Rossi et al., 2009).

PROCEDURE

The procedure of this experiment is similar to Experiment 1, except for the cue-TMS interval duration (Figure 36); while in Experiment 1 this duration was jittered, in Experiment 2 it was kept constant as well as longer, measuring 1300 ms. Visual stimuli were presented on a liquid crystal display computer monitor at 1680 x 1050 pixels resolution with a refresh rate of 100Hz (monitor model: SyncMaster 2233RZ, Samsung). Participants performed a training block in which TMS was not applied, consisting of 60 trials. The training block consisted solely of trials of the "visual stimulus present" type, whose timeline is illustrated in Figure 36.

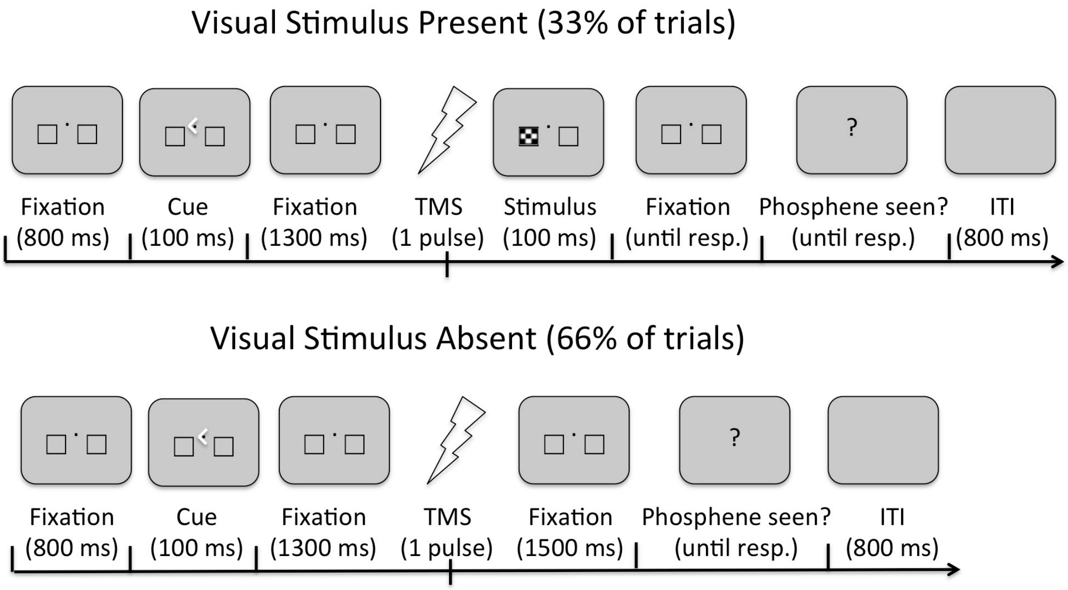


Figure 36. Timeline of a sample trial. Trial duration was identical in no-TMS and TMS trials; in no-TMS trials the fixation cross was presented for 2800 ms, uninterrupted.

The stimulus-response key combination was counterbalanced across subjects. After 1500 ms from stimulus onset, whether or not subjects responded, feedback was given in the shape of written text in the centre of the screen indicating whether the participants made a mistake. Afterwards, a question mark was presented in the centre the screen, prompting participants to respond whether or not they perceived a phosphene. Response keys for phosphene reports were adjacent on the keyboard (keys Y and X on a German keyboard), and subjects were instructed to press them with the index and middle finger of their left hand. During the training block participants were instructed to always respond with the “no” key for phosphenes, as no TMS stimulation took place.

After the end of the training block, participants’ performance was displayed on the monitor. Participants with a mean reaction time greater than 2000 ms and an error rate greater than 20% had to repeat the training block until their response met these minimum requirements.

During the experiment, the TMS pulse was always delivered after 1300 ms from cue onset at 100% intensity of phosphene threshold i.e. at threshold. In each block (consisting of 60 trials), one third of the trials contained a visual stimulus (see Figure 36, top panel), while two thirds had no visual stimulus (see Figure 36, bottom panel); of the visual stimulus present trials 80% were validly cued, and 20% invalidly cued. In visual stimulus absent trials, after cue onset, fixation lasted 2800 ms, after which the phosphene question mark was directly presented. Throughout the experiment, cue direction, visual stimuli positions and target type were balanced within each block.

Participants were instructed to respond as fast and as accurately as possible to the visual stimulus, and as accurately as possible without time limit for their response about their phosphene perception. After the response, a blank screen was presented for 800 ms, allowing participants to briefly rest and blink if necessary.

PHOSPHENE PERCEPTION

Figure 37 summarizes the phosphene characteristics reported by participants concerning colour (left panel) and shape (right panel).

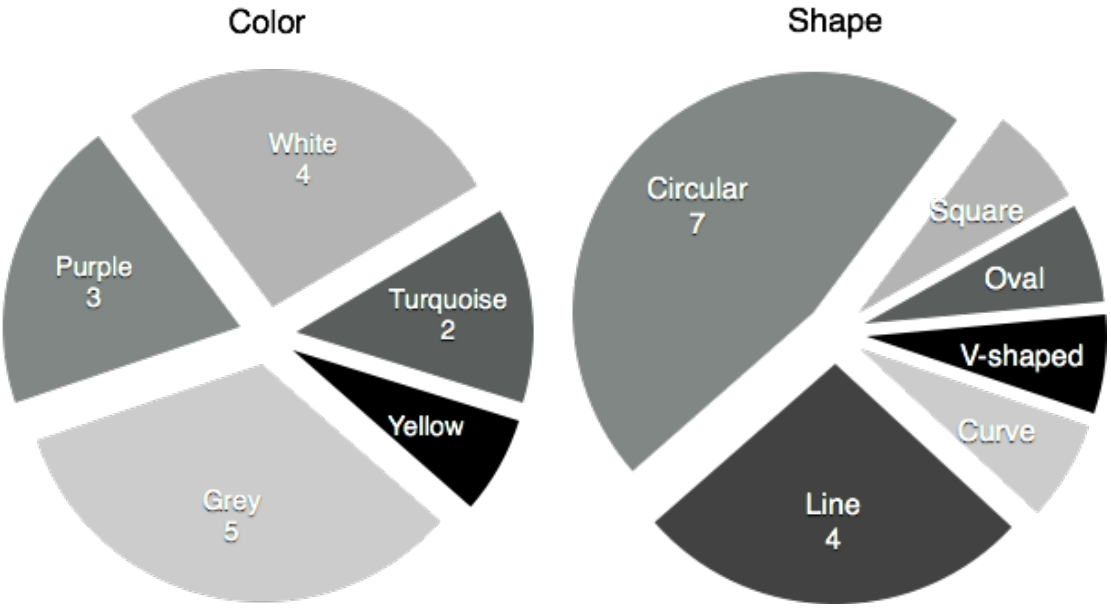


Figure 37. Pie charts summarizing the colour (left panel) and shape (right panel) characteristics reported by participants to describe their phosphene experience. The numbers inside the wedges represent the number of participants choosing the option; wedges without numbers represent categories chosen by only one participant.

Similarly to what observed for the first experiment, most participants (9) did not ascribe a colour to the phosphene, but only described it as a change in luminance, ranging from dark grey to white. Participants who did perceive a colour described their phosphenes as purple (3), turquoise (2) or yellow (1).

Shape judgements were similar to the first experiment; circular shapes were the most reported (7). Lines were also observed frequently (4), while curves, v-shaped objects, ovals and squares were observed only by one participant each.

Figure 38 summarizes the phosphene characteristics reported by participants concerning motion (left panel) and texture (right panel).

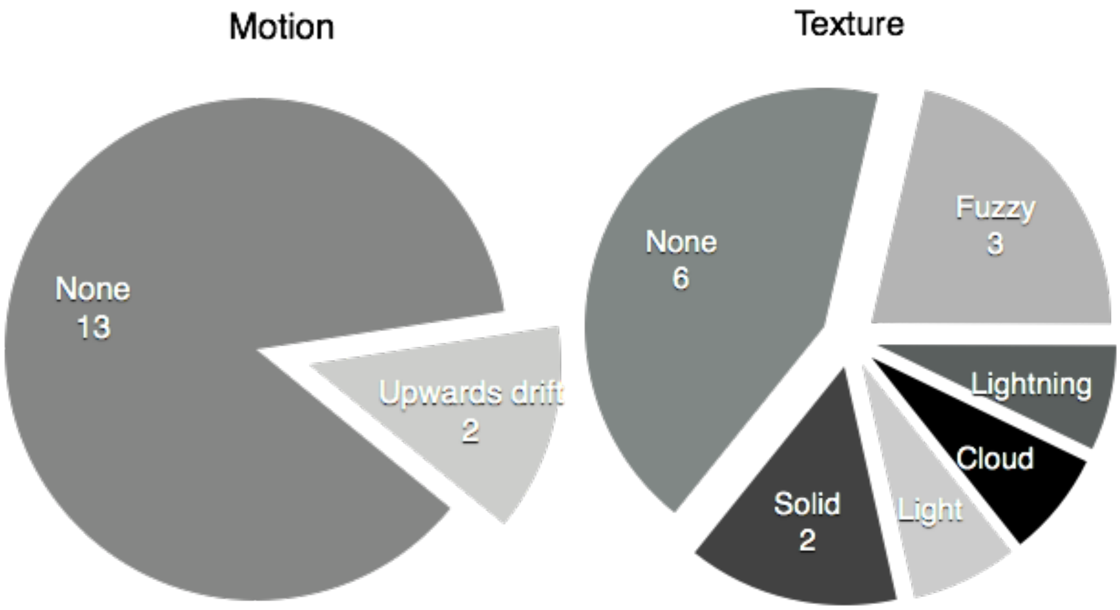


Figure 38. Pie charts summarizing the motion (left panel) and texture (right panel) characteristics reported by participants to describe their phosphene experience. The numbers inside the wedges represent the number of participants choosing the option; wedges without numbers represent categories chosen by only one participant.

Subjective phosphene motion reports were also compatible with what found in the first experiment, with the majority of participants not experiencing phosphene motion (13). Two participants reported motion in the form of upwards drift.

Finally, texture was not present for six participants. Those who observed a phosphene texture differed greatly in their reports: they reported a fuzzy texture (3), or a homogenous, solid perception (2). Single participants reported perceiving a lightning texture, a background light or a cloud.

TMS

We applied stimulation to the right hemisphere using a ‘PowerMag Research’ TMS machine (Mag & More, GmbH) with a figure-of-eight coil at 100% of the participant’s phosphene threshold. As we observed phosphene threshold values tend to increase during an experiment, if the block feedback reported less than 40% or more than 60% phosphenes were seen, the threshold was re-calculated in the inter-block interval (a procedure that needed to be performed at least once per participant).

10 out of 15 participants took part in a preliminary structural MRI scan. We employed the brain scan to perform coregistration of the stimulated areas through the Brainsight software (Rogue Research Inc.)

The images were processed with FSL (FMRI Software Library, Version 2.7.6) using the Brain Extraction Tool (BET) and an automated tool for linear intra- and inter-modal brain image registration (FLIRT). Figure 39 shows the stimulated area for individual participants, overlaid on a custom template of the MNI-transformed average of their structural images.

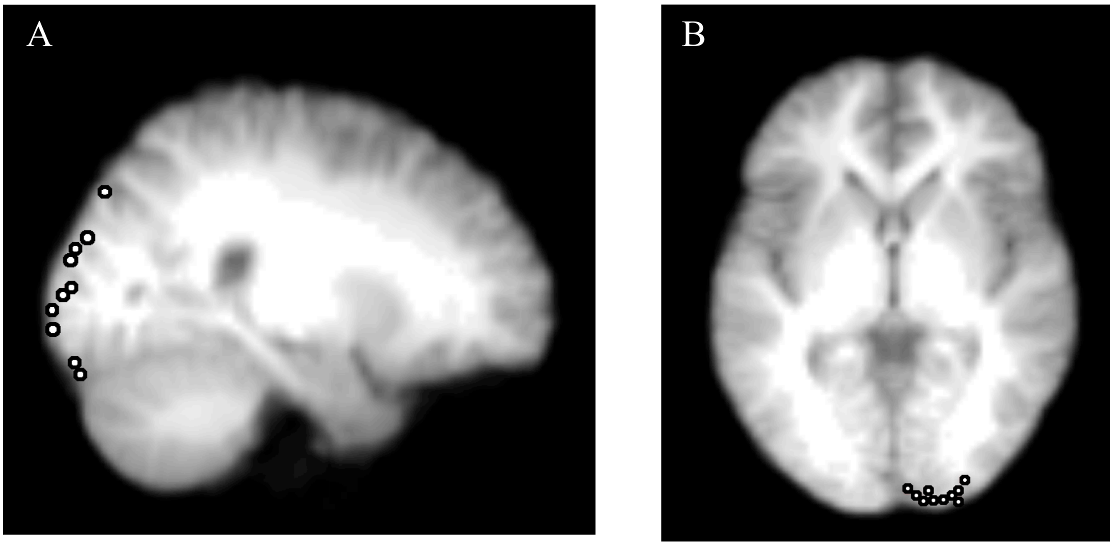


Figure 39. Phosphene TMS sites for individual subjects overlaid on a custom template constituted by the average of individual brains. TMS sites are centred to the right occipital lobe (average: x = 17,59, y = -92,50, z = 7,99). (A) transverse view (B) sagittal view.

The present experiment contained 10 blocks. In all of them, the stimulation coil was placed with the handle pointing towards the right (Kammer et al., 2001), and with the centre of the coil over the phosphene-eliciting area.

Whenever the phosphene generating area would fall on top of an electrode, a foam ring would be used to avoid the coil touching the electrode, and the TMS intensity would be adjusted accordingly.

EEG RECORDING

The EEG was digitized from Ag-AgCl electrodes mounted on an elastic cap (EasyCap, Brain Products, Munich) referenced to the earlobes. Electrode positions were accordingly to the international 10-20 system (American Electroencephalographic Society, 1994), their position was: AF3, AF4, AF7, AF8, Afz, C1, C2, C3, C4, C5, C6, CP1, CP2, CP3, CP4, CP5, CP6, CPz, Cz, F1, F10, F2, F3, F4, F5, F6, F7, F8, F9, FC1, FC2, FC3, FC4, FC5, FC6, FCz, Fp2, FPz, FT7, FT8, Fz, O1, O2, Oz, P1, P2, P3, P4, P5, P6, P7, P8, PO3, PO4, PO7, PO8, POz, Pz, T7, T8, TP7, TP8, and Fp1. The online reference was set to the left ear. EEG and Eog were recorded with a BrainAmp amplifier (Brain Products, Munich, Germany) with all online filters turned off and a digitization rate of 5000 Hz. All electrodes impedances were kept below 5 kΩ. Impedance was checked at the end of each block, and readjusted if necessary. The clock of the EEG amplifier was synchronized to the clock output of the TMS machine using a SynchBox (Brain Products, Munich).

DATA ANALYSIS

For each subjects, trials with a reaction time higher than 3000 ms or lower than 100 ms, as well as trials containing an error, were removed from reaction times analyses. RTs and Errors were analysed by way of a 2x2x2 repeated-measures ANOVA with factors Cue Validity (Valid, Invalid), Cue Direction (Left, Right) and Phosphene (Present, Absent).

EEG Data was re-referenced to the right ear electrode. Prior to epoching the EEG, we removed 1ms before and 39 ms after the TMS pulse through linear interpolation, in order to delete the TMS artefact from the data. After artefact removing, the EEG was down sampled to 1000 Hz. After epoching the EEG, artefact rejection was applied - as described in the *Data Analyses* section of *Experiment 1*.

For the cue-evoked potentials (Cue ERPs) analyses, the EEG was segmented starting from 200 ms before the cue onset until 700 ms after. Baseline was corrected in the 200 ms before cue onset. The ADAN was calculated as a lateralized component for electrode positions FC5/FC6 in the time bin 300-500 ms post cue onset, while the LDAP as the lateralized component for PO7/PO8 in the time bin 500-700 ms.

For the TMS-evoked potentials (TEP) analyses, the EEG was segmented starting from 200 ms before the TMS pulse until 400 ms after. Baseline was corrected in the 200 ms before TMS pulse. Data was also pooled into four electrode groups: a right parietal (including electrodes P4, P6, PO8), a central parietal (Cpz, Cp1, Cp2), a left parietal (P3, P5, PO7) and an occipital one (Oz, O1, O2). Figure 40 shows the locations of the electrodes belonging to different groups. The electrodes constituting the central parietal and occipital group, as well as electrodes P6 and P5 were not present in Experiment 1 and therefore could not be included in Experiment 1 analyses.

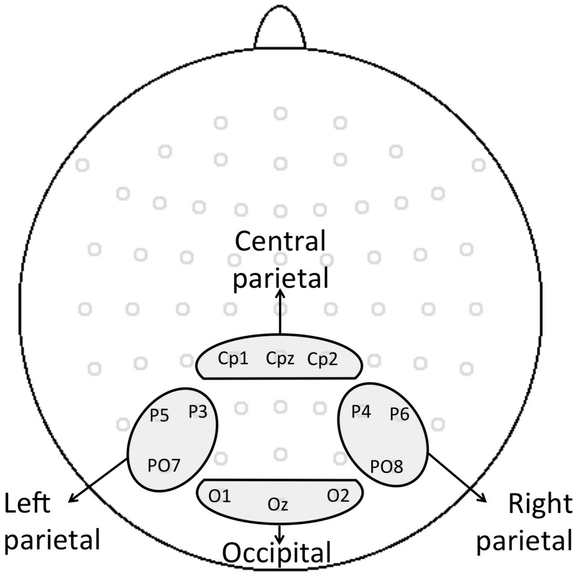


Figure 40. Electrode groups employed in the data analyses of the TEP.

For all EEG analyses (cue- and TMS- locked) we made sure that each condition for each individual participant contained at least 40 trials after outliers rejection, in order to include only meaningful and reasonably stable data. For this reason, it was not possible to look at visual stimulus present data, in which most of the participants did not pass criterion.

RESULTS

ERRORS

We observed a marginal interaction between *Cue Validity and Cue Direction* (F(1,11)=3.72, p=0.08). All other F's<1.8, all p's>0.2. (Figure 41) given by a marginal difference between cue valid and invalid trials only after right cues (t(14)=-1.77, p=0.09, mean difference: 6%), but not for left cues (t(14)=0.21, p=0.84, mean difference: 0.08%). This interaction could be due to TMS capturing attention exogenously to the hemifield in which a phosphene would appear (i.e. the left hemifield), therefore reducing the validity effect.

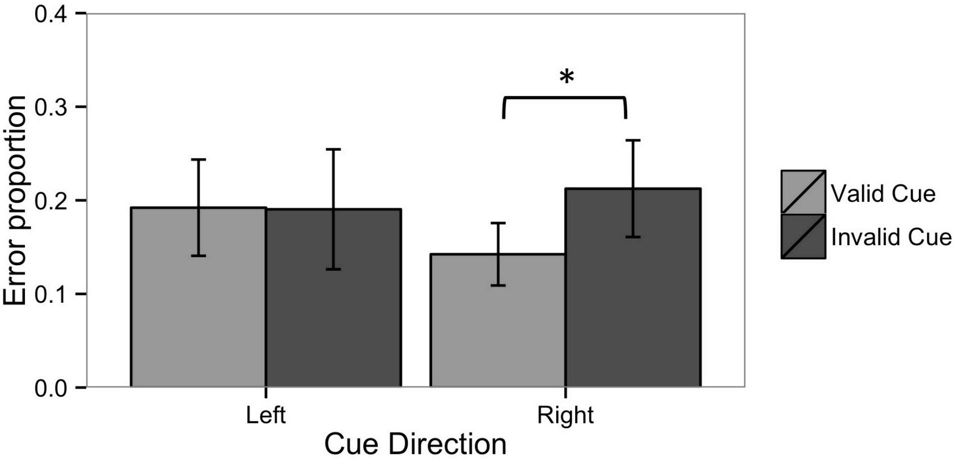


Figure 41: Error proportion depending on cue validity and cue direction. Bars represent SEM.

REACTION TIMES

The validity effect (F(1,11)=19.1, p=0.001) (Figure 28) was given by valid trials generating faster responses than invalid ones (t(14)=2.16, p=0.048, mean difference: 60 ms), showing that attention was allocated to the cued direction. No other significant main effects or interactions were present (all F's<2.5, all p's>0.15).

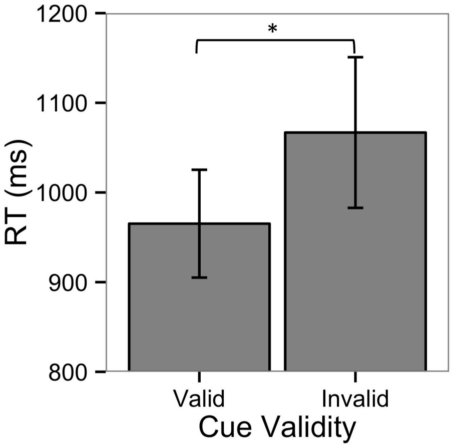


Figure 42. RTs depending on cue validity. Bars represent the SEM.

PHOSPHENE REPORTS

Figure 43 shows the proportion of phosphenes reported depending on cue direction and visual stimulus presence. A repeated measures 2 * 2 ANOVA with factors Cue Direction (left or right) and Visual Stimulus Presence (present or absent) showed a main effect of *Visual Stimulus Presence* (F(1,14)=5.087, p=0.041), caused by phosphenes being perceived more when the visual stimulus was absent (t(14)=-2.45, p=0.028, mean difference: 19%). This effect could be due to visual stimuli interfering with phosphene perception, and therefore increasing phosphene threshold. The main effect of Cue Direction as well as the two-way interaction did not reach significance (all ps>0.2, all Fs<1).

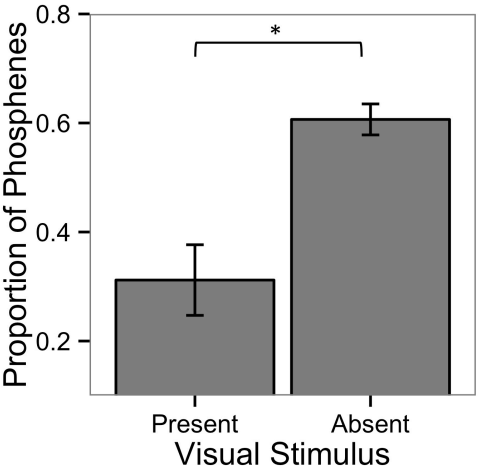


Figure 43. Proportion of phosphenes seen depending on visual stimulus presence and cue direction. Error bars represent the SEM.

Within trials in which a visual stimulus was present, we also investigated whether Phosphene reports varied with Cue Direction and Stimulus Side: phosphenes were perceived slightly more often when the visual stimulus appeared on the right (F(1,14)=2.98, p=0.1, t(14)=-1.8, p=0.08, mean difference: 3%). This effect may be caused by the lack of any masking effect of the visual stimulus on the phosphene when the former appeared on the right, given that phosphenes only appeared on the left. There were no other significant effects (all Fs<1, all ps>0.7),

ANTERIOR-DIRECTING ATTENTION NEGATIVITY (ADAN)

The ADAN (Figure 44, left panel) was present for both phosphene absent (t(14)=-2.34, p=0.034) and phosphene present (t(14)=-2.47, p=0.03) with no difference between them (t(14)=-0.72, p=0.49, mean difference:-0.13).

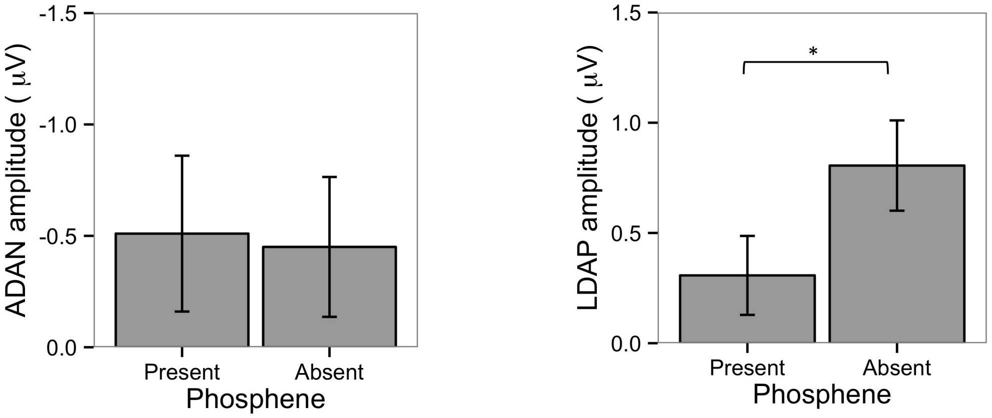


Figure 44. Left panel: amplitude of the ADAN component in the time bin 300-500 ms post cue. Right panel: amplitude of the LDAP component in the time bin 500-700 ms post cue. Error bars represent the SEM.

LATE-DIRECTING ATTENTION POSITIVITY (LDAP)

LDAPs were present when no phosphene was perceived (t(14)=4.58, p<0.001) with only a marginally significant difference from zero when the phosphene was perceived (t(14)=2.09, p=0.054). We also ran a paired-sample t-test between phosphene conditions, and observed that the LDAP amplitude for phosphene absent was bigger than for phosphene present. (t(14)=-3.15, p=0.007, mean difference: -0.56).

Given the nature of the LDAP as a lateralized component, and that our experiment applied TMS only to the right occipital cortex (and therefore phosphenes could be perceived only on the left hemifield), we separated the LDAP data by electrode and cue direction. Figure 45 shows the amplitude of the ERP for electrodes PO7/PO8 divided by experimental condition (cue direction and phosphene perception).

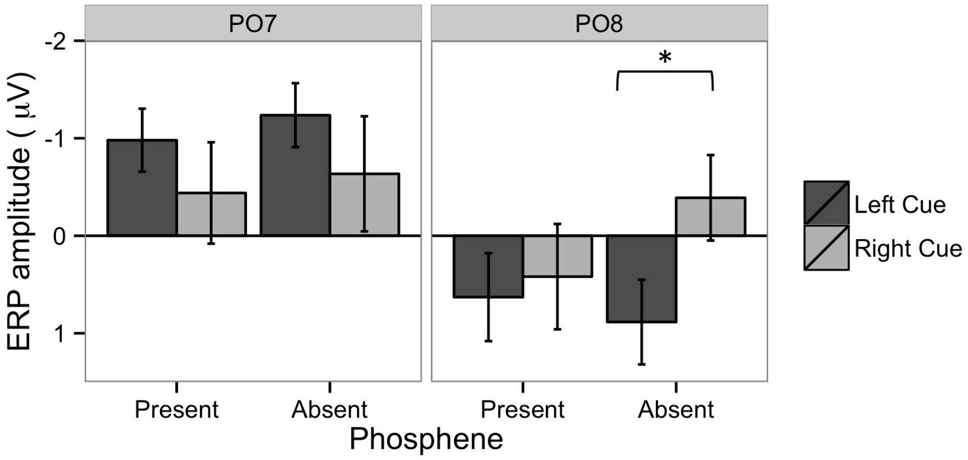


Figure 45. ERP amplitude in the time bin 500-700 divided by electrode (panel), phosphene condition (x axis) and cue direction (colour). Error bars represent the SEM.

We observed a main effect of *Electrode* (F(1,14)=15.984, p=0.001), which was driven by PO8 detecting more positive ERPs than PO7 (t(14)=-3.998, p=0.0013, mean difference: 1.2μV). The interaction between *Cue Direction and Electrode* (F(1,14)=14,841, p=0.002) and a significant three-way interaction *between Electrode, Cue Direction and Phosphene* (F(1,14)=9.948, p=0.007) were also present. No other main effect or interaction reached significance (all F*s*<1, all p*s*>0.3).

The two-way interaction between *Electrode and Cue Direction* was given by cue right eliciting marginally less negative responses than cue left for electrode position PO7 (t(14)=-1.94, p=0.07, mean difference: 0.57μV), and by cue right eliciting marginally less positive responses than cue left for electrode position PO8 (t(14)=2, p=0.064, mean difference: 0.7µV). This interaction describes the presence of an LDAP in the data.

The three-way interaction between *Electrode, Cue Direction and Phosphene* was followed up with separate ANOVAs within each electrode: The 2-way ANOVA within PO7 only revealed a marginal main effect of cue (F(1,14)=3.78, p=0.072), which was given by cue left trials generating a marginally more negative amplitude ERP than cue right ones (t(14)=-1.95,p=0.07), while no other effect reached significance (All Fs<0.5, all ps>0.5). Within PO8 by contrast, the ANOVA showed a marginal effect of Cue Direction (F(1,14)=4.01, p=0.065) as well as a significant interaction between Cue Direction and Phosphene (F(1,14)=4.91, p=0.044), while the main effect of Phosphene did not reach significance (F(1,14)=0.56, p=0.47). The interaction between Cue Direction and Phosphene was given by cue left and cue right differing significantly when no phosphene was observed (t(14)=2.53, p=0.024, mean difference: 1.3µV), and not differing when a phosphene was present (p=0.58).

To summarize, the LDAP effect was caused by a cueing difference on electrode PO8 when the phosphene was absent.

TMS-EVOKED POTENTIAL (TEP)

In the TEP, the EEG data was divided into four electrode groups (Figure 40).

70-140 MS: PHOSPHENE EFFECT

Figure 46 shows the waveforms of the TMS-evoked potentials, comparing between phosphene present and absent, separately for different electrode groups.

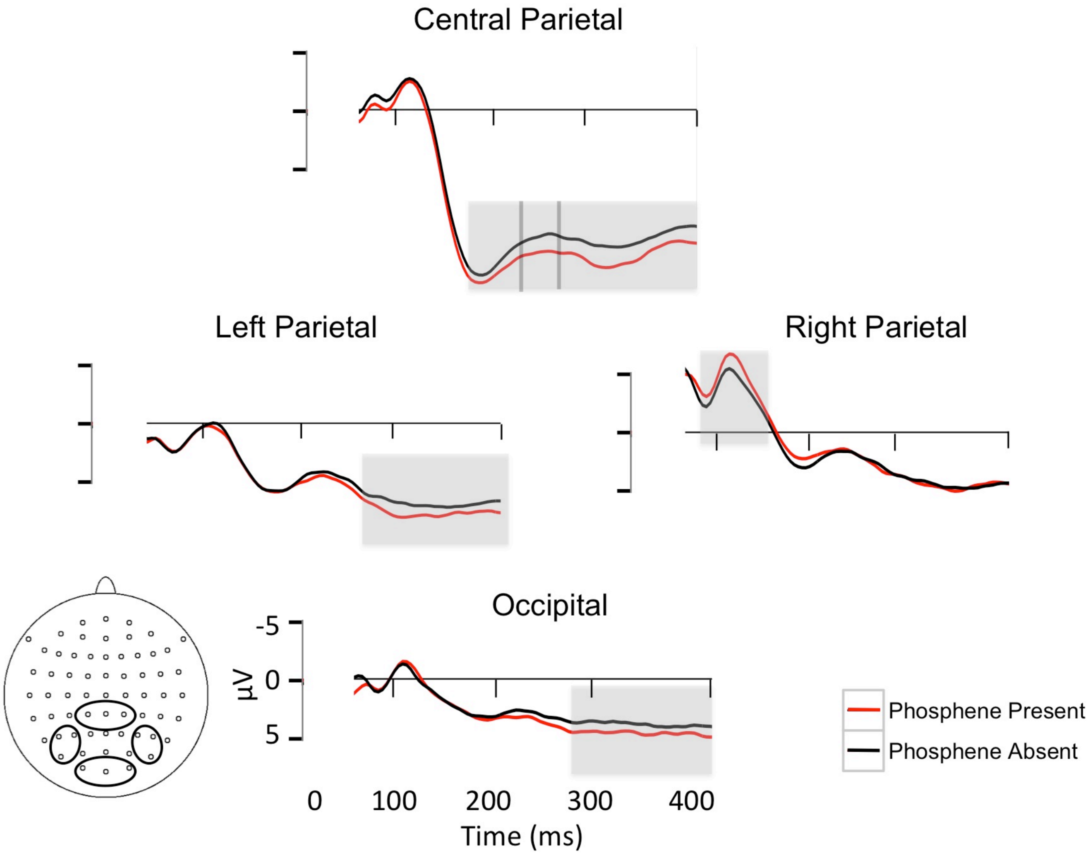


Figure 46. TEP comparing phosphene conditions (line colour) divided by electrode group (panel). Shaded areas represent the time bins in which a phosphene effect reached significance. The first 40 ms after the TMS pulse are not represented and were not analysed.

For the time bin 70-140 ms post TMS, we ran a 4*2*2 repeated measures ANOVA with factors Electrode Group (Parietal Right, Parietal Central, Parietal Left, Occipital), Cue (Left, Right) and Phosphene (Present, Absent). We observed a main effect of Electrode Group (F(3,42)=7.46, p<0.001) and an interaction between *Electrode Group and Phosphene* (Figure 47, left panel. F(3,42)=4.5, p=0.027). No other effect reached significance (All Fs<2, all ps>0.2).

A phosphene effect was present only in the Parietal Right electrode group (t(14)=-2.33, p=0.035, mean difference: 1.1 µV, all other t's<1.5, all p's>0.2). From figure 48 it can be seen that the maximum difference between phosphene conditions is clearly present over right parietal electrodes.

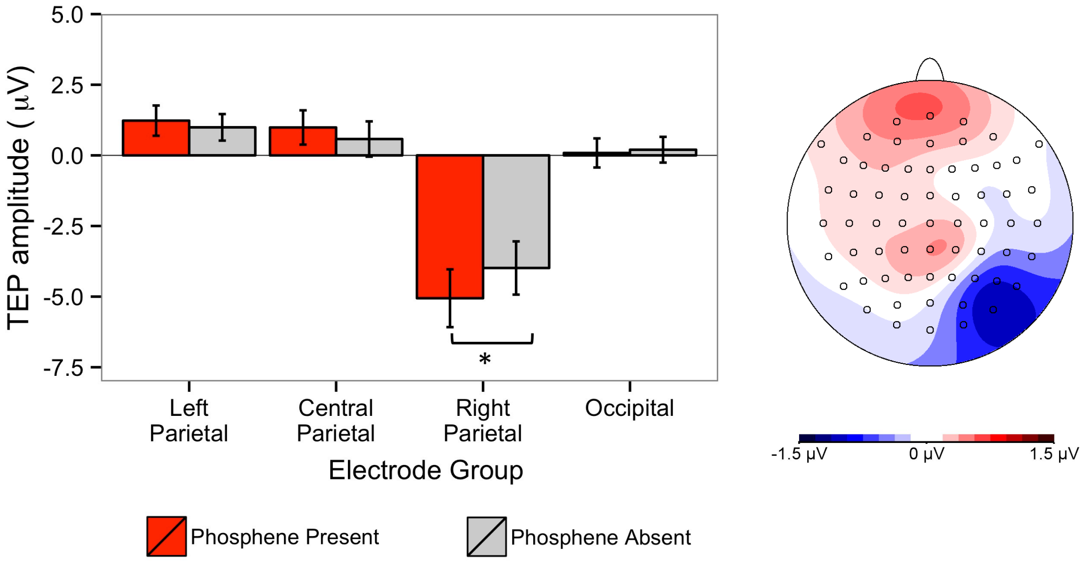


Figure 47. TEP amplitude in the time bin 70-140 ms. Left panel: bar graph of the main effect of phosphene divided by electrode group; error bars represent the SEM. Right panel: Electrode map showing the amplitude of the difference wave (present-absent) for the TEP at different locations.

180-240 MS: PHOSPHENE EFFECT AND CUE*PHOSPHENE INTERACTION

For the time bin 180-240, a main effect of *Group* (F(3,42)=45.2, p<0.001), an interaction between *Electrode Group and Phosphene* (F(3,42)=4.3, p=0.025), as well as the three-way interaction between *Electrode Group, Cue and Phosphene* (F(3,42)=2.91, p=0.05) were present. No other effect reached significance (all Fs<2.6, all Ps>0.13).

The interaction between *Electrode Group and Phosphene* (Figure 48, left panel) was the result of a difference between phosphene conditions in the Parietal Central group (t(14)=2.2, p=0.044, mean difference: 1.2 μV), but not in the other three groups (all t's<1.7, all p's>0.12). Figure 48, right panel, shows the topography of the difference between phosphene conditions; depicting a central-parietal positivity peaking at electrode position Cpz.

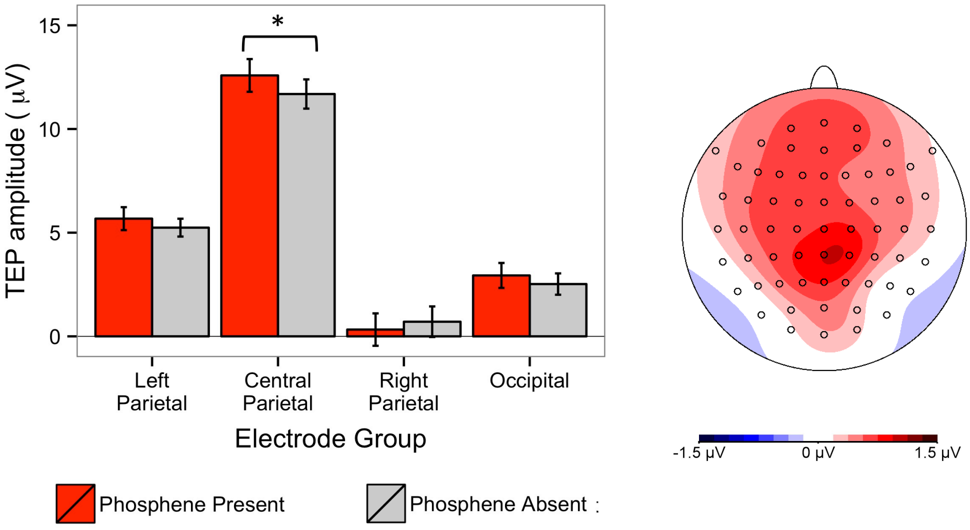


Figure 48. TEP amplitude in the time bin 180-240 ms. Left panel: bar graph of the main effect of phosphene divided by electrode group; error bars represent the SEM. Right panel: Electrode map showing the amplitude of the difference wave (present-absent) for the TEP at different locations.

Figure 49 shows the TEP waveforms for different groups of electrodes divided by cue as well as phosphene conditions.

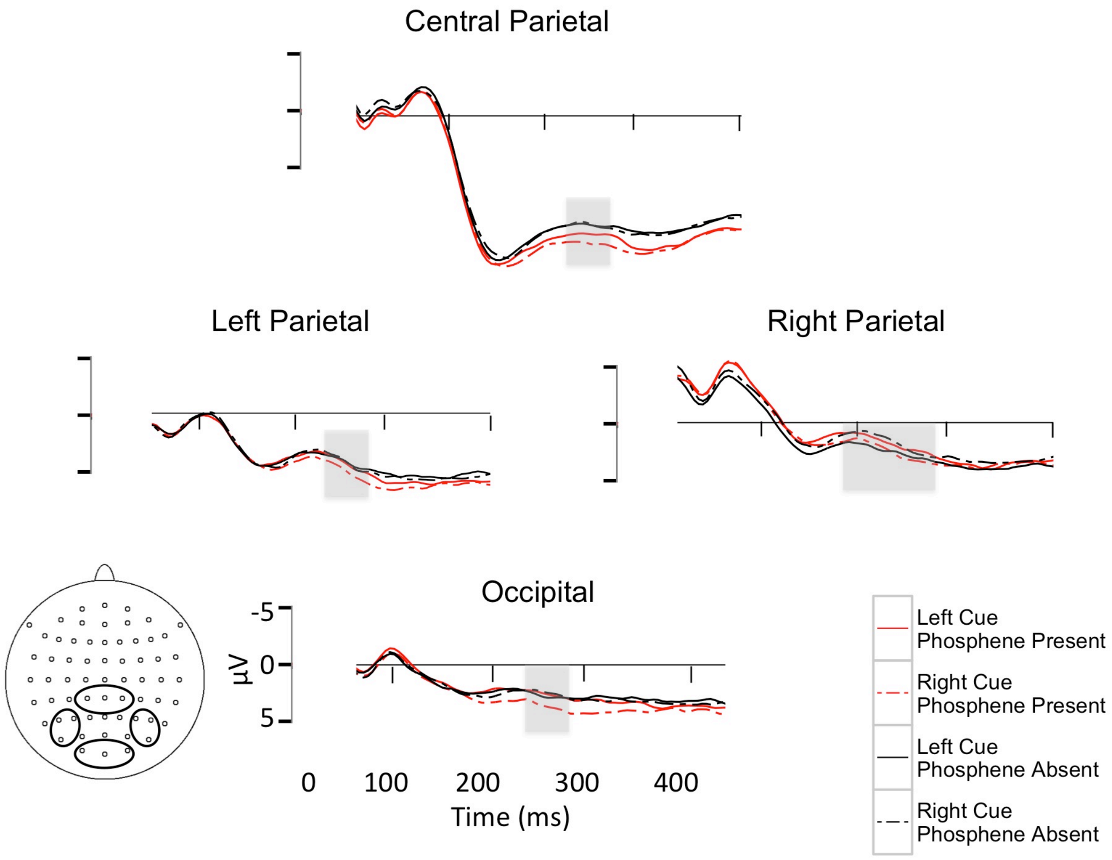


Figure 49. TEP waveforms divided by electrode group (panel). Line colour represents phosphene condition, while line type represents cueing. Shaded areas represent the time bins in which an interaction between phosphene and cueing reached significance, separately for each electrode group.

The interaction between *Electrode Group, Cue and Phosphene* in the time bin 180-240 ms was further analysed by running separate two-way ANOVAS within each electrode group, with factors Cue (Left, Right) and Phosphene (Present, Absent). The only significant effect was an interaction between *Cue and Phosphene* in the Parietal Right electrode group (F(1,14)=5.8, p=0.03). No other effect reached significance in any group (all F's<2, all p's>0.13).

In the Parietal Right group, cueing had an effect only when the phosphene was absent (t(14)=2.16, p=0.048, mean difference: 1 µV), but not when the phosphene was present (t(14)=-1.4, p=0.19, mean difference: 0.6 µV) (Figure 50).

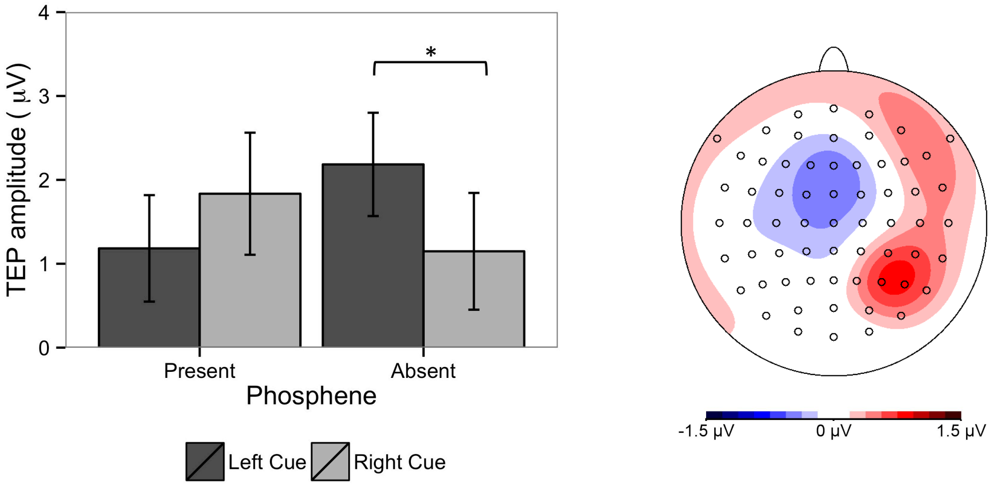


Figure 50. Left panel: bar graph of the interaction between cueing and phosphenes for electrode group Parietal Right. Error bars represent the SEM. Right panel: Topography map of the difference between cueing conditions (left-right) for phosphene absent

240-280 MS: PHOSPHENE EFFECT AND CUE * PHOSPHENE INTERACTION

For the time bin 240-280 ms after TMS we measured a main effect of *Group* (F(3,42)=36, p<0.001), a significant interaction between *Group and Phosphene* (F(2,28)=6.24, p=0.008), and a significant interaction between *Cue and Phosphene* (F(1,14)=4.7, p=0.048). No other effect reached significance (all Fs<1.6, all Ps>0.2).

The interaction between *Group and Phosphene* (Figure 51, left panel) was similar to the one reported for the time bin 180-240; it was caused by a significant difference between phosphene condition for the Parietal Central group (t(14)=2.8, p=0.015, mean difference: 1.1 µV). We also observed a marginal difference within the Parietal

Left (t(14)1.93, p=0.074, mean difference: 0.62 µV) and Occipital (t(14)=1.85, p=0.085, mean difference: 0.69 µV), while no difference was present within the Parietal Right group (t(14)=-0.38, p=0.71, mean difference: 0.18 µV). This pattern is visible in the topography in Figure 51, right panel.

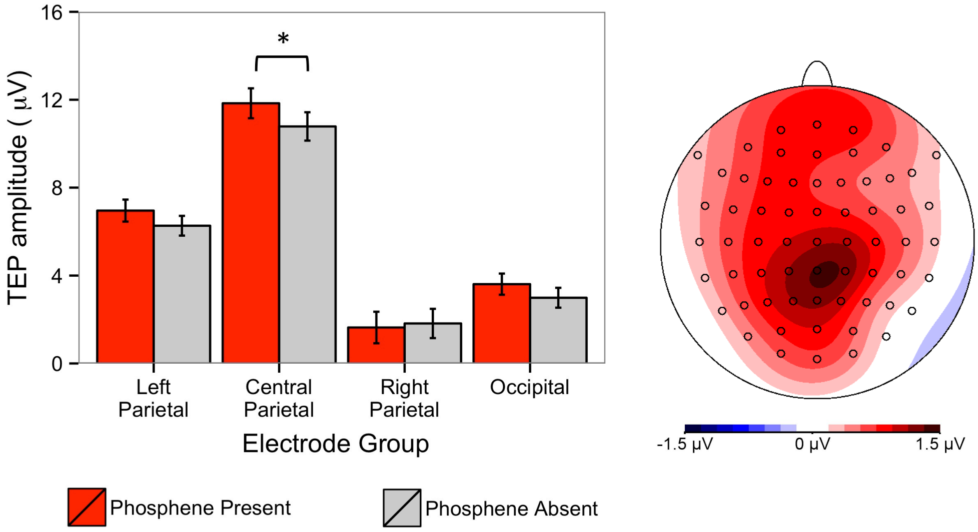


Figure 51. TEP amplitude in the time bin 240-280 ms. Left panel: bar graph of the main effect of phosphene divided by electrode group; error bars represent the SEM. Right panel: Electrode map showing the amplitude of the difference wave (PhY-PhN) for the TEP at different locations.

The interaction between Cue and Phosphene (Figure 52) was caused by cueing conditions differing when a phosphene was present (t(14)=-2.19, p=0.046, mean difference: 1.1 µV), and not when it was absent (t(14)=0.3, p=0.778, mean difference: 0.13 µV).

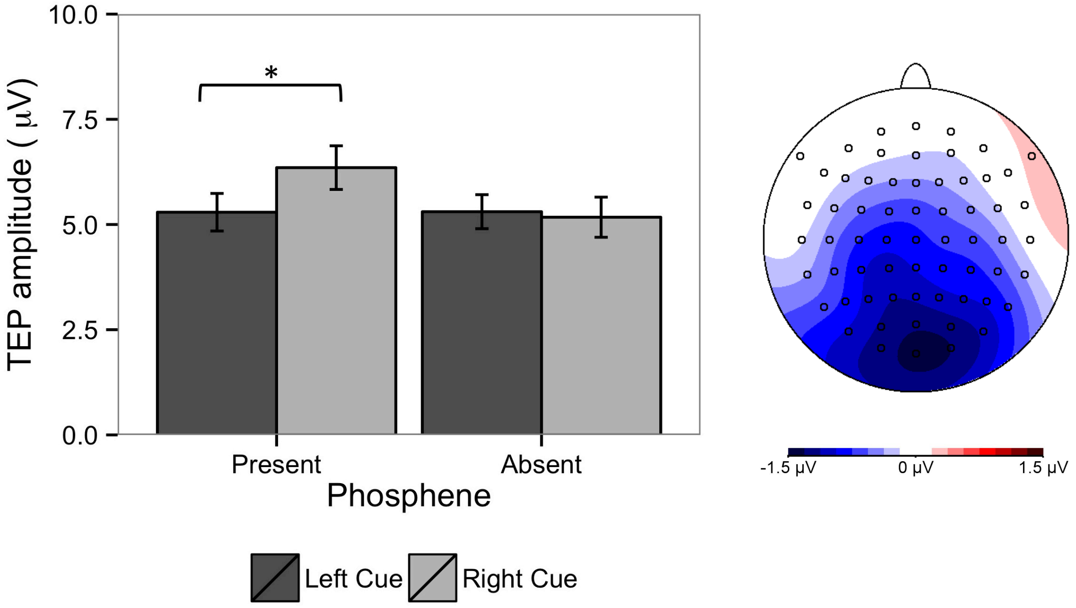


Figure 52: Left panel: bar graph of the interaction between cueing and phosphenes for electrode group Parietal Right in the time bin 240-280 ms. Error bars represent the SEM. Right panel: Topography map of the difference between cueing conditions (left-right) for phosphene present.

280-400 MS: PHOSPHENE EFFECT

For the latest time bin, between 280-400 ms post TMS, a main effect of *Group* (F(3,42)=36.1, p<0.001) and an interaction between *Electrode Group and Phosphene* (F(3,42)=6.2, p=0.004) were present. No other effect reached significance (all Fs<2.6, all Ps>0.11).

The interaction between *Electrode Group and Phosphene* (illustrated in Figure 53, left panel) was given by a significant difference between phosphene present and absent conditions for the Parietal Central (t(14)=2.8, p=0.013, mean difference: 1.4 µV), Parietal Left (t(14)=2.2, p=0.042, mean difference: 0.9 µV) and Occipital group (t(14)=1.8, p=0.046, mean difference: 0.79 µV), while the difference was not present in the Parietal Right group (t(14)=-0.3, p=0.75, mean difference: 0.2 µV). This pattern is clearly visible in Figure 53, right panel, where the topography maps highlights a central positivity spreading to occipital and left parietal regions, but not to right parietal electrodes.

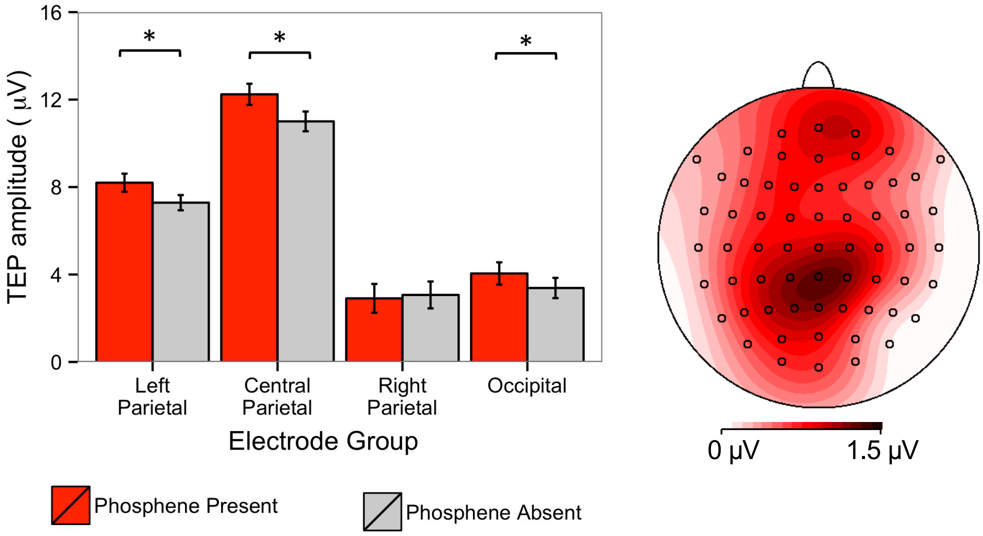
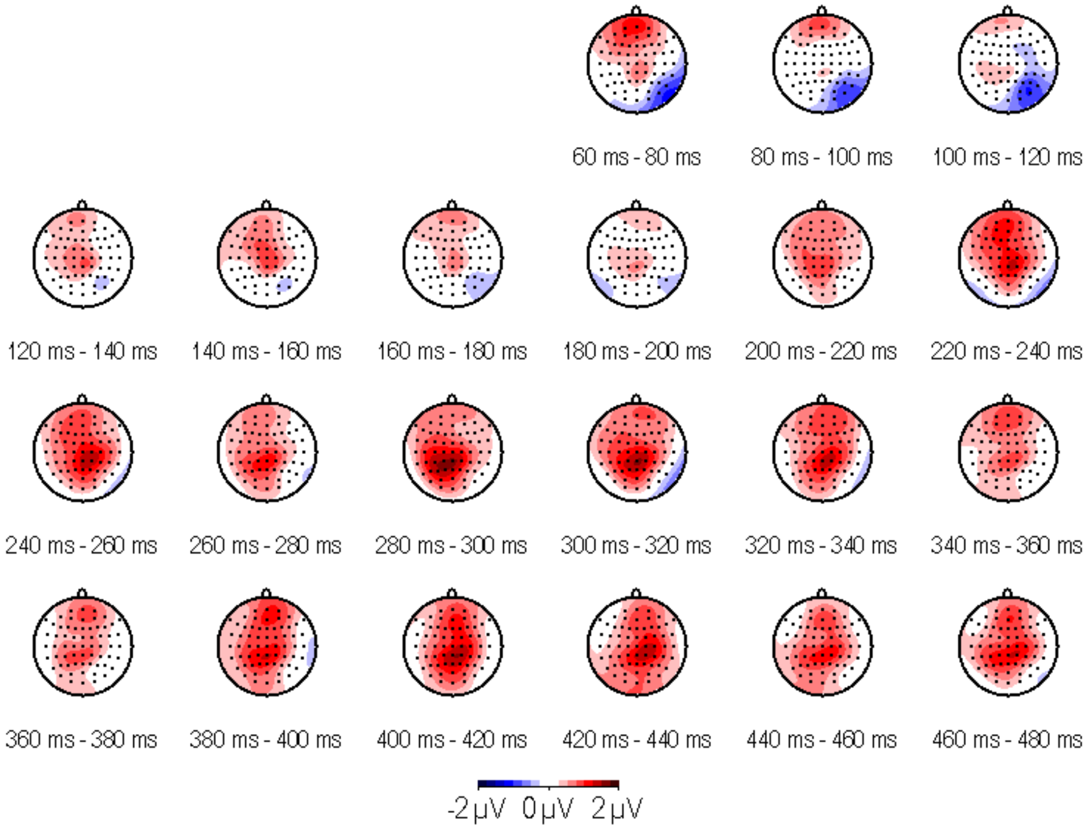


Figure 53. TEP amplitude in the time bin 280-400 ms. Left panel: bar graph of the main effect of phosphene divided by electrode group; error bars represent the SEM. Right panel: Electrode map showing the amplitude of the difference wave (PhY-PhN) for the TEP at different locations.

The TEP results, to summarise, can be divided into two categories; phosphene effects and interactions between cues and phosphenes. The phosphene effects could be divided into an early (70-140 ms) right parietal effect, and later ones (180-240, 240-280 and 280-240) starting from central parietal electrodes and spreading to other groups except the right parietal ones. Phosphenes also interacted with cueing; when no phosphene was reported a cueing difference was present in the right parietal electrode group (180-240 ms), while when a phosphene was reported, the cueing difference was observable over all electrodes groups (240-280 ms).

TEP TOPOGRAPHIES

Qualitatively, we also looked at the topography maps comparing our effect of phosphene presence within cue right with those reported by Taylor and colleagues (2010). Figure 54 shows the comparison.



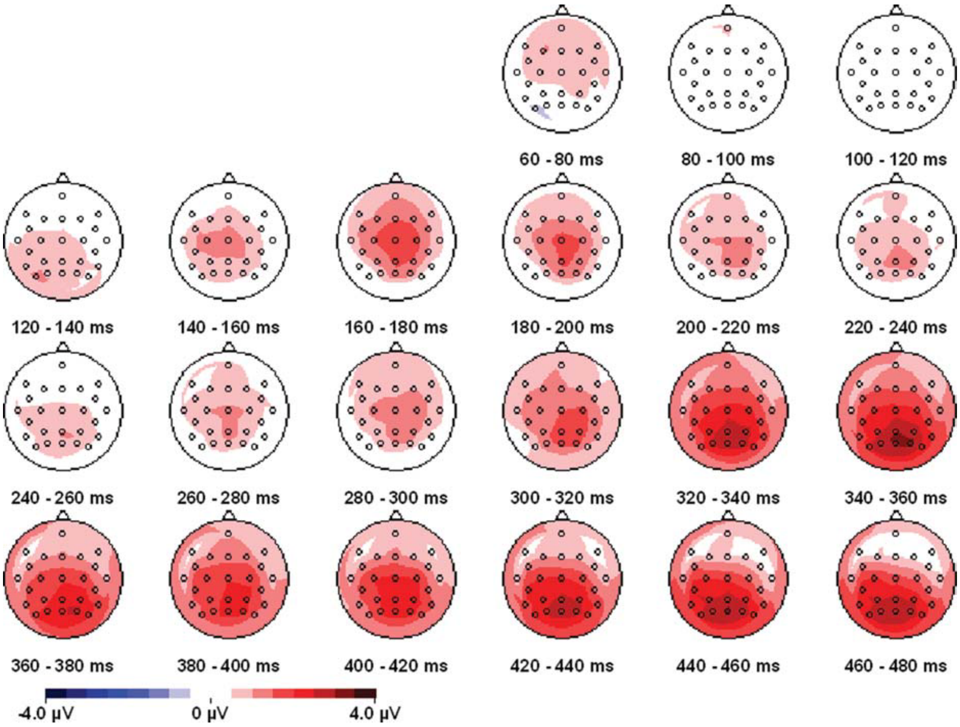


Figure 54. Topography maps in 20 ms bins. Top panel: Maps corresponding to the current experiment, subtracting phosphene absent from phosphene present. Bottom panel: Maps published in Taylor et al. 2010, subtracting phosphene absent from phosphene present.

Note the striking similarity between our data and that previously presented by Taylor et al. (2010). In particular, we also observe a central positivity in the time bin 160-180, which becomes more prominent in later time bins (in our experiment at 180-240 ms after TMS pulse).

DISCUSSION

In Experiment 2, we applied TMS at phosphene threshold to the right occipital cortex while participants performed a discrimination task on rare visual stimuli appearing either at the potential phosphene location, or in the opposite hemifield. We observed that TMS modulates behavioural results and cueing processes. Phosphene perception elicited several effects, both early and late. We also observed an interactive pattern between phosphene perception and cueing in the TEPs, with temporally and neutrally dissociable cueing effects depending on phosphene perception. These results are relevant to two topics; first they speak to the early-vs-late hypothesis of phosphene generation, and secondly that attention affects neural processes differently depending on the presence or absence of a percept.

BEHAVIOURAL EFFECTS

The probability of seeing a phosphene was modulated by the presence of a visual stimulus: when a target was presented, the probability of perceiving a phosphene was lower. As it has been reported in the literature that phosphenes increase the threshold for visual stimuli identification (Kammer, 1998), we believe our results highlight a complementary phenomenon: by keeping the TMS intensity constant, phosphene threshold was modulated by visual stimulus presence. This effect could be caused either by masking, or by attentional capture triggered by the visual stimulus appearing simultaneously to the TMS pulse, and would be an interesting topic for future research.

On the other hand, the observation that the proportion of phosphenes seen was not influenced by cue direction seems to contradict recent studies that have adjusted phosphene threshold for cued and uncued sides of the visual hemifield, finding that phosphenes appearing in the cued area required a lower intensity to be perceived (Bestmann et al., 2007). It is relevant to note, however, that the experimental procedures employed by Bestmann (2007) were very different from the current experiment; There are quantitative methodological differences between the two studies that might have affected the results: visual stimulus prevalence was different between the studies (our study employed 33% visual stimuli, compared to 50-66%) and therefore participant expectations might have been different; the cue-target interval also differed (we chose 1300 ms fixed interval, compared to a variable 500-1000 ms one), which might have influenced the stage of cueing processing being affected.

In our experiment, participants only received TMS pulses on the right hemisphere, and might have become accustomed to expecting to see a phosphene on the left hemifield, therefore not allocating the entire attentional resources towards the cued side. However such an account would fail to accommodate the behavioural and ERP evidence from our current dataset that participants did orient their attention.

CUEING EFFECTS

ADANs were found for both phosphene present and absent conditions, confirming that attentional control was employed when the cue was presented; hence the attentional-control processes which are traditionally associated with the ADAN (Eimer et al., 2002), are not predictive of later phosphene perception. The amplitude of the LDAP component, by contrast, did differ depending on whether a phosphene would be perceived later on during the trial. Given the nature of the LDAP as a lateralized component calculated as the double difference of contralateral and ipsilateral ERPs for PO7 and PO8, and the fact that in our experiment TMS was only administered to the right hemisphere, we investigated this difference further by analysing the average ERPs divided by side and electrode. This analysis revealed that the LDAP difference between phosphene present and absent was driven by a difference originating at electrode position PO8, where ERPs for cue left compared to cue right differed when no phosphene was perceived. The explanation of this difference probably lies in the functional role of the LDAP, which is thought to reflect processing of the location to be ignored (McDonald & Green, 2008). Therefore, when no phosphene is perceived and the cue points to the right, the left hemifield has been suppressed efficiently; conversely, when no phosphene is perceived and the cue points to the left, we can hypothesize that attentional allocation was not performed as efficiently as when the phosphene was perceived, and that attentional suppression perhaps was not as efficient as well. In other words, the LDAP effect is caused by the difference between trials where participants fail to attend (cue left), and those where they actively inhibit (cue right).

This finding supports the view of attention as modulating excitability in the visual cortex, as the difference in the LDAP suggests that when attention is allocated correctly and TMS stimulation is applied to a suppressed area, excitability is reduced and therefore no phosphene is perceived.

PHOSPHENE EFFECTS

We observed three phosphene effects in our dataset: an early (70-140 ms post TMS) right parietal, a middle central (180-240 ms post TMS) and a late global effect (280-400 ms)

The earliest effect's timing and location are relevant to the ongoing debate concerning the nature of phosphenes; namely the early vs. late hypotheses (Taylor et al., 2010). Although the presence of early phosphenes effects could seem to agree with the early hypothesis, suggesting that these percepts are generated in a feed-forward manner, there may not be any such clear-cut dichotomy between “early” and “late” origin of phosphenes. Qualitatively similar effects were found by del Cul and colleagues employing visual stimuli (Del Cul et al., 2007); although early effects were present (in their case at the time of P1 and N1 components), they were interpreted to be representing unconscious sensory activation, whereas perception itself would be generated through later recurrent and distributed processing, reflected by the P3 component. According to such an interpretation, the early effect in our data is a correlate of the later event of awareness reporting, but does not indicate that phosphenes have already become conscious at this early stage. Hence the current early effect of phosphene perception shows that the brain signal between stimuli that will eventually be perceived and those that will not starts differing at 70-140 ms post TMS, but does not allow concluding which of the phosphene effects observed is the crucial one to determine conscious perception (this could be studied with TMS experiments delivering a second pulse at the time of each of those effects, disrupting them and then evaluating perception). Several different stages of processing may occur within visual cortex over time. The presence of both feedforward and recurrent processes occurring relatively early in the visual cortex has been recently highlighted TMS in a study employing visual masking and stimulating the occipital cortex (de Graaf, Goebel, & Sack, 2012a).

Previous studies (Pins & Ffytche, 2002) employing combined ERP-fMRI have highlighted V1 activity, starting 100 ms after the presentation of a visual stimulus, which is correlated with the subsequent conscious reporting of the participants. Our effects include this time-bin, but it should be noted that phosphene-generating TMS provides a direct activation of the underlying visual cortical neurons, bypassing several subcortical structures (Bestmann et al., 2007)

Although the low spatial resolution of ERP prohibits making strong claims about the location of effects based on ERP topography, the proximity of the ERP effect to the occipital cortex where the coil generates the phosphene would suggest that the early phases of phosphene perception might be local. Phosphenes caused by occipital stimulation may be generated through stimulation of several different areas, the most widely suggested being V1 (Kammer et al., 2005; Pascual-Leone & Walsh, 2001), but with some authors suggesting it is extrastriate areas or the optic radiation to be responsible for phosphene generation (Kammer et al., 2005). In the current experiments, the area stimulated by TMS was coregistered on individual participants' structural brain scan through the use of neuronavigation systems. The MNI coordinates of the stimulated area are similar to those reported in the literature for right V1 (Anderson, Ferguson, Lopez-Larson, & Yurgelun-Todd, 2011); which suggests that our early effect of phosphene might indeed be generated by primary (or secondary) visual areas.

The topography of the ‘middle’ effect of phosphene in the time bin 180-240, is remarkably similar to that reported by Taylor et al. (2010), but the timing of our effect is delayed by 20 ms. One explanation for this difference is that participants in our experiments were performing a dual task, which might have slowed down certain stages of processing (Sigman & Dehaene, 2008). However the substantial overlap in terms of timing and topography between our effect and the one of Taylor et al. (2010) suggests that the current results are replicating the same effect.

The latest phosphene effect also matches an effect reported by Taylor et al. (2010). Both are present in the time bin 280-400 ms; and both are observable for central, occipital and left parietal electrodes. In the present analyses, we did not observe the latest effect of phosphenes in the parietal right electrodes; while Taylor et al. (2010) found a difference between phosphene present and absent while including those electrodes in a larger group. We are unable to determine whether our difference is caused by using smaller groups of electrodes for this analysis, or by genuine difference in the topography of the effects. The presence of an interaction between cueing and phosphene perception involving right parietal electrodes in our experiment would support that the difference might be caused by additional cueing processes, and that therefore the topography of the effect is changed by the cueing task the participants were performing simultaneously. Future work, possibly manipulating the presence of a secondary task, would help testing this hypothesis.

Taken together, our phosphene effects agree with the hypothesis put forwards by Taylor et al (2010), suggesting that phosphenes are perceived through a chain of activations starting locally and then spreading to other areas.

INTERACTION BETWEEN CUEING AND PHOSPHENE REPORT

In our dataset, we observed two interactions between cueing and phosphene perception; the first one (180-240 ms) reflected a difference between cueing conditions for phosphene absent trials, measurable over parietal right electrodes. The second interaction (240-280) was caused by a difference between cueing conditions for phosphene present trials, measurable on all groups of electrodes, but being more prominent over occipital electrodes. We believe the interactions reflect differences in how cueing affects unconscious and conscious processing, respectively.

The presence of cueing effects on phosphene absent trials is consistent with single cell recordings showing that when monkeys directed their attention to a certain location, neurons containing the attended location in their receptive field increase their firing rate compared to unattended ones even before the visual stimulus is presented (Kastner & Ungerleider, 2000). This phenomenon of “baseline shifts” may also support the current cueing effect in the absence of phosphene perception.

The later interaction between cueing and phosphene was dissociable from the earlier one in several ways; it was present only for phosphene present trials (not phosphene absent), its polarity was opposite (with right cue being more positive than left cue), and it was separable both temporally and in terms of the electrodes at which it was measurable. Interestingly, this effect occurred at a time in which some researchers argue consciousness takes place (Del Cul et al., 2007); it is possible that it reflects the conscious perception of a phosphene. When discussing neural correlates of consciousness, however, one should keep in mind that such an effect could represent a simple consequence of awareness, and not awareness itself (de Graaf & Sack, 2014; de Graaf, Hsieh, & Sack, 2012b) and therefore we cannot say which of our effects are the prerequisite, correlate or consequence of consciousness.

Despite the differences in methodology between Experiment 1 and Experiment 2, both experiments found effects of attention on the TEP even when no phosphene was perceived. The differences in timing and topographies between the two effects could be due to several factors. The longer SOA in Experiment 2 might have substantially altered which stage of the cueing processes was probed the TEP. It is possible that more effort would have been required by the participants to keep their attentional focus on the cued side for much longer, and that therefore in Experiment 2 we are seeing the results of the system when it is put under more strain. In Experiment 2, furthermore, participants saw a phosphene in half of the trials; we can hypothesize that phosphene absent trials were those characterized by a spontaneous lower excitability of the cortex. In Experiment 1, instead, we had no way of assessing the trial-by-trial excitability making the two cueing effects hard to compare; as a cueing difference within phosphene absent trials in Experiment 2 represents a difference within low-excitability trials, while a cueing difference in Experiment 1 represents a difference involving both high- and low- excitability trials.

THE RELATIONSHIP BETWEEN CONSCIOUSNESS AND ATTENTION

In our data, correlates of consciousness (the main effect of phosphene perception at time 70-140 ms) were present before the TEP as modulated by attention (the effect of cueing within phosphene present at time 240-280 ms).

Even though this pattern of result might seem counterintuitive, there are at least two observations that might explain it; the first is that, as noted above, an early difference between phosphene presence and absent in the ERP does not mean that phosphenes are already conscious at that early stage. It is possible that our early phosphene effect is an activation signal that later gets modulated by attention before reaching consciousness. Secondly, it could be that although early effects predicted phosphene perception i.e. whether or not a percept was reported, processes defining the vividness and appearance of the phosphene occurred later (for a review of effects of attention on appearance see Carrasco, 2011). Future studies in which a parametric phosphene vividness rating is required in addition to the present/absent discrimination would help testing this later hypothesis.

It has been proposed that even though very early effects of consciousness are observed in primary sensory areas (Pins & Ffytche, 2002), it is likely that consciousness 'happens' later and is mediated by further activations of higher-order cortical areas (Lamme, 2006). The crucial role of later feedback from secondary areas

(V5) has been investigated with TMS, showing that phosphene awareness can be manipulated by disrupting those processes (Pascual-Leone & Walsh, 2001).

To clarify the relationship between our experimental results and the underlying dynamics of attention and consciousness, Figure 55 shows a scheme of the temporal and hypothetical relationship between them.

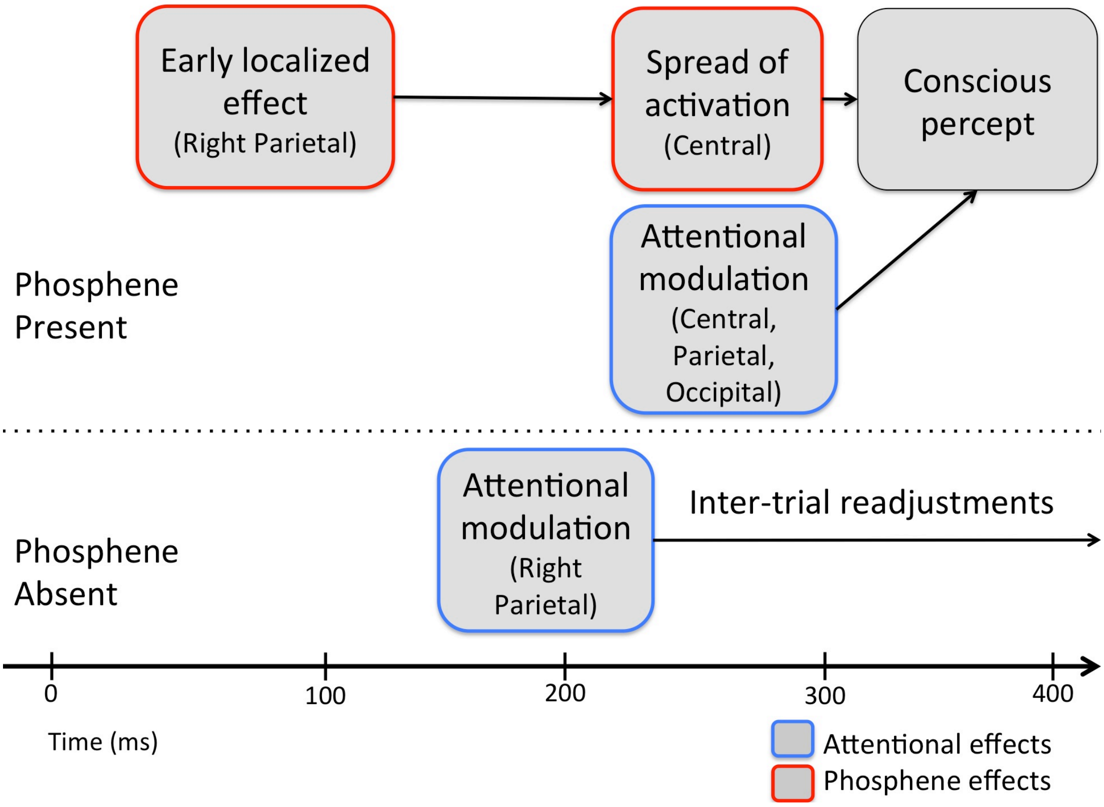


Figure 55. A schematic representation of the TEP effects, and their suggested function and relationship. Location on the x-axis is approximate for illustration purposes. Blue-bordered items represent attentional effects, while red-bordered items phosphene effects.

We have divided the effects into two categories: phosphene present and phosphene absent. When no phosphene is perceived, the presence of an attentional modulation could represent trial-to-trial readjustment, in relationship to the expectation the participant formed towards seeing a percept. In the presence of a percept, on the other hand, we can identify two effects; the early localised effect of phosphene perception, and then a later attentional modulation; it is conceivable that both these effects may contribute to the creation of the conscious percept, and future work may attempt to disentangle them.

CONCLUSION

To conclude, our results have shown that occipital TMS during an attentional task employing Posner cues can affect the TMS-related potential; we also have replicated the previous finding of a neural signature for phosphene perception (Taylor et al., 2010), and we have shown new, earlier effects of phosphenes.

Concerning phosphene perception, the presence of several effects, differing in timing and location, agrees with current models of consciousness asserting that conscious perception is determined by later feedback reverberations, and not by the first feed-forward pass of activation in the visual cortices (Lamme, 2006).

In the present experiment we have also shown for the first time that visual perception and cueing interact in specific times in the TMS-evoked potential. We have shown that the interactions are different in trials in which a phosphene is perceived compared to when no perception is reported.

Taken together, our results have highlighted a variety of effects of phosphenes, and its interaction with cueing, showing that perception of phosphene is the results of elaborate processing, being characterized both by early feedforward processing and later top-down modulations.

GENERAL DISCUSSION

AIM OF THE EXPERIMENTS

The combination of TMS and EEG offers a unique tool to investigate the causal role of different cortical areas, and the timing of their involvement (Miniussi, Bortoletto, Thut, & Veniero, 2012; Taylor et al., 2008; Thut & Pascual-Leone, 2009). In this thesis, we presented experiments applying two widely employed paradigms in visual attention; visual search and Posner cueing, to investigate cortical functions.

In the visual search experiment, we employed a feature search paradigm in which participants were instructed to perform a compound task. We applied repeated-pulse TMS on the rAng in the inter-trial interval in order to modulate inter-trial effects. This paradigm allowed us to dissociate the response- and stimulus- related task components, and to assess different theories of the role of the rAng.

In the two experiments involving cueing, we employed central endogenous cues in the shape of arrows pointing to the left or right side of the screen. Participants were instructed to orient their attention covertly, and perform a discrimination task on a checkerboard that was presented with a validity of 80%. Visual stimuli were present in 33% of the trials. At the same time, a TMS pulse was applied to the right occipital cortex, in an area observed to elicit phosphenes.

In the first cueing experiment, we employed sub- threshold TMS pulses, so that participants never reported seeing a phosphene. We therefore were able to investigate the interaction between cueing and sub-threshold cortical activation.

In the second cueing experiment, we employed TMS pulses at phosphene threshold intensity; participants saw a phosphene half of the trials. We were therefore able to investigate the correlates of phosphene perception as well as the interaction between spatial attention and phosphene perception.

VISUAL SEARCH AND THE RIGHT ANGULAR GYRUS

KEY FINDINGS

In this experiment investigating the function of the rAng in visual search, we observed a facilitatory effect of TMS; reaction times were faster in trials in which both the target-defining feature and the response-defining feature repeated, an effect mirrored by an enhanced amplitude of the N1 component.

THEORETICAL CONTRIBUTIONS

The results of this experiment have several implications to the field of visual search and to the models of rAng functions; they also fit in the growing body of works finding that TMS improves performance in a variety of tasks (Luber & Lisanby, 2014).

By speeding reaction times in trials characterized by a complete repeat of stimulus- and response- defining characteristics, our results suggest that behavioural models of the processing of compound task that include purely serial components of stimulus- and response-processing should be updated by including a parallel component representing combined expectancies (Kingstone, 1992; Memelink & Hommel, 2013). This addition could explain how TMS applied over a single area could affect a trial type characterized by both stimulus and response repeats, and only this type of trials. In recent years, many psychological and neuroscientific models have advocated a connection between action and perception, or between different (and often independent) dimensions of a stimulus (Memelink & Hommel, 2013) and our results strongly support this connection. That TMS was delivered in the inter-trial interval also suggests that the effect modulated was an implicit expectancy that the system forms after being presented with a particular stimulus-response association, expecting the same occurrence to repeat in the next trial. A recent theory connecting perception and action and agreeing with our data is the Theory of Event Coding (TEC) (Memelink & Hommel, 2013); it postulates that action representations automatically prime task-relevant features in subsequent trials. Interestingly, recent EEG evidence based on the TEC showed that early perceptual processing can be modulated by action intention (Wykowska & Schubö, 2012), agreeing with our results involving the N1 component.

Our results are also relevant to characterize the function of the rANG; although it has been shown through neuroimaging studies that the rANG is activated in a multitude of tasks, our results fit with the Visuomotor Hypothesis of parietal function (Ellison et al., 2003). Earlier experiments stimulating different sub-regions of the PPC with TMS during a visual search task failed to find any effect of TMS during feature search, while an impairment was found when TMS was applied during conjunction search (Ashbridge et al., 1997; Ellison et al., 2004). Although most of the studies applying TMS to study visual search have delivered TMS pulses at the time of stimulus onset, therefore affecting very different processing stages than those investigated by us applying TMS in the inter-trial interval, they have suggested that the role of the right PPC in visual search tasks is to perform binding (Ashbridge et al., 1997); it would be therefore needed when a conjunction of dimensions is necessary to perform the task, but not when the target is characterized by a unique dimension. Instead, the Visuomotor Hypothesis of the PPC proposes that the tasks in which the PPC is crucially relevant are those characterized by the need of a new visuomotor association, and in the updating of this association.

The results presented in this thesis concerning visual search and the rAng represent a contribution to the debate of the nature of inter-trial effects, to the function of the rAng, as well as to the more general understanding of the relationship between action and perception.

SPATIAL ATTENTION AND PHOSPHENE PERCEPTION

KEY FINDINGS

The main finding of the first experiment investigating the interaction between spatial attention allocation elicited by cueing and sub-threshold TMS was the presence of a late (240-280) difference in the TMS-evoked potential only after the occipital TMS, for right parietal electrodes. We also observed that TMS did not interact with cue-locked ERPs, nor with other time bins of the TEP.

The second experiment investigated the interaction between spatial attention and phosphene perception: we observed that these two factors interacted in the TMS-locked ERP; when the phosphene was absent we observed an earlier (180-240 ms) difference between cueing conditions for right parietal electrodes, while when the phosphene was present the difference was later (240-280), of opposite polarity, and observable over all electrode groups. We also found earlier effects of phosphene perception than those reported in the literature (Taylor et al., 2010), with phosphene present trials generating a more negative ERP in the time bin 70-140 ms over right parietal electrodes. We also replicated later effects of phosphenes, showing a spread of activation over parietal, central and occipital electrodes (Taylor et al., 2010).

THEORETICAL CONTRIBUTIONS

The results from Experiment 1 support the claim that spatial attention modulates cortical excitability; It is important to stress that in Experiment 1 TMS pulses did not generate any percept, and therefore our results solely concern cortical excitability below consciousness threshold, avoiding any confound that usually comes with perception, like exogenous orienting of attention.

The results from Experiment 2 are relevant concerning two topics: the nature and timing of phosphene perception, and the effects of attention on phosphene perception and therefore excitability of the visual cortex. Concerning phosphene perception, although we replicated earlier findings showing that phosphene present trials elicit a late (240-280 and 280-400 ms post TMS) central positivity when we compared it to phosphene absent; we also observed an earlier effect (70-140 ms post TMS), with phosphene present trials eliciting a more negative ERP in the right parietal group than phosphene absent. These results are relevant to the debate concerning the nature of phosphenes (Taylor et al., 2010), as well as to the topic of neural correlates of consciousness (Lamme, 2010). A possible interpretation of the phosphene results is that although phosphenes are generated early and locally, they are sensitive to later attentional and top-down modulations, which might be the result of feedback neural processes after the first feed-forward signal, which represented by our early effect. Studies that employed visual stimuli have found that it is possible to discriminate very early on whether or not the stimulus will be perceived, but that later factors affect consciousness as well; these findings view consciousness as the fruit of recurrent processes (Del Cul et al., 2007), and situate consciousness at the same time in which we observed a spreading of the phosphene effect as well as an interaction between phosphenes and cue (240-280 ms).

In Experiment 2 we also observed cueing differences when the phosphene was absent over right parietal electrodes (180-240 ms), of an opposite polarity to the difference within phosphene present. The difference in timing and topography of this effect to the effect in Experiment 1 might suggest that either they are different effects, or that the methodological differences between the two experiments (in terms of TMS intensity and cue-TMS SOA) modulated the effect significantly.

CONCLUSION

Taken together, the experiments included in the present thesis provide contributions towards a better understanding of the linkage between attention and other brain functions; action and consciousness. Although we employed very different paradigms (both in terms of task, visual stimuli, and TMS protocols), and stimulated different areas, the studies presented in this thesis strengthen a view of the brain in which different systems interact to optimize performance.

In the first part, we have been able to show that the right angular gyrus is causally involved in the formation of expectancies involving target- and response- defining features. Our study is the first to demonstrate rANG functional specificity in improving visual search performance when target- and response- defining features repeat. Our results contribute to the understanding of the function of the rAng, a complicated substructure in the parietal cortex which has been defined “a multisensory hub” (Seghier, 2012). Our findings are also relevant to the debate concerning the nature of intertrial effects; they suggest that parallel components are needed to address the formation of combined expectancies (Kingstone, 1992; Memelink & Hommel, 2013). Finally, our experiment shows that the N1 component, traditionally thought to be involved in early analyses of stimulus features (Luck, 2005), is sensitive to how the rANG contributes to combined perceptual and motoric intertrial expectancies.

In the second part, we have also provided additional evidence to the connection between attention and excitability of the visual cortex, both when no percept is present, and when a phosphene is perceived. The results of Experiment 1, showing that a TMS pulse over the phosphene-generating occipital cortex modulates the TEP differently depending on cueing condition, supports the view that attention can affect baseline shifts (Kastner & Ungerleider, 2000; Serences & Kastner, 2014), and specifically shifts of excitability below perceptual threshold. The results of Experiment 2, showing earlier phosphene-related effects than those previously found in the literature, as well as the presence of later interactions involving cueing condition and phosphene presence, hint towards a more nuanced view of phosphene perception, where early and late effects contribute in creating dynamic patterns of neural activity that can be altered by attention.

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Date of Birth September 14th, 1987
Nationality Italian

Education

2006: Diplome (full marks), Istituto Magistrale Statale G.M. Colombini (major: psychology), Piacenza (Italy),
2009: B.Sc. (cum laude) In Cognitive-Quantitative Psychology, Università Vita-Salute San Raffaele, Milan (Italy)
2011: M.Sc ("very good") in Elite study Program in Neuro-Cognitive Psychology, LMU, Munich (Germany)
2015 (Expected): PhD in Systemic Neurosciences, LMU, Munich (Germany)

Research Activities

Period: 2012-Present
Supervisor: Dr. Paul Taylor paul.taylor@lmu.de
At: Transcranial Magnetic Stimulation Laboratory
Ludwig-Maximilians Universität, Leopoldstraße 13, München,
Germany
Position: PhD student
Research Field: Transcranial Magnetic Stimulation + EEG study on dimensional weighting account of attention.

Period: 2010-2011
Supervisor: Dr. Paul Taylor paul.taylor@lmu.de
At: Transcranial Magnetic Stimulation Laboratory
Ludwig-Maximilians Universität, Leopoldstraße 13, München,
Germany
Position: MSc Thesis student
Research Field: Transcranial Magnetic Stimulation study on dimensional weighting account of attention.

Period: 2010-2011
Supervisor: Prof. Jeremy Wolfe wolfe@search.bwh.harvard.edu
At: Visual Attention Laboratory
Harvard Medical School, 64 Sidney St., Cambridge, MA,
Position: Pre-doctoral Research Fellow
Research Field: Neuropsychological assessment of dry eye-patients and experimental work in the guided search model.

Period: 2009-2010
Supervisor: Dr. Michael Zehetleitner mzehetleitner@lmu.de
At: Attention Laboratory
Ludwig-Maximilians Universität, Leopoldstraße 13, München, Germany
Position: Research Assistant
Research Field: Experimental work about temporal dynamics of visual attention allocation and its relationship with feature contrast.

Period: 2008 – 2009
Supervisor: Prof. Maria Concetta Morrone concetta@in.cnr.it
At: Vision Science Laboratory DIBIT
Vita-Salute San Raffaele University , Via Olgettina 58, Milan, Italy
Position: Research Assistant
Research Field: Contrast and motion discrimination are measurements that can provide many insights about neuropsychological deficits. As my thesis project, I programmed an experiment to test those visual properties in dyslexic patients. The neurological basis of developmental dyslexia are still controversial and the data we collected present further suggestions for a visual theory of dyslexia.

Period: 2006 – 2009
Supervisor: Prof. Gabriel Baud-Bovy baud-bovy.gabriel@hsr.it
at: Haptics Neuroscience & Robotics Unit
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Vita-Salute San Raffaele University Via Olgettina 58, Milan
Position: Research Assistant
Research Field: Force perception in one-dimensional space using haptic interfaces. After optimizing the control law of the robot (Omega, Force Dimension, Lausanne), experiments to model human force perception were conducted.

Publications

Bocca F., Taylor P., Töllner T., Müller H., “The dimensional weighting account of attention investigated with TMS-EEG” (in preparation)

Morrone M.C., Cicchini M., Consonni M., Bocca F., Mascaretti S., Scifo P., Marino C. And Perani D., “Pronounced visual motion deficits in developmental dyslexia associated with a specific genetic phenotype” 10,11doi: 10.1167/11.11.428 Journal of Vision September 23, 2011 vol. 11 no. 11 article 428

Morrone M.C., Cicchini M., Consonni M., Bocca F., Mascaretti S., Scifo P., Marino C. And Perani D., “Pronounced visual motion deficits in developmental dyslexia associated with a specific genetic phenotype”, Vision Science Society Conference Proceedings, 2011

Bocca, F., and Baud-Bovy, G., “A model of perception of the central point of elastic force fields”, Wold Haptics Conference Proceedings, 2009.

Conference participations and poster presentations

- Invited speaker in the conference of the “European society of cognitive and affective neurosciences, ESCAN”, Dortmund (Germany) 2014.
- Participation to the summer school “Coupling to the brain dynamics using TMS-EEG” in Helsinki (Finland) 2013. Winner of the 1st prize for student presentations.
- “The dimensional weighting account of attention investigated with TMS” Visual Search and Selective Attention Conference (VSSA), Ammersee (Germany), 2012. Poster presenter: Francesca Bocca
- “Visual deficits in dry eye syndrome: a case study” Ludwig-Maximilans-University, NCP Poster Session, December 2010. Poster presenter: Francesca Bocca
- “Time-course of attention and the dot-probe paradigm” Ludwig-Maximilians-University, NCP Poster Session, May 2010. Poster presenter: Francesca Bocca
- “A model of perception of the central point of elastic force fields” Third Joint Eurohaptics Conference and Symposium of Haptic Interfaces for Virtual Environment and Teleoperator Systems. March 18-20, 2009, Salt Lake City (UT), USA. Poster presenters: Francesca Bocca and Gabriel Baud-Bovy
- “The perception of force fields’ null points” San Raffaele Scientific Retreat 2009, February 18-20, Stresa (VB), Italy. Poster presenter: Francesca Bocca

Prizes

- Enel-ARCA scholarship for Bachelor students (2006-2009)
- 1st prize for student presentations at the summer school “Coupling to the brain dynamics using TMS-EEG” in Helsinki (Finland) 2013

Teaching Activities

- Lecturer of “Child Psychology” at the Islamic Online University (2012-present). The course is constituted by 30 hours of classes covering the major topics of developmental psychology including references from classical Arabic and Islamic philosophy.
- Lecture for Max-Weber excellence students network “Cognitive Neuroscience: an Overview” Prof. Thomas Rübig (2010)
- Lecture at Università Cattolica del Sacro Cuore (Milan) “Experimental data and Philosophy of mind”, Prof. G.D. Bolis (2008)

Skills

Cognitive science expertise

- Independent in programming, running and analysing psychophysical experiments
- Good knowledge of the main neurophysiological paradigms of neuroscience, their applications and statistical procedures:
    - EEG / ERP
    - TMS
    - fMRI

Languages:

Mother tongue: Italian

TOEFL certification for English knowledge: 107. My higher education (Master and PhD) has been accomplished in an English-speaking environment.

Intermediate knowledge of Classical Arabic, German and French.

Programming skills

R/S/S+:	both as statistical environments and programming languages;
C/C++:	at a basic level. I know mainly their application in robotics and haptics;
MatLab:	both as a statistical tool and as a programming language;
SPSS:	good usage
SPM:	analysis of fMRI data

BrainVision Analyser: Analysis of EEG data

LIST OF PUBLICATIONS

Bocca F., Taylor P., Töllner T., Müller H., “The dimensional weighting account of attention investigated with TMS-EEG” (submitted to Brain Stimulation on 20/11/2014)

Morrone M.C., Cicchini M., Consonni M., **Bocca** F., […] “Pronounced visual motion deficits in developmental dyslexia associated with a specific genetic phenotype” Journal of Vision 10, 2011

Bocca, F., and Baud-Bovy, G., “A model of perception of the central point of elastic force fields”, Wold Haptics Conference Proceedings, 2009.

Eidesstattliche Versicherung/Affadavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation dissertation ‘Combined TMS-EEG studies of Visual Attention’ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that this dissertation ‘Combined TMS-EEG studies of Visual Attention’ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation. A full list of the references employed has been included. For parts of the work that contains or is based on co-authored manuscripts or published articles, my contributions to the article and of all co-authors are declared.

Munich, November 2014

Francesca Bocca

Dr. Paul Taylor

DECLARATION OF AUTHOR CONTRIBUTIONS

Visual Search

Francesca Bocca, Paul Taylor and Thomas Töllner designed the study, based on experimental procedures formerly designed by Thomas Töllner. Francesca Bocca programmed and conducted the experiment, analysed the data, and wrote the paper. Paul Taylor, Hermann Müller and Thomas Töllner commented and revised the manuscript. The manuscript was submitted to the journal "Brain Stimulation" on 20/11/2014.

Cueing and Visual Attention

Experiment 1

Francesca Bocca, Hermann Müller and Paul Taylor designed the study. Francesca Bocca programmed the experiment, which was conducted by Francesca Bocca and Paul Taylor. Francesca Bocca analysed the data.

Experiment 2

Francesca Bocca and Paul Taylor designed the study. Francesca Bocca programmed the experiment, which was conducted by Francesca Bocca and Aleya Flechsenhar. Francesca Bocca analysed the data. A subset of the analyses has been reported in the Master Thesis of Aleya Flechsenhar titled "Effects of Spatial Attention and Excitability: Combined TMS-ERP Data", submitted as a fulfilment for her Master in Neuro-Cognitive Psychology (NCP), Ludwig-Maximilians University, in August 2014.