

## Go with the flow

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# *Go with the flow*

Multimodal brain research  
on communication in the  
vision-attention network

Shanice Elisabeth Wilhelmus Janssens

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# *Go with the flow*

Multimodal brain research on communication  
in the vision-attention network

Dissertation

to obtain the degree of Doctor at Maastricht University,  
on the authority of the Rector Magnificus, Prof. Dr. Pamela Habibović,  
in accordance with the decision of the Board of Deans,  
to be defended in public on

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by

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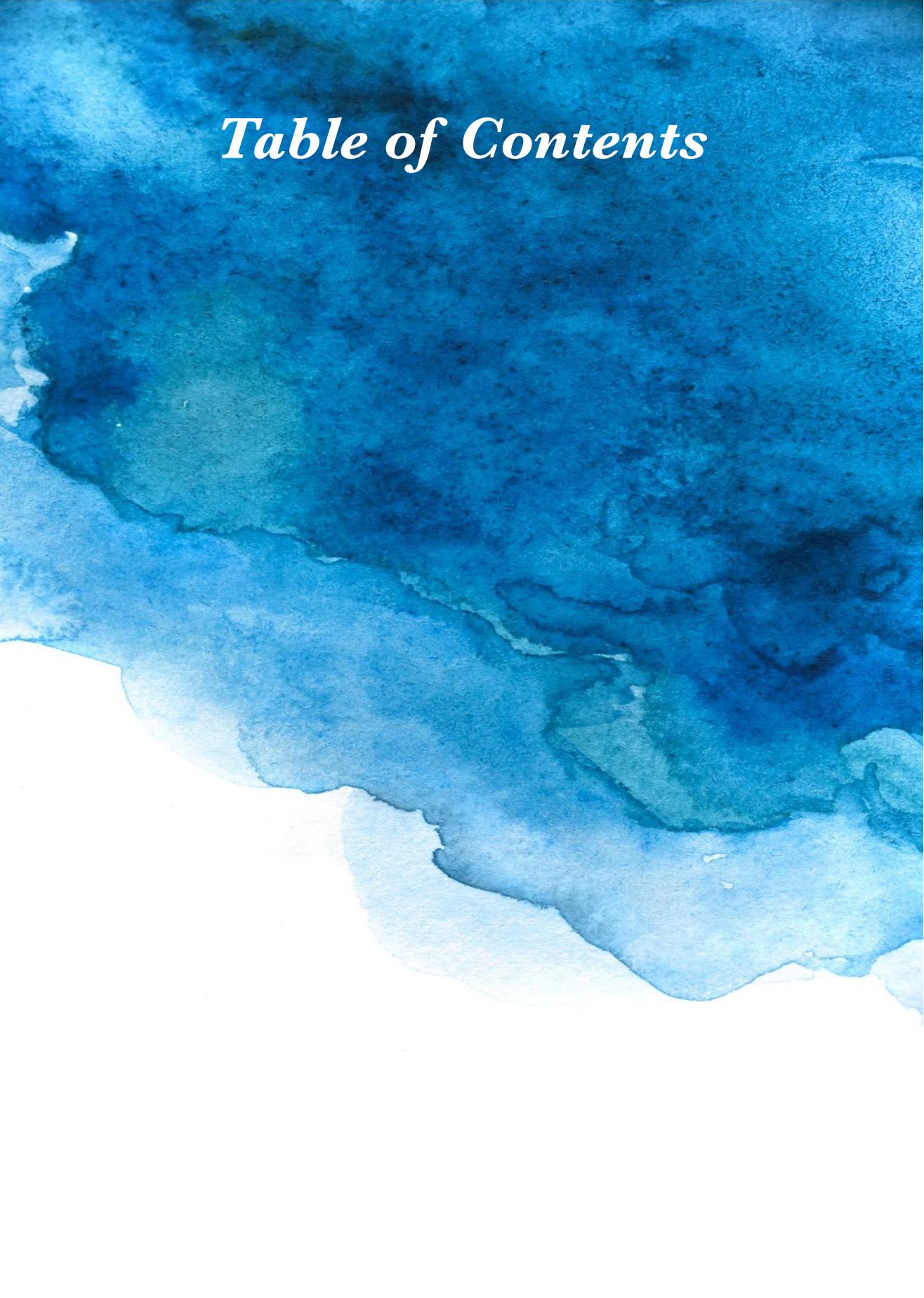
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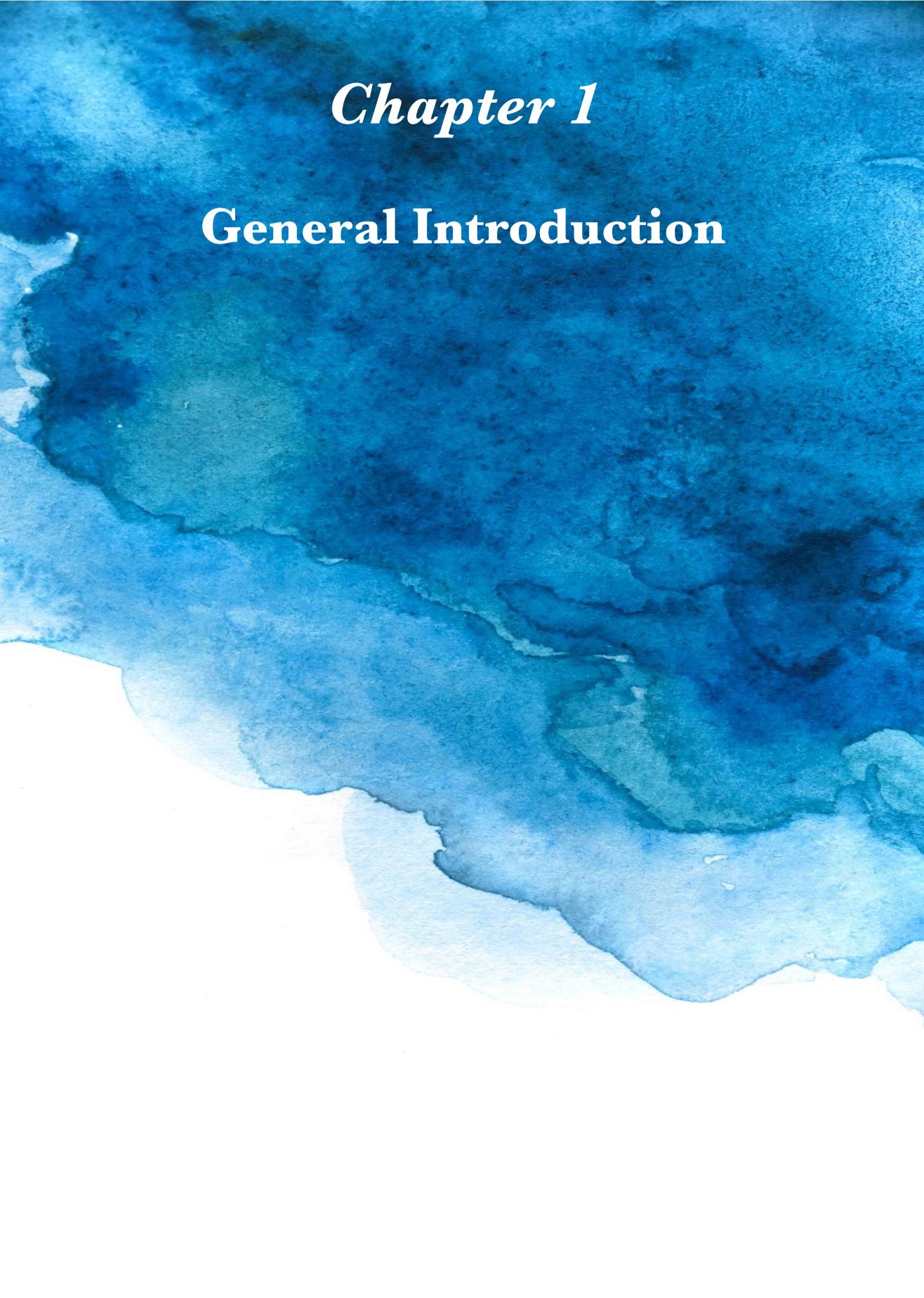
The background of the page is a watercolor wash in various shades of blue and teal. The colors are blended and layered, creating a textured, organic appearance. The top portion is a darker, more saturated blue, which gradually transitions into lighter, more translucent washes of teal and light blue towards the bottom. The edges of the washes are soft and irregular, characteristic of watercolor painting.

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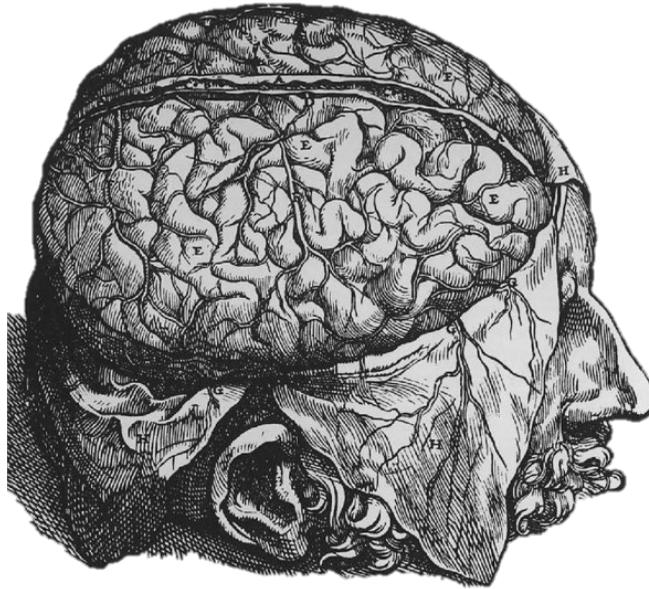
# *Chapter 1*

## **General Introduction**

The human brain is an intriguing organ. Somehow, through billions of interacting cells, called neurons, our brain enables us to move, perceive, and think. Scientists have been investigating the human brain for many centuries, using a variety of ever-evolving tools. Throughout their quest for understanding the intricate workings of the human brain, scientists must rely on the intellectual and behavioral capabilities of that same brain – in essence, the brain is studying itself. When did we come to understand that the brain is the organ responsible for our cognition and behavior? And how did we proceed to map the anatomical and functional properties of the human brain?

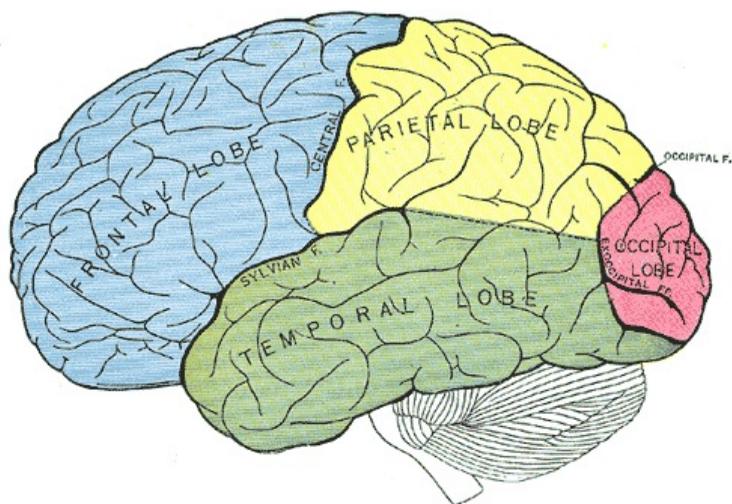
## 1.1 Historical highlights and limitations of human brain mapping before the establishment of modern cognitive neuroscience

The oldest known reference to the human brain can be found in the *Edwin Smith Papyrus*, a medical text dating back to approximately 1600 B.C. (Wilkins, 1964). This text already described that brain injuries were associated with symptoms in other body parts. Nevertheless, it was only a century later that the Greek philosopher and scientist *Alcmaeon* was the first to suggest that the brain is the central organ responsible for human behavior. This stood in stark contrast with the *Aristotelian* view, which believed the heart to be the seat of human intelligence (Adelman, 1987). Knowledge about the anatomy of the human brain advanced greatly during the Renaissance, thanks to two of the most prominent anatomists of all time: *Andreas Vesalius* (16<sup>th</sup> century) and *Thomas Willis* (and his illustrator *Christopher Wren*, 17<sup>th</sup> century) (Abbott, 2015). Their legacy includes several detailed drawings of the human brain, exposing the nowadays well-known winding pattern of its sulci and gyri, along with its blood vessels and its two hemispheres (for an example, see Figure 1.1).



**Figure 1.1:** A drawing of the human brain by **Andreas Vesalius**, from *De Humani Corporis Fabrica* (1543). Image from Bibliothèque de la Faculté de Médecine, Paris/Bridgeman Images.

While the knowledge of human brain anatomy was expanding, significant advancements in the mapping of specific functions to certain brain areas only occurred in the mid-19<sup>th</sup> century, when the scientific utility of brain lesions became apparent (Savoy, 2001). Perhaps one of the most influential cases stems from 1848, when the personality of *Phineas Gage* was forever altered after he suffered rather localized but profound damage of his frontal lobe (see Figure 1.2), after a tragic railroad accident (Macmillan, 2000; Ratiu et al., 2004). There are other textbook examples of cognitive functions that were mapped onto specific brain areas because of patients with brain lesions. For instance, language production and understanding are generally lateralized to the left hemisphere (as first shown by *Paul Broca* in 1861 and *Carl Wernicke* in 1876, respectively). Memory formation was shown to involve the temporal lobes (see Figure 1.2), thanks to the famous patient *Henry Molaison* (“H.M.”) (Savoy, 2001). During this period of time, an extensive atlas of the human cerebral cortex was published by *Korbinian Brodmann* (Brodmann, 1909; Finger, 2001; Garey, 2006), dividing the outer and evolutionary most recent part of the brain into 52 distinct numbered areas (Rakic, 2009). This atlas was based on the cellular composition of different parts of the cortex, and is still being used in contemporary human brain mapping research (Strotzer, 2009).



**Figure 1.2: Anatomy of the human brain with its four cortical “lobes”.** Left sided view (thus, the front side of the brain is shown on the left side of the image). The cerebral cortex is the outermost part of the brain, and consists of four lobes (frontal, temporal, parietal, and occipital). The cerebellum (striped) and brain stem (white) are situated below the cortex. Original illustration by *Henry Vandyke Carter* (Public domain, via Wikimedia Commons, from Gray, H. (1918). *Anatomy of the human body* (Vol. 20). Lea & Febiger).

Anatomical brain mapping and lesion studies have clearly taught us a considerable amount about how the human brain functions. Yet, those early attempts at understanding the brain are limited in several ways. Firstly, the brain could only be observed post-mortem or during surgery, limiting the conclusions that could be drawn in real time. In particular, lesion studies suffer from the limitation that by the time the observation was taking place, the brain might have already undergone significant reorganization – since the human brain can show remarkable plasticity (e.g., Dimyan and Cohen, 2011; Li et al., 2014). Secondly, lesion studies do not allow any experimental control, in the sense that researchers cannot influence when and where brain lesions occur (Rorden and Karnath, 2004). On the one hand, lesions often lack specificity as they tend to cover multiple brain areas, making it difficult to distinguish the functions of the affected areas. On the other hand, not all brain areas are equally prone to brain damage, for instance because of vascular anatomy and its relation to stroke susceptibility, limiting the brain areas that could be investigated (Caviness et al., 2002). These issues could be circumvented thanks to the development of modern neuroimaging and non-invasive brain stimulation (NIBS) techniques in the late 20<sup>th</sup> century. At the writing of this

thesis, the term “cognitive neuroscience” was coined 45 years ago by *Michael Gazzaniga* and *George Miller* (Gazzaniga et al., 2014). The field of cognitive neuroscience is at the intersection of neuroscience and psychology, and concerns itself with the neurobiological processes that underlie human cognition and behavior.

## 1.2 Modern human brain mapping methods

What are the tools that we – contemporary neuroscientists – have available, that allow us to overcome the limitations discussed in the previous section? Below, I will present a brief overview of the neuroimaging and NIBS methods that are relevant for this thesis, in the order of appearance in this General Introduction (for the chronological order, see Figure 1.4). These methods are: functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), electroencephalography (EEG), and transcranial alternating current stimulation (tACS).

### 1.2.1 Functional magnetic resonance imaging

fMRI is a non-invasive neuroimaging method that measures brain activation in an indirect way (Ogawa et al., 1990). In essence, fMRI can detect the ratio between oxygenated and de-oxygenated hemoglobin in the blood, since the latter is slightly magnetic in the presence of a strong magnetic field (Huettel et al., 2004; Uludag et al., 2015). That strong magnetic field, typically in the range of 1.5 to 7 Tesla, is generated by the MRI scanner itself. When a brain area is active, an overflow of oxygenated blood is transported to that area. Therefore, the blood oxygen-level dependent (BOLD) signal as measured with fMRI increases when a brain area is active (Logothetis, 2003). Since it takes time for the oxygenated blood to be transported towards an active brain area, the BOLD response peaks approximately 6 seconds after the neuronal activity started (e.g., 6 seconds after presenting a stimulus that activates the brain area). The temporal resolution of fMRI is therefore relatively low (i.e., on the scale of seconds), but the spatial resolution is high (i.e., on the scale of millimeters, or even sub-millimeter) (Huettel et al., 2004; Uludag et al., 2015). fMRI is often used to provide correlational evidence for the involvement of a certain brain area in a specific cognitive function (Gazzaniga et al., 2014). Already since 1978, MRI scanners can also be used to obtain in-vivo

anatomical images of the human brain (New Scientist, 1978). FMRI activation is typically visualized onto such an anatomical MRI scan (see Figure 1.5).

### 1.2.2 Transcranial magnetic stimulation

To establish the causal relevance of a certain brain area for cognition, experimental manipulation of processing in that brain area is required. This can be achieved with TMS (Bergmann and Hartwigsen, 2020; Polanía et al., 2018; Sack, 2006), which is a form of NIBS that was first introduced by *Anthony Barker* in 1985 (Barker et al., 1985). TMS allows virtually pain-free and direct stimulation of the cortex (see Figure 1.3) (Hallett, 2000; Pascual-Leone et al., 2000; Walsh and Cowey, 2000). It has been used for numerous purposes (Silvanto and Muggleton, 2008; Ziemann, 2010). For instance, single TMS pulses can briefly interfere with processing in a certain brain area. Single pulse TMS can therefore be used to establish whether and when a brain area is causally involved in a specific cognitive function (“virtual lesioning” and “TMS chronometry” approach) (de Graaf et al., 2014; Kammer, 2007a; Walsh and Pascual-Leone, 2003). Besides this, TMS can also induce longer-lasting modulations in neuroplasticity when applied in a repetitive fashion (Y. Huang et al., 2005; Stefan et al., 2000; Ziemann, 2004). The latter already indicates why TMS is also increasingly being explored as a treatment option for various brain-based disorders, including depression, motor stroke, and schizophrenia (de Graaf, Janssens, et al., 2021; de Graaf, Thomson, Duecker, et al., 2021; Lefaucheur et al., 2020; Lefaucheur et al., 2014; Rossi et al., 2021).



**Figure 1.3: Transcranial magnetic stimulation (TMS) equipment.** *Top left:* TMS machine. *Top right:* Example TMS coil that can be used for spatially precise stimulation. *Bottom:* the TMS coil is placed onto the scalp of a participant, to non-invasively stimulate a cortical brain area. *Photos:* Sas Schilten Photography & national newspaper “de Volkskrant”.

### 1.2.3 Electroencephalography

The first human electroencephalogram was reported by *Hans Berger* in 1929 (Berger, 1929, 1933; Haas, 2003; Quigley, 2021). By using electrodes placed on the scalp, EEG can non-invasively record the electrical potentials generated by large pools of neurons (Cohen, 2014; Gazzaniga et al., 2014). In contrast to fMRI, EEG does not rely on the hemodynamic (blood flow) response and can thus measure brain activation in a more direct way. However, the electrical activity generated by the brain cannot pass completely unhindered through the different brain tissues and the skull towards the scalp. Since the electrical potentials are distorted on their way to the scalp, a single configuration of scalp EEG signals can be caused by numerous underlying neuronal activation patterns (Biasucci et al., 2019). This so-called “inverse problem” explains why EEG inherently suffers from low spatial resolution: it is unclear where exactly the signals are coming from. At the same time, EEG has excellent temporal resolution (i.e., in the order of milliseconds) (Cohen, 2014; Gazzaniga et al., 2014). It is therefore ideally suited for measuring cyclic activations of neuronal ensembles, which are called “neuronal oscillations” (Buzsáki and Draguhn, 2004). Neuronal oscillations in different frequency bands have been linked to different cognitive processes (Bonfond and Jensen, 2012; Bonfond et al., 2017; Cabral-Calderin and Wilke, 2020; Clayton et al., 2018; Jensen and Mazaheri, 2010; Klimesch, 1999; Riddle et al., 2019). Since EEG merely measures neuronal oscillations rather than manipulating them, EEG can only establish a correlational link between neuronal oscillations and cognition (Herrmann et al., 2016).

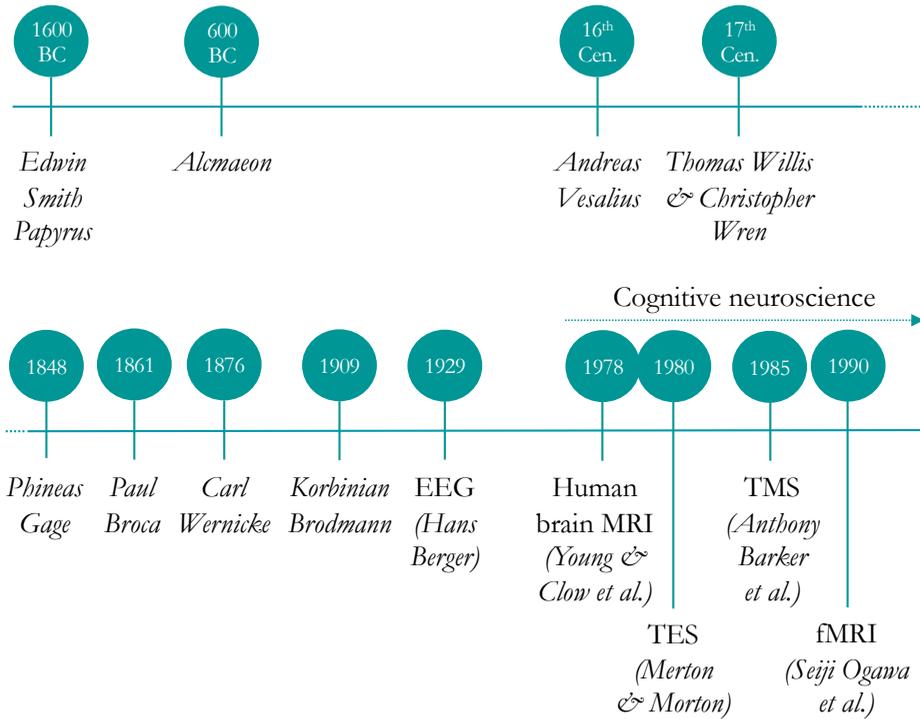
### 1.2.4 Transcranial alternating current stimulation

TACS is a form of non-invasive transcranial electric stimulation (TES) (Antal and Paulus, 2013; Paulus, 2011a; Polanía et al., 2018). It can be used to establish the causal relevance of neuronal oscillations for cognition. With tACS, the brain is stimulated with an alternating electric current through two or more electrodes that are connected to a battery. In contrast to TMS, tACS does not directly cause action potentials in the targeted neurons, but rather modulates their membrane potential, making the neurons more or less likely to “fire” (Paulus, 2011b). Compared to TMS, tACS is less spatially precise, but it does not suffer from auditory side-effects

(associated with the TMS “click” sound). TACS has been shown to enhance the “power” (strength) of endogenous oscillations at a specific (targeted) frequency (Herrmann et al., 2013; Thut, Schyns, et al., 2011; Thut, Veniero, et al., 2011), with subsequent effects on cognitive task performance (Klink et al., 2020).

### 1.2.5 Multimodal brain research

Each of the described neuroscientific methods has their own strengths and weaknesses, and different methods can often provide complementary information (Reithler et al., 2011; Sack and Linden, 2003; Uludağ and Roebroek, 2014). Though the simultaneous combination of several of these methods comes with additional technical challenges (Peters et al., 2013), it can also help us obtain a more complete understanding of the human brain. The research described in this thesis therefore presents a multimodal approach, as it combines behavioral methods, NIBS, and neuroimaging. Such multimodal approaches allow us to study a vast range of human capabilities and characteristics in the field of cognitive neuroscience.



**Figure 1.4: Timeline of the events and persons described in this General Introduction.** EEG = electroencephalography; (f)MRI = (functional) magnetic resonance imaging; TES = transcranial electric stimulation; TMS = transcranial magnetic stimulation.

### 1.3 Visual perception and attention

From the countless processes that have been studied within the field of cognitive neuroscience in the past 50 years, visual perception and attention are perhaps among the most familiar. This is only logical, because *vision* is generally the most dominant one out of our five senses. If you look up from this page and pay attention to your senses of vision, hearing, touch, smell, and taste, which of those seems most impactful or prominent for knowing what is happening around you? Unless you are in an unusually noisy or smelly environment, you would probably answer “vision”. In fact, we often experience an overflow of incoming visual stimuli, which our brains cannot process in full detail all at once (Broadbent, 1957; Kastner and Ungerleider, 2001). Visual perception is therefore intimately linked to *attention* – a selective process that determines which stimuli are currently relevant

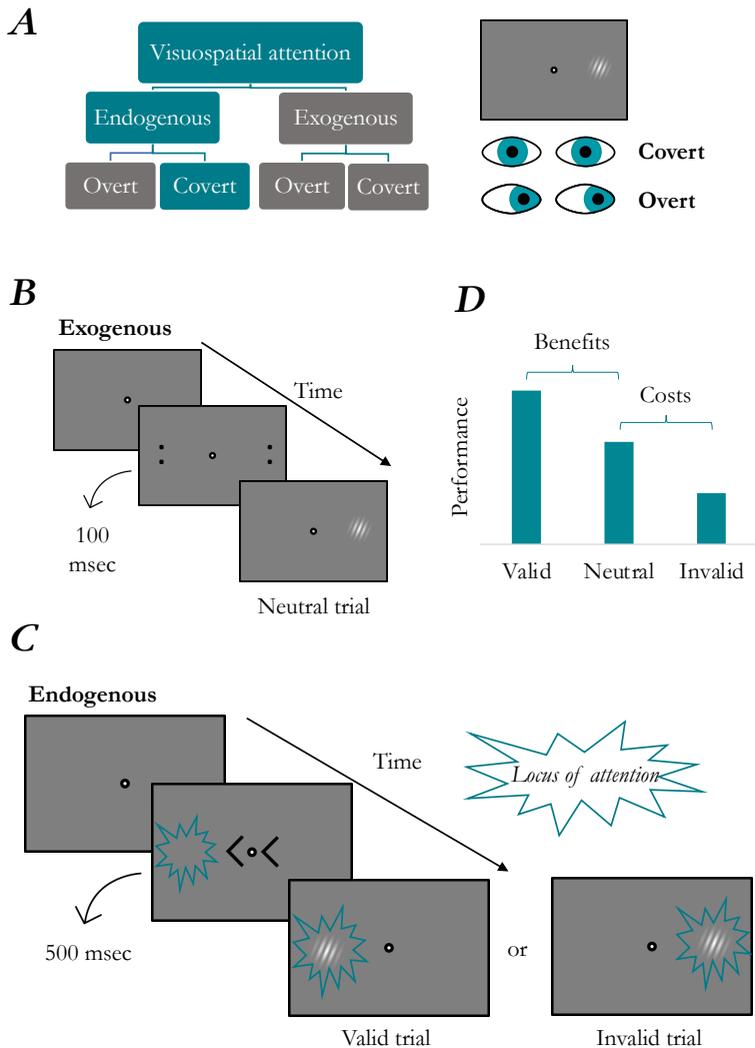
and should be further processed, and which ones are irrelevant or distracting and should be ignored (Broadbent, 1957; James, 1890; Wright, 1998).

We can distinguish between different types of visual attention (see Figure 1.5a). For instance, we can shift our attention to specific locations in space, which subsequently benefits visual perception at the attended location and may suppress visual task performance at unattended locations (Carrasco, 2018). This so-called process of “visuospatial attention” can occur automatically, when a salient stimulus grabs our attention (exogenous or bottom-up), or voluntarily, when we willfully orient our attention to a particular location in space (endogenous or top-down) (Corbetta and Shulman, 2002). Orthogonal to these two mechanisms, attention can be shifted to a certain location overtly, through eye movements (also called “saccades”), or covertly, while maintaining gaze at a fixed location in space (Carrasco, 2011). Though widely studied, it is still not clear whether the neuronal mechanisms underlying overt and covert attention are entirely distinct (Chica et al., 2013; Haan et al., 2008; Peelen et al., 2004; Rizzolatti et al., 1987; Smith and Schenk, 2012). There is also no consensus yet about how exactly visuospatial attention moves across space. Does it simply “jump” from one place to the next, as if it is highlighting certain regions of a topographical map (Silver and Kastner, 2009; Silver et al., 2005)? Does it move like a flashlight across visual space, highlighting everything along its path across visual space up to its destination (the famous “spotlight of attention” metaphor) (LaBerge, 1983; Posner, 1980)? To answer such questions, we require highly precise methods that can tap into the supposed attentional mechanisms and test their (in)dependence. For instance, if we modulate the brain mechanisms underlying covert attention, that should affect covert attention task performance. If overt attention task performance is affected as well, this may indicate that the brain mechanisms of overt and covert attention are dependent. And if we modulate the brain mechanisms underlying attention shifts to a particular location in space, does that also influence (the brain mechanisms underlying) attention shifts to other locations? One of the aims of this thesis was to develop and explore a novel behavioral paradigm that could be used to investigate unresolved and highly debated research questions like these (**Chapter 2**).

Numerous behavioral paradigms have already been developed to study voluntary attention shifts and their relation to visual perception (Carrasco, 2011). A commonly used paradigm is the cueing task developed by *Michael Posner* (see

Figure 1.5b and c) (Posner, 1980, 1994; Posner and Petersen, 1990; Posner et al., 1980). In a conventional implementation of this task, target stimuli are presented on the horizontal meridian in either hemifield, and participants are asked to respond as quickly and as accurately as possible to these stimuli – by either simply detecting them, or by discriminating a certain stimulus feature (e.g., its orientation). In the endogenous version of this task, target stimuli are preceded by symbolic cues that point to either one or both hemifield(s) (e.g. arrows pointing to the left and/or right). A cue pointing in both directions is called a neutral cue and provides temporal (but not spatial) information, given a fixed cue-target interval. By contrast, directional cues can either be valid or invalid, depending on whether the arrows pointed to the location where the target then indeed also appeared, or to the other side, respectively. Participants are instructed to use the directional cues to shift their attention to the indicated hemifield. In this paradigm, both the duration and the predictability of the symbolic cues are essential. Participants should have sufficient time to shift their attention willfully (a cue-target interval of 500 msec is often used). Symbolic cues that point towards either hemifield generally have a predictive value, in the sense that they point towards the correct hemifield (i.e., are valid cues) more often than they point towards the incorrect hemifield (i.e., are invalid cues). Such predictive cues can help promote compliance with task instructions (Duecker and Sack, 2015).

As originally proposed by *Franciscus Cornelis Donders* in 1869, contrasting reaction times in different task conditions can be informative about the duration of cognitive processes (Gazzaniga et al., 2014). For instance, performance in valid versus neutral cue trials quantifies the advantage of having spatially predictive information on top of temporally predictive information, and informs us about the time it takes to orient attention to the “correct” location (this behavioral performance enhancement is also known as attention benefits; see Figure 1.5d) (Duecker et al., 2019). Instead, performance in invalid versus neutral cue trials quantifies the disadvantage of having to re-orient attention towards the opposite hemifield, after having attended to the “false” location (attention costs; see Figure 1.5d) (Duecker and Sack, 2015; Posner, 1980; Posner et al., 1980).



**Figure 1.5: The different types of visuospatial attention and the Posner cueing task.** **A) Attention types.** Visuospatial attention can be willfully (endogenous) or automatically (exogenous) drawn to a specific location in space. This can happen either by moving the eyes (overt), or while maintaining central fixation (covert). The work in this thesis focuses on endogenous covert visuospatial attention. **B) An example exogenous Posner task trial.** A peripheral cue is briefly presented on a computer screen, after which a target (grating) stimulus is presented in the left or right hemifield. This is a neutral cue trial because the peripheral cue highlighted both hemifields. **C) An example endogenous Posner task trial.** A central symbolic cue is presented for (at least) 500 msec, after which the target appears in the left or right hemifield. In a valid cue trial, the cue points towards the upcoming target. In an invalid cue trial, the cue points away from the upcoming target. The “locus of attention” is indicated by the star. In invalid cue trials, participants have to re-shift their “locus of attention” from the cued hemifield towards the target hemifield. **D) Typical behavioral performance as seen in the Posner task.** Performance enhancements in valid cue trials compared to neutral cue trials are called “attention benefits”. Performance impairments in invalid cue trials compared to neutral cue trials are called “attention costs”.

There is no doubt that behavioral methodology is imperative for investigating visual perception and attention. Yet, with a purely behavioral paradigm, we cannot visualize or confirm what exactly the brain is doing, and we thus cannot capture the underlying neuronal mechanisms. According to *David Marr's* tri-level hypothesis, we only fully understand a cognitive process if we can also explain how it is implemented (Marr, 1982; Peebles and Cooper, 2004). At the same time, brain research can help us constrain our models of cognitive processes and can help us distinguish between closely related constructs. For instance, as already asked above, are overt and covert attention truly distinct? Similarly, what is the relation between attention and awareness? (Koch and Tsuchiya, 2020; Posner, 1994; Watanabe et al., 2011). Gaining an understanding of how the brain accomplishes complex cognitive functions such as visuospatial attention can thus significantly advance fundamental scientific knowledge. On top of that, understanding the neuronal mechanisms underlying visuospatial attention in the healthy human brain might also help us understand what might cause brain-based disorders such as visuospatial neglect (Corbetta and Shulman, 2011; He et al., 2007; Pirondini et al., 2020), with the ultimate goal of developing novel treatment strategies. To name a practical example, our knowledge of how visual perception is implemented in the healthy human brain can aid the development of cortical implants for restoring vision in cortically blind individuals (Farnum and Pelled, 2020). Furthermore, our understanding of the role of neuronal alpha oscillations in attention processing (see below) led to novel neurofeedback trainings that can alleviate attention-deficit hyperactivity disorder (ADHD) symptoms (Deiber et al., 2020).

To understand how visuospatial attention is implemented in the healthy human brain, several relevant questions must be answered. Which brain areas are involved in visuospatial attention? Do those regions have a true (causal) role in visuospatial attention? How are signals propagated between the relevant brain areas? To answer such questions, behavioral methodology needs to be supplemented with neuroimaging methods such as fMRI and EEG.

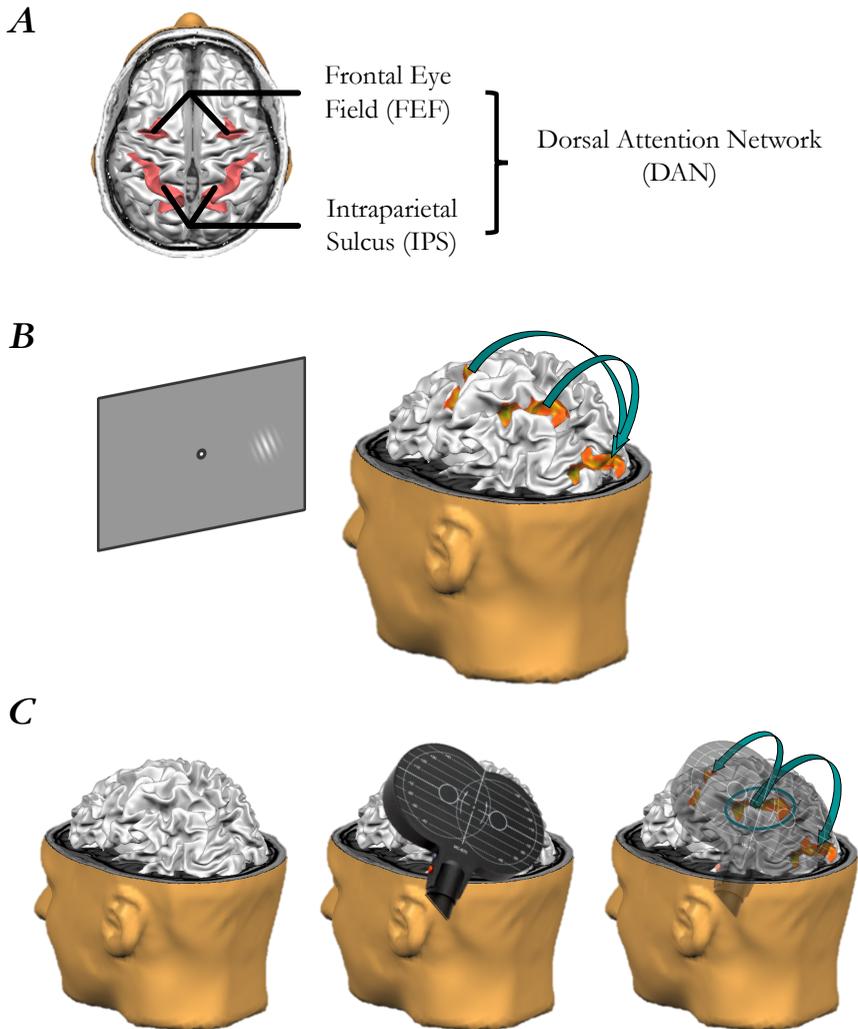
## 1.4 Visual perception and attention rely on information exchange between interconnected brain areas

In the past 30 years, fMRI has been used extensively to measure human brain activation during task performance, with the goal of linking brain activation to specific cognitive processes (Huettel et al., 2004; Ogawa et al., 1990). The voluntary control of visuospatial attention modulated fMRI activation in a set of frontoparietal areas, together named the “Dorsal Attention Network” (DAN) (Chica et al., 2011; Corbetta and Shulman, 2002; Duecker and Sack, 2015; Petersen and Posner, 2012; Szczepanski and Kastner, 2013; Szczepanski et al., 2010; Szczepanski et al., 2013). Most notably, the DAN comprises the frontal eye fields (FEF) and the intraparietal sulcus (IPS) (see Figure 1.6a). fMRI activation in these areas was also linked to behavioral performance, since it could partially explain interindividual differences in attention benefits (Mayrhofer et al., 2019). Besides these higher-level areas, lower-level areas also play a role in visuospatial attention, since activations in visual cortex retinotopically followed the current locus of attention (Brefczynski and DeYoe, 1999; Gandhi et al., 1999; Liu et al., 2005; Somers et al., 1999; Tootell et al., 1998), even in the absence of visual stimuli (Kastner et al., 1999). Interestingly, attention increased the functional connectivity between parietal and visual areas (Lauritzen et al., 2009), and fMRI signals in FEF and IPS predicted fMRI activation in visual areas (Bressler et al., 2008). These findings suggest that higher-level DAN areas top-down modulate lower-level visual areas to achieve the performance benefits that are typically seen for attended compared to unattended visual stimuli (see Figure 1.6b). However, brain activation was merely observed in these studies, instead of externally manipulated. These findings therefore only provided correlational evidence for top-down signal propagation between the DAN and lower-level visual areas. For instance, these studies could not exclude the possibility that activation in DAN and/or early visual areas was an epiphenomenon (i.e., consequence) of visuospatial attention, rather than a prerequisite. This crucial distinction will determine whether top-down signal propagation is essential for visuospatial attention or not.

To investigate whether DAN areas causally modulate visual areas, fMRI can be combined with TMS (see Figure 1.6c) (Driver et al., 2010). As discussed above, TMS is mostly known for its brief disruptive effects, and for its ability to induce longer-lasting changes in neuroplasticity. In the context of this thesis, TMS also serves

another purpose: it can be used as a “system probe”, to assess how signals propagate throughout the brain. The effects of TMS can extend well beyond the targeted brain area, since TMS-induced activations can spread towards interconnected brain areas (Blankenburg et al., 2010; Ruff et al., 2006; Sack et al., 2007). Though the local effects of TMS do not reach deeper than the superficial cortex, remote effects can even be observed in subcortical areas (Bergmann et al., 2021). Simultaneous TMS-fMRI thus gives the unique opportunity to visualize TMS signal propagation throughout the entire brain with good spatial resolution (Bestmann et al., 2008; Reithler et al., 2011; Sack, 2006; Sack and Linden, 2003; Walsh and Cowey, 2000).

Using this simultaneous TMS-fMRI approach, it was established that both the FEF and IPS top-down modulate lower-level visual areas (Ruff et al., 2008; Ruff et al., 2006), and that such top-down signal propagation may enhance visual perception (Ruff et al., 2006). These results were in line with research in macaque monkeys showing that micro-stimulation of FEF increased single cell responses in V4 (Armstrong and Moore, 2007) and modulated fMRI activation in early visual areas (Ekstrom et al., 2008). Taken together, these studies imply that DAN areas and the visual cortex essentially form one distributed and interconnected functional system, which we here refer to as the “vision-attention network”. Interestingly, the top-down interactions in this network can be flexible. For instance, the effect of TMS to posterior parietal cortex on fMRI activation in visual cortex differed as a function of the currently attended hemifield (Blankenburg et al., 2010). Similarly, TMS to FEF led to fMRI activation in the visual cortical area responsible for processing an attended stimulus feature, but not in the visual cortical area responsible for processing an unattended stimulus feature (Heinen et al., 2014).



**Figure 1.6: Brain areas that are involved in voluntary attention shifts.** **A)** Areas of the Dorsal Attention Network (DAN) from a top view. **B)** Reconstructed brain from a structural magnetic resonance imaging (MRI) scan, with superimposed functional MRI data showing activations in frontal, parietal, and visual cortices (created in BrainVoyager software version 22.0). These areas together form the “vision-attention network”, that is typically active during voluntary spatial attention shifts to the contralateral side of space. In the example, the participant is shifting their attention to the target grating stimulus in the right hemifield, causing fMRI activation in the left hemisphere. fMRI studies provided correlational evidence for the involvement of top-down signal propagation from DAN to lower-level visual areas in visuospatial attention. **C)** Simultaneous TMS-fMRI can provide causal evidence that DAN areas top-down modulate visual areas. In the example, TMS is applied to the posterior parietal cortex (middle). Simultaneous fMRI shows activation not only in the targeted area, but also in functionally connected areas such as lower-level visual cortex (right). This activation was not present before the application of TMS (left).

These findings suggest that TMS-induced activations do not spread along a stable, fixed top-down pathway from the DAN towards the same visual cortical area(s). Instead, top-down signal propagation seems to flexibly adjust based on the current attentional context. The so-called “neurocognitive state” of the brain at the time of TMS may thus influence to which brain areas the TMS signals are propagated. This has important implications for the consistency and reproducibility of TMS effects. It shows that we cannot simply assume that there is a standard brain network response to TMS. Perhaps, TMS signal propagation could be better predicted or controlled when the neurocognitive brain state is considered while designing TMS experiments (or treatments). It is conceivable that other neurocognitive brain states may also modulate (TMS) signal propagation. One goal of this thesis was therefore to evaluate TMS signal propagation from the posterior parietal cortex across the whole brain in different neurocognitive states. As a first manipulation of neurocognitive state, we assessed the effect of “eye closure” (eyes open versus eyes closed resting state in the absence of visual inputs) on TMS signal propagation (**Chapter 4**).

## 1.5 The vision-attention network communicates through neuronal alpha oscillations

To summarize, top-down signal propagation from DAN to visual areas is a crucial aspect of visuospatial attention, and signals may spread differently depending on the current neurocognitive brain state. But how can information be communicated along the relevant processing pathways? Communication between different brain areas operates through neuronal oscillations (Buzsáki and Draguhn, 2004; Engel et al., 2001; Fries, 2005). These are waves of activation that occur when groups of neurons fire in a temporally aligned manner. In the noisy brain, two distant brain areas that activate in the same rhythm can affect each other on top of the background noise (created by neurons firing in a non-rhythmic manner, or in another rhythm) (Zhang et al., 2019).

The most dominant brain rhythm is the 7 – 13 Hertz alpha band. This rhythm is particularly prominent in posterior (parieto-occipital) brain regions, and even more so when the eyes are closed compared to open (Berger, 1929, 1933; Quigley, 2021). Neuronal alpha oscillations play a pivotal role in visual perception and

attention (de Graaf et al., 2020; Diepen et al., 2016; Klimesch, 2012; Nelli et al., 2017; Ruzzoli et al., 2019). Visuospatial attention shifts are associated with alpha power modulations in posterior brain areas, with alpha power typically decreasing in the hemisphere contralateral to the attended hemifield (Gallotto et al., 2020; Sauseng et al., 2005). Furthermore, alpha power is negatively related to the excitability of the visual cortex, as measured by its reactivity to single-pulse TMS (Romei, Rihs, et al., 2008; Samaha et al., 2017). Alpha oscillations thus seem to have a primarily inhibitory role (Klimesch et al., 2007; Schneider et al., 2021; Wöstmann et al., 2019). More specifically, it has been proposed that signal propagation is gated by alpha oscillations, by inhibiting the information flow to task-irrelevant brain areas (Jensen and Mazaheri, 2010; Klimesch et al., 2007; Mathewson et al., 2011). In that way, top-down signals from the DAN may be directed towards the lower-level visual areas that are responsible for processing task-relevant information. Yet, oscillatory brain activity was merely measured in these EEG studies, rather than experimentally manipulated. This begs the question whether the connection between alpha oscillations and visuospatial attention is of causal nature or not (Peylo et al., 2021).

As explained previously, this issue can be investigated with tACS. TACS applied to posterior parietal cortex at alpha frequency has been shown to enhance posterior alpha power (Helfrich et al., 2014; W. Huang et al., 2021; Kasten et al., 2016; Kasten and Herrmann, 2017; Neuling et al., 2013; Stecher et al., 2017; Vossen et al., 2015a; Witkowski et al., 2016; Zaehle et al., 2010). If neuronal alpha oscillations would have a causal role in gating the propagation of signals relevant for visuospatial attention, then the enhancement of posterior alpha power by tACS should subsequently affect attention task performance. Such a causal link has indeed been demonstrated in several behavioral paradigms, including the endogenous Posner task (Kasten et al., 2020; Kemmerer et al., 2020; Schuhmann et al., 2019), visual conjunction search (Müller et al., 2015), the Erikson flanker paradigm (Wiesman and Wilson, 2019), and inattentive blindness (Hutchinson et al., 2020). In sum, several studies successfully applied alpha-tACS to enhance the power of neuronal alpha oscillations and to provide causal evidence for the involvement of alpha oscillations in visuospatial attention.

## 1.6 Increasing the consistency of tACS effects by individualizing tACS protocols based on oscillatory markers

Given the widespread use of alpha-tACS in visuospatial attention research (Klink et al., 2020), one might expect that consensus had been reached regarding its effects. Unfortunately, this does not seem to be the case, since not all alpha-tACS results have been positive and consistent (Veniero et al., 2015). For instance, a recent study found no modulations in attention task performance or EEG alpha power after 10 Hertz tACS to posterior parietal cortex (Coldea et al., 2021). Moreover, 10 Hertz tACS modulated visuospatial attention in a line bisection task in a first experiment, but this was not internally replicated in a second experiment (Veniero et al., 2017). These inconsistencies may in part be due to inter-individual variations in the dominant endogenous oscillatory frequency, or “individual alpha frequency” (IAF) (Haegens et al., 2014; Janssens et al., 2021). TACS might only increase posterior alpha power and consequently cause a modulation in task performance if the endogenous oscillatory frequency is closely matched with the driving (tACS) frequency (Feurra et al., 2011; Kemmerer et al., 2020; Klink et al., 2020) – especially since the electric current induced in the brain by tACS (i.e., the effective stimulation intensity) is generally small (Herrmann and Strüber, 2017; Kemmerer et al., 2020; Stecher and Herrmann, 2018).

Increasingly, tACS protocols therefore involve individually calibrated stimulation frequencies (e.g., the IAF) rather than a standard (e.g., 10 Hertz) frequency (Fresnoza et al., 2018; Kasten et al., 2016; Kasten et al., 2020; Vossen et al., 2015b; Zaehle et al., 2010). Typically, IAF is calculated based on a short EEG measurement performed during eyes closed resting state from limited EEG electrodes. IAF-tACS is then often applied across multiple sessions and during a different cognitive state (i.e., during cognitive task performance) (e.g., Kemmerer et al., 2020; Mioni et al., 2020; Ronconi et al., 2018). Though IAF has been shown to be reliable within the same individual over time during resting state (Grandy, Werkle-Bergner, Chicherio, Lövdén, et al., 2013; Grandy, Werkle-Bergner, Chicherio, Schmiedek, et al., 2013), the dominant alpha frequency can fluctuate considerably even over the course of one hour during visual task performance (Benwell et al., 2019). If we aim to use IAF-tACS to enhance the power of neuronal alpha oscillations to establish their relevance for visuospatial attention, it is essential that we target the correct frequency. One of the goals of this thesis was

therefore to establish how the relevant IAF during task can be approximated most reliably in a practically constrained lab setting (**Chapter 5**).

But even if tACS is applied at IAF instead of at a standard (e.g., 10 Hertz) frequency, sometimes there are no detectable effects on alpha power (Fekete et al., 2018), and behavioral results have not always been as expected (de Graaf et al., 2020). Furthermore, even if effects are detected, tACS effect sizes are generally small (Antal et al., 2008; Schutter and Wischnewski, 2016), and there are substantial inter-individual differences in the induced effect (Kasten et al., 2019). The inconsistency of tACS effects is a highly relevant area of research, since tACS is increasingly explored as a treatment strategy for numerous neuropsychiatric disorders (Ahn et al., 2019; Alexander et al., 2019; Daughters et al., 2020; Elyamany et al., 2020; Riddle et al., 2020). Any effort at improving the consistency of tACS effects is thus not only relevant for research, but also in a clinical context. Another aim of this thesis was therefore to develop a more complex, biologically inspired tACS protocol that could potentially have more consistent effects than IAF-tACS (**Chapter 6**).

## 1.7 Moving from standard structure-to-function mapping towards the exploration of dynamic cortico-subcortical brain networks

It is not only tACS effects that show considerable variability: the effects of TMS are also not set in stone (Corp et al., 2021; Corp et al., 2020; Schilberg et al., 2017). For instance, single TMS pulses applied to early visual cortex (EVC) can induce “phosphenes” (illusory percepts) in some individuals, but TMS pulses of the same intensity do not always induce phosphenes. As discussed previously, the neurocognitive brain state can influence the effects of TMS. The “phosphene threshold” (i.e., the minimal TMS intensity required to induce phosphenes in half of the cases) depends on the neurocognitive state (eyes open versus eyes closed) during TMS application (de Graaf et al., 2017). Furthermore, TMS signal propagation throughout the brain depends on the current neurocognitive state (Blankenburg et al., 2010; Heinen et al., 2014).

Besides the neurocognitive brain state, the oscillatory brain state can also influence the effects of TMS. For example, pre-TMS alpha power was inversely related to the probability of TMS inducing phosphenes (Romei, Brodbeck, et al.,

2008; Romei, Rihs, et al., 2008). It is conceivable that TMS signal propagation depends on the oscillatory state as well. This was recently investigated using an innovative and technically challenging simultaneous TMS-EEG-fMRI set-up (Peters et al., 2013). Indeed, TMS-induced fMRI activations within a cortico-subcortical motor network depended on the pre-TMS EEG alpha power (Peters et al., 2020). To better predict or control the brain's network response to TMS, we must gain a thorough understanding of how fluctuations in the oscillatory and neurocognitive brain state contribute to TMS effect variability (Sauseng et al., 2009; Schilberg et al., 2021). This can be especially relevant in clinical settings, when TMS is used to modulate the information flow in the brain to achieve desirable changes in cognition, behavior, and mood (de Graaf, Janssens, et al., 2021; Lefaucheur et al., 2020; Lefaucheur et al., 2014). Therefore, one aim of this thesis was to review the literature that suggests that the variability of TMS effects can in part be attributed to fluctuations in oscillatory brain state, and to discuss how multimodal TMS approaches can be used to account for such fluctuations during TMS (**Chapter 3**).

The early lesion studies discussed in the first section of this General Introduction already noted the association between single brain areas and specific cognitive functions, but it seems that this does not tell the whole story (Rorden and Karnath, 2004). The standard structure-to-function brain mapping approach is inherently limited. Instead, complex cognitive functions most likely involve information exchange within dynamically changing functional brain networks. These dynamic networks are governed by the momentary oscillatory and neurocognitive brain state. Yet, it is not trivial to convincingly demonstrate that signal propagation within the human brain indeed critically depends on the current brain state. One way to potentially achieve this is to employ the technically challenging experimental triad of simultaneous TMS, EEG and fMRI. In this set-up, TMS serves as a direct brain network probe, fMRI can visualize the brain-wide TMS-evoked response with high spatial resolution, and EEG is required to measure the oscillatory brain state at the time of TMS. As explained above, brain state-dependent TMS signal propagation was already shown in the motor system (Peters et al., 2020; Peters et al., 2013). It remains elusive to what extent similar mechanisms are at play in other brain networks, such as the vision-attention network. Thus, another aim of this thesis was to explore signal propagation from a higher-level DAN area as a function of oscillatory and neurocognitive brain state, using the multimodal TMS-EEG-fMRI approach (**Chapter 4**).

## 1.8 The causal relevance of the early visual cortex: the lowest part of the vision-attention network cortical hierarchy

Most chapters of this thesis focus on top-down information exchange between the posterior parietal cortex (PPC) and lower-level areas within the vision-attention network. However, it is also useful to investigate information flow within or through the early visual cortex (EVC): the lowest point of the cortical hierarchy. In essence, TMS can be used to disrupt visual processing at an early stage, to prevent information from flowing along cortical visual pathways unhindered – and it can do so with high temporal precision (Pascual-Leone et al., 2000). This approach allows us to understand the role of the EVC within the vision-attention network, and to causally relate its activity to cognitive processes such as visual perception and attention. For instance, performance in visual tasks such as orientation discrimination is impaired when TMS is delivered to EVC at around 70 – 130 msec after stimulus onset (e.g., Amassian et al., 1989; Masur et al., 1993; Potts et al., 1998, for reviews see de Graaf et al., 2014; Kammer, 2007a, 2007b). This indicates that EVC is causally relevant for low-level visual perception within that period of time.

Interestingly, several studies reported a dissociation between the effects of TMS on objective versus subjective processing of the same visual stimuli, which can capture either unconscious versus conscious processing, respectively (Boyer et al., 2005; Jolij and Lamme, 2005; Koenig and Ro, 2018; Ro et al., 2004). More specifically, while the subjective perception of stimulus features (as measured by visibility ratings) was impaired by TMS to EVC, the objective (forced-choice) performance was preserved. The investigated stimuli were highly evolutionarily relevant, as they involved emotional expressions. These types of stimuli can normally be processed even with extremely short stimulus presentation times (de Gelder et al., 2001). It would be evolutionarily beneficial to process such salient stimuli as quickly and as efficiently as possible, and it therefore makes sense that such signals might bypass the EVC to take a faster (e.g., subcortical) route within the brain. While this has been shown for emotional facial expressions, it has not yet been established for facial properties characterized by a more complex arrangement of features, such as trustworthiness. The final aim of this thesis was therefore to establish whether the processing of face trustworthiness can occur without EVC or not (**Chapter 7**).

## 1.9 Outline of the thesis

Visual perception and attention involve information exchange between the DAN and lower-level areas such as the EVC. This thesis explores how signals propagate within this vision-attention network, and how neuronal alpha oscillations are involved in gating those signals. It presents a multimodal approach, as it combines psychophysics, eyetracking, non-invasive brain stimulation (TMS and tACS), and neuroimaging (fMRI and EEG). It furthermore assesses the roles of oscillatory and neurocognitive state in the variability of NIBS effects.

### 1.9.1 Part I: Signal propagation within the vision-attention network

The first part of this thesis explores how parietal and visual cortex exchange information. In **Chapter 2**, we aimed to develop a behavioral paradigm to isolate (i.e., specifically modulate) top-down neuronal sub-systems responsible for voluntary covert attention shifts to particular locations in space. It was based on the concept of “neuronal adaptation”, in which repeated activation of neurons leads to a suppression of their baseline activation, and consequently a decrease in behavioral performance (in tasks requiring the adapted neurons) (Clifford et al., 2007; Sanchez-Vives et al., 2000; Webster, 2011). We hypothesized that repeated attention shifts to a certain location in space should decrease attention task performance specifically at that (adapted) location. Our first aim was to develop and test this paradigm with behavioral and eyetracking measurements in three experiments. Our second aim was to apply this paradigm to two unresolved questions in the spatial attention literature, namely, the question whether covert and overt attention share the same underlying neuronal mechanisms, and the question how spatial attention moves through visual space.

**Chapter 3** presents an overview of the literature regarding inter- and intra-subject variability of TMS effects in research and clinical settings. It distinguishes between immediate TMS effects (such as cortical reactivity/excitability to TMS, and TMS signal propagation), and TMS aftereffects (long-lasting changes in neuroplasticity). It posits that spontaneous fluctuations in neuronal oscillations play an important role in the variability of TMS effects. It highlights the importance of individually calibrating TMS protocols to oscillatory markers and explains how this can be achieved using simultaneous tACS-TMS or

closed-loop M/EEG-based TMS.

Though the relevance of momentary oscillatory state and neurocognitive state has been established for TMS signal propagation within the motor network, it is not yet clear whether similar mechanisms are at play for other brain networks. In **Chapter 4**, we therefore used simultaneous TMS-EEG-fMRI to assess how TMS pulses spread within the vision-attention network, from posterior parietal cortex to other functionally connected brain areas, as a function of oscillatory state (pre-TMS alpha power) and neurocognitive state (eyes open or eyes closed in the absence of visual inputs).

### 1.9.2 Part II: Neuronal alpha oscillations within the vision-attention network

After evaluating how behavioral and multimodal TMS paradigms can be used to investigate signal propagation across the vision-attention network, the question becomes how such signal propagation can be controlled by the brain. The second part of this thesis focuses on the role of neuronal alpha oscillations as a gating/communication mechanism within the vision-attention network. As explained previously, the causal role of neuronal oscillations can be established with rhythmic stimulation protocols such as tACS. But before we can study such oscillatory interactions, it is crucial to investigate which exact stimulation frequency we should use in our experiments. Alpha-tACS has already been applied at IAF instead of the standard 10 Hertz. IAF is often measured once during resting state from limited M/EEG electrodes, and then applied over the duration of a session and across different days, during a different cognitive state (e.g., attention task performance). It is unclear how (in)accurate this approach is. In **Chapter 5**, we therefore investigated how best to calibrate rhythmic stimulation protocols to individual oscillatory markers, such as IAF. To evaluate this, we assessed IAF consistency within and between days, in two cognitive states (attention task versus eyes closed resting state), and from the two hemispheres. We furthermore compared two analysis methods for calculating IAF: the traditional “maximum” method, and a “Gaussian fit” approach.

Though IAF-tACS is superior to 10 Hertz-tACS, its effects have been inconsistent and difficult to replicate. In **Chapter 6**, we investigated whether a more complex, biologically calibrated tACS protocol might show more consistent

effects. Human EEG power spectra typically show alpha peaks that contain more than just a single frequency. Incorporating this full range of frequencies within our tACS protocol might target a larger pool of functionally relevant neurons, and thereby produce larger net effects on alpha power and/or attention task performance. We therefore developed a “broadband” tACS protocol to stimulate the entire alpha range ( $\text{IAF} \pm 2$  Hertz) from the individual EEG power spectrum measured during resting state. We compared the effects of broadband tACS versus sham (ineffective) tACS to the effects of IAF-tACS and alpha-removed tACS (which essentially was the opposite of the broadband tACS protocol). We expected that broadband tACS should lead to the most consistent shift in spatial attention and/or modulation of posterior EEG alpha power.

### 1.9.3 Part III: The causal role of the early visual cortex

In the third part of this thesis, we go back to the beginning of the cortical hierarchy, to further investigate the role of the EVC. Though often studied, it was still unclear whether EVC is causally involved in (un)conscious processing of highly relevant stimuli such as (un)trustworthy faces, or whether such information can bypass EVC via other pathways. In **Chapter 7**, we employed a TMS masking paradigm to address this question. More specifically, we shortly presented rotated (un)trustworthy face stimuli while applying TMS to EVC at stimulus onset asynchronies (SOAs) of 50, 100, 150 msec, or not at all. We expected that TMS to EVC should decrease rotation (control) task performance and subjective visibility of trustworthiness at the 100 msec SOA compared to no TMS. If objective trustworthiness processing can bypass EVC, then TMS to EVC should not influence forced-choice discrimination performance. By contrast, if EVC cannot be bypassed, objective (forced-choice) trustworthiness performance should be impaired by TMS to EVC at the 100 msec SOA. This chapter highlights how behavioral TMS studies might be used to draw conclusions about which path signals take within the brain. It furthermore demonstrates that the network approach to human brain mapping is not complete without the investigation of lower-level brain areas.

Finally, **Chapter 8** summarizes the main findings of this thesis, discusses them in a broader context, and highlights their potential implications for fundamental and applied science.

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## *Chapter 2*

**Developing an adaptation  
paradigm to isolate neuronal  
subsystems underlying visual  
attention shifts**

## 2.1 Abstract

The state of our brain fluctuates spontaneously and constantly. Brain state fluctuations can be measured using neuroimaging and can subsequently be related to behavior, to understand their functional relevance. But a more experimentally controlled approach is to *manipulate* brain state, for instance by using “neuronal adaptation”: a paradigm in which specific neuronal sub-systems can be isolated by selectively fatiguing them. Here, we aimed to develop a *cognitive* adaptation paradigm for the study of endogenous attentional control. If successful, this paradigm can be used to tackle unanswered neuroscientific questions, such as how attention moves through visual space. In three experiments, participants repeatedly and covertly shifted their attention to a specific location in space (“adaptation phase”) or fixated centrally without shifting their attention (“fixation phase”). After each adaptation/fixation phase, participants performed 12 endogenous attention task trials, reporting as quickly and as accurately as possible the orientation of a briefly presented grating stimulus. If attention can indeed be adapted, then endogenous attention task performance should be worsened compared to baseline (fixation) performance at specifically the adapted location. Unfortunately, we could not reveal consistent adaptation affects across the three experiments. We provide suggestions to improve the attention adaptation paradigm and propose ways to better control participants’ covert attention shifts. We furthermore highlight the potential benefits of combining attention adaptation with transcranial magnetic stimulation (TMS), to improve behavioral performance and to enhance the spatial resolution of TMS.

### *Key words*

Visuospatial attention; neuronal adaptation; state-dependency; covert attention; overt attention; eyetracking.

## 2.2 Introduction

Neuroscientific research has a long history of mapping specific cognitive functions to certain brain areas (Poldrack, 2010). It has become increasingly clear that, in order to fully understand brain-behavior relationships, we must take into account the concept of “state dependency”, because brain areas generally do not have a single, stable function (Silvanto, Muggleton, Kwong, et al., 2008). Instead, they can flexibly adjust according to current environmental needs, internal goals, and current task demands. This is true even at the level of single neurons. For instance, it has been shown that receptive fields are not necessarily a stable property of individual visual cortical cells – they can be dynamic, being influenced by factors such as spatial attention, overall vigilance, and the spatial and temporal context of the presented stimuli (Wörgötter and Eysel, 2000). Fluctuations in brain state should thus not be regarded as mere nuisance factors, but as meaningful contributors to the functional organization of the brain.

To understand their functional contributions, we first must *measure* changes in brain state using neuroimaging methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). We can then include such measurements into our statistical analysis models. This approach enables us to investigate whether any behavioral or neural effects are linked to the current brain state, but it does not offer much experimental control. An intriguing alternative approach is therefore to *manipulate* the state of the brain rather than to measure it. For instance, experimental paradigms using adaptation exploit brain state-dependent effects to isolate (i.e., specifically target) certain neuronal sub-systems to unravel their functional properties (Bradley et al., 1988).

Traditionally, adaptation has been used to characterize the functions of sensory brain areas (Engel, 2005; Kohn, 2007; Webster, 2011, 2012). After prolonged exposure to a stimulus, the neurons encoding certain features of that stimulus will lower their baseline firing rates. For example, after presenting a high contrast grating, neurons that are selective to contrast showed decreased activity in cat primary visual cortex (Carandini and Ferster, 1997; Sanchez-Vives et al., 2000). Subsequently, such neuronal changes can lead to perceptual and behavioral changes (Clifford et al., 2007). After adaptation to a certain direction of motion, for instance, we tend to perceive a still image as moving in the opposite direction

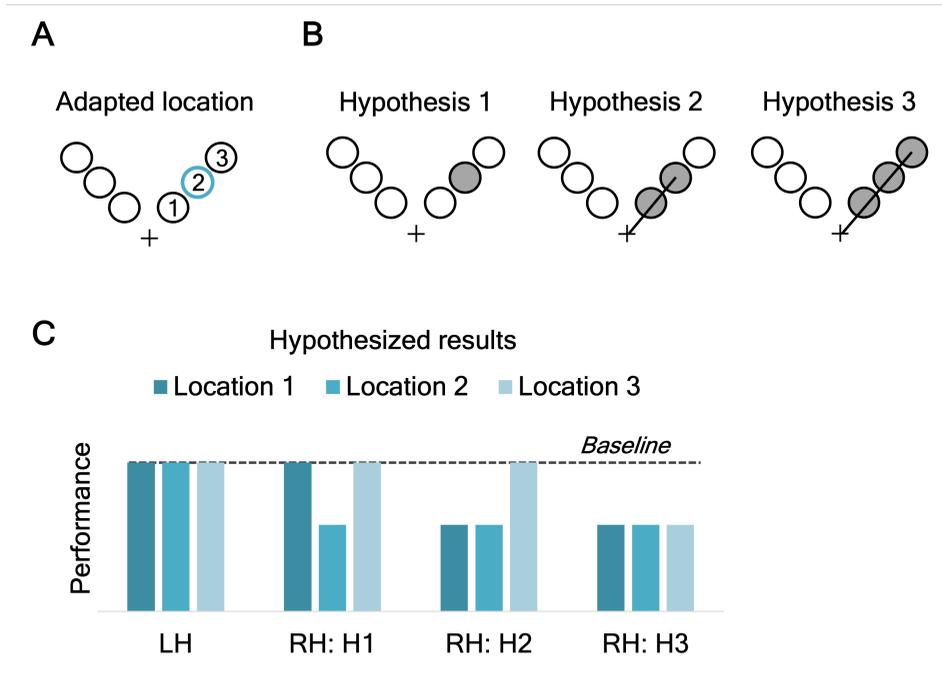
as the adapting stimulus, and we become worse at detecting the adapted motion direction (Z. Cattaneo and Silvanto, 2008a). Besides its utility for studying low-level sensory processing, the adaptation paradigm has also been extended to more abstract and higher order cognitive functions. Examples include the domains of face perception (Webster et al., 2004), number processing (Kadosh et al., 2010), short term memory (Saad and Silvanto, 2013), mental imagery (Z. Cattaneo et al., 2012), the processing of affective body movements (Mazzoni et al., 2017), abstract letter selectivity (Z. Cattaneo et al., 2009), spoken language processing (Pattamadilok et al., 2019), and processing of observed acts (L. Cattaneo et al., 2010).

Although these studies showed that complex cognitive functions can be adapted, they all involved “passive” adaptation in the sense that a stimulus was being presented. It remains to be investigated to what extent adaptation can be applied to cognitive processes that are fully internal, or willfully performed. For instance, as with any cognitive function, the ability to endogenously and covertly shift attention to certain locations in space is enabled by specific neuronal subsystems. In theory, such higher-level neuronal subsystems might also become over-stimulated after repeated activation, and as a result, become adapted (i.e., fatigued). The current chapter presents three behavioral experiments that test this proposal using a novel “attention adaptation” paradigm. We speculated that repeated attention shifts to a certain location in space could lead to adaptation of the underlying neuronal subsystems responsible for covertly shifting attention to that location. Consequently, performance should then decrease in tasks requiring spatial attention shifts to the adapted location. For example, repeated endogenous attention shifts from left to right might impact subsequent attention allocation in specifically those directions, as compared to vertical attention shifts. In Experiments 1 and 2, we investigated whether our newly developed attention adaptation paradigm could indeed induce spatially specific performance decreases in an endogenous cueing task (Posner, 1980; Posner et al., 1980).

If successful, this methodology can be used to investigate various open issues. For instance, it has been shown that the center of visuospatial attention moves across space (Zhou et al., 2017), but it is not yet clear how exactly this happens. There are three plausible, mutually exclusive answers to this question (see Figure 2.1b). The first possibility is that spatial attention “jumps” across locations in the visual field.

This idea is based on previous studies showing that parietal and frontal cortices contain topographic maps of attention (Silver and Kastner, 2009; Silver et al., 2005). Attention might act by activating subsections of these maps which then send top-down signals to retinotopically corresponding early visual areas (Brefczynski and DeYoe, 1999; Kastner et al., 1999; Tootell et al., 1998). Depending on the spatial resolution of these top-down connections, attention might indeed “jump” across the visual field. A second possibility is that attention spreads along a path, affecting all locations leading up to a certain target location. This idea is inspired by the spotlight theory of attention, which postulates that attention acts like a flashlight moving across space (LaBerge, 1983; Posner et al., 1980), and by the fact that activity within visual cortical areas gradually spreads across the representation of objects (Houtkamp et al., 2003; Pooremaeili and Roelfsema, 2014; Wannig et al., 2011). The third possibility is that attention enhances an entire directional axis. This theory is based on the fact that processing of orientation and motion are governed by similar computational mechanisms (Clifford, 2002), and neuronal selectivity for entire axes of motion has been shown (Dubner and Zeki, 1971; Zimmermann et al., 2011).

In Experiment 3, we employ the attention adaptation paradigm to test which of these three theories is most likely. Each theory leads to a different prediction in terms of behavioral effects following adaptation of attention to a specific location (see Figure 2.1c). If attention were to jump across visual space, performance should decrease specifically at the adapted location. If attention were to spread along a path, performance should decrease at the locations leading up to and including the adapted location. If attention were to enhance a directional axis, performance should decrease at locations within the same directional axis as the adapted location.



**Figure 2.1: Different ways in which covert visuospatial attention might move across space. A) Stimuli and (example) adapted location.** A fixation cross and six peripheral placeholder circles are shown: three in the left hemifield and three in the right hemifield, at three different eccentricities. The circles in the right hemifield are numbered for illustrative purposes (not shown on the computer screen). In this example, the second location in the right hemifield is adapted (highlighted in blue for illustration). **B) Three mutually exclusive hypotheses.** When a participant is fixating on the cross and moves their covert locus of attention to the second location in the right hemifield, three different things might happen. In Hypothesis 1, attention “jumps” directly to the location of interest. In Hypothesis 2, attention spreads along a path towards the location of interest. In Hypothesis 3, attention enhances the entire directional axis. The grey circles indicate those spatial locations that would be affected by adaptation to the second location in the right hemifield, according to the three hypotheses. **C) Hypothesized behavioral results after adapting attention to the second location in the right hemifield.** All three hypotheses predict that attention task performance in the left hemifield (“LH”) is unaffected by adaptation of attention to a location in the right hemifield (“RH”). Hypothesis 1 (“H1”) predicts that attention task performance decreases specifically at the adapted location (Location 2). Hypothesis 2 (“H2”) predicts that attention task performance decreases at all locations leading up to, and including, the adapted location (Locations 1 and 2). Hypothesis 3 predicts that attention task performance decreases at all locations on the same directional axis as the adapted location (Locations 1, 2, and 3).

As another example, the attention adaptation paradigm can be used to help resolve the longstanding debate about the relation between overt (with eye movements) and covert (without eye movements) visuospatial attention (Hunt and Kingstone, 2003). The premotor theory of attention postulates that overt and covert attention share the same underlying neuronal mechanisms (Rizzolatti et al., 1987). Multiple neuroimaging studies indeed show overlapping brain areas to be

active when participants were overtly or covertly attending to particular stimuli (Beauchamp et al., 2001; Corbetta et al., 1998; Haan et al., 2008; Nobre et al., 2000; Perry and Zeki, 2000). However, it could still be the case that overt and covert attention rely on different neuronal subpopulations within the same brain area (Juan et al., 2004). Indeed, it has been shown that the frontal eye fields (FEF) contain neurons that are active only during covert attention shifts or only during overt attention shifts (Schall, 2002; Thompson et al., 2005). At the same time, though, other neurons are active during both covert and overt attention shifts (Colby et al., 1996; Snyder et al., 1997). Other support for the premotor theory came from micro-stimulation studies showing that neurons within FEF are involved in both overt and covert attention (Moore and Fallah, 2000, 2004; Wardak et al., 2006). Nevertheless, the premotor theory predicts that covert attention is equivalent to saccade preparation (Smith, 2012), but evidence showed that covert attention shifts are not always accompanied by saccade preparation (Belopolsky and Theeuwes, 2012). Clearly, it remains unclear to which extent overt and covert attention share the same neuronal mechanisms. The attention adaptation paradigm could be used to investigate this issue, since even overlapping neuronal populations can be segregated with this approach (Z. Cattaneo et al., 2012; Renzi et al., 2011; Yee et al., 2010). If overt and covert attention share the same underlying neuronal substrates, then adaptation of covert attention should lead to changes in overt attention. By contrast, if they rely on different neuronal mechanisms, then adaptation of covert attention should not affect overt attention. In all three experiments, we test these contrasting predictions by assessing fixation stability (i.e., a measure of overt attention) within our covert attention adaptation paradigm.

In sum, we innovated an adaptation paradigm and applied it in a novel setting, targeting a high-level internal cognitive process. We explored in various ways whether this paradigm can be used to study the neuronal mechanisms underlying endogenous visuospatial attention in the human brain. Firstly, we investigated whether adaptation can indeed be used to affect attention task performance at specific locations in space (*Experiments 1 & 2*). We then used the attention adaptation paradigm to explore how attention moves through visual space (*Experiment 3*). Lastly, we exploited the attention adaptation paradigm to investigate whether overt and covert visuospatial attention share the same underlying neuronal mechanisms (*Experiments 1, 2, & 3*).

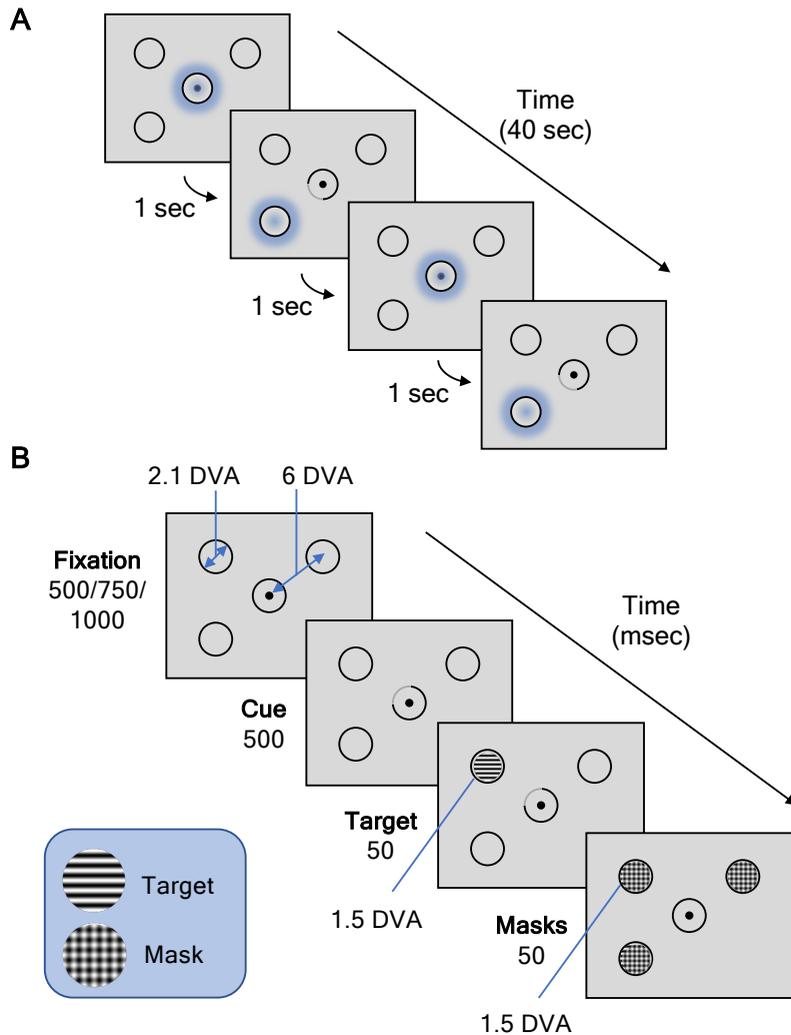
## 2.3 Experiment 1: Materials and Methods

### Participants

Twenty-one healthy volunteers participated in this experiment (5 males, ages 19 – 31). All participants had (corrected to) normal vision and provided written informed consent. The local ethical committee approved the experiment. Participants were compensated with either 1 participation credit or 7.50 euros in vouchers per hour.

### Stimuli, Tasks and Design

In two 1.5-hour sessions, participants performed a newly developed “attention adaptation” task. The visual display consisted of a fixation dot with one central and three peripheral placeholder circles. Participants were instructed to covertly shift their attention to certain spatial locations by means of a central cue. More specifically, participants covertly shifted their attention from central fixation to a peripheral location and back, for 40 seconds (see Figure 2.2a). During this adaptation phase, attention could be shifted to and from the lower left, upper left or upper right location, or not at all (fixation/baseline). After each adaptation phase, participants performed 12 orientation discrimination trials (see Figure 2.2b). Orientation discrimination involved a two-alternative forced-choice (2AFC) task, indicating as quickly and as accurately as possible by button press whether the grating stimulus was horizontally or vertically oriented. In each trial, the appearance of a target grating was preceded by either a valid or a neutral cue (factor “cue type” with two levels). A grating stimulus was then shortly presented at the lower left, upper left or upper right location (factor “stimulus location” with three levels). The grating stimulus could be presented at the previously adapted location (“adapted”), at a different location than the adapted location (“other-adapted”), or after a 40-second fixation period without covert attention shifts (“fixation”). We expected that orientation discrimination performance would decrease specifically at adapted locations as compared to baseline. To prevent floor and ceiling effects, grating contrast was individually calibrated prior to the main task. Eye movement data were collected to exclude trials containing saccades and blinks, to assess fixation stability during the adaptation phase, and to investigate whether adaptation of covert attention affected subsequent overt attention.



**Figure 2.2: Attention Adaptation Paradigm. A) Example adaptation phase.** Participants covertly shifted their attention from central fixation to a peripheral location and back for 40 seconds, with a switching rate of 1 per second. Brightening of one quarter of the central circle served as a cue to shift attention to the indicated location. Absence of the cue instructed participants to attend to the center. The blue circle represents the locus of covert spatial attention. **B) Example orientation discrimination trial.** After each adaptation phase, participants performed 12 orientation discrimination trials. After a randomly varied inter-trial fixation period, a cue appeared for 500 msec. This cue could either be valid, indicating where the target would appear (as in this example), or neutral (i.e., brightening of the entire central circle) in which case it provided temporal but not spatial information. A horizontally or vertically oriented target grating was then presented for 50 msec. Mask stimuli were presented for 50 msec at all peripheral locations. Participants reported target orientation as quickly and as accurately as possible. The placeholder circles were placed at 6 degrees visual angle (DVA) eccentricity diagonally from the fixation dot, and were 2.1 DVA in diameter, as indicated by the blue arrows (not shown on the computer screen, only for illustrative purposes).

## Procedures

Stimuli were presented on a 24 inch monitor (resolution 1920 x 1080 pixels) with a 60 Hertz refresh rate using MATLAB Version 2017a (The MathWorks, Inc., Natick, Massachusetts, United States) and the Psychophysics Toolbox (Brainard, 1997). A black fixation dot of 0.1 degrees visual angle (DVA) was presented on a gamma-corrected uniform grey background of  $107 \text{ cd/m}^2$ . Participants rested their heads in a chin rest at 65 cm distance from the screen, fixating at all times. The visual display furthermore contained one central and three peripheral placeholder circles (lower left, upper left, upper right) with a diameter of 2.1 DVA (see Figure 2.2). The peripheral placeholder circles were centered at 6 DVA eccentricity (diagonally) from the screen center. Target stimuli were horizontally or vertically oriented sinusoidal gratings with a diameter of 1.5 DVA and a spatial frequency of 2.5 cycles/DVA. Participants reported target orientation as quickly and as accurately as possible by pressing the “left arrow” or “down arrow” button for horizontal and vertical stimuli, respectively. During the main task, an EyeLink1000 camera (SR Research, Mississauga, Ontario, Canada) was used to track gaze position of the right eye with 1000 Hertz sampling rate.

Stimulus contrast was individually calibrated prior to the main task to prevent floor and ceiling effects and to ensure similar task difficulty across participants. We determined the required grating contrast for 75% 2AFC orientation discrimination performance using psychophysical staircases. To this aim, Quest (Watson and Pelli, 1983) was used with the following parameters: starting contrast level  $^{10}\log(20)$ ,  $SD = 20$ ,  $\beta = 3.5$ ,  $\delta = 0.01$ , and  $\gamma = 0.5$ . Each trial started with a randomly selected fixation period of 500, 750, or 1000 msec (see Figure 2.2). Afterwards, a valid cue (brightening of a quarter of the center circle) was presented for 500 msec, instructing the participant to covertly shift their attention to the indicated location. A target grating then appeared at the cued location for 50 msec. Mask stimuli of 0.8 Michelson contrast were presented for 50 msec at all peripheral locations to prevent a target afterimage. If participants responded within 1.7 seconds after target onset, target contrast was adjusted by Quest (increasing or decreasing target contrast after false or correct responses, respectively). The task contained 32 trials per peripheral location, 96 trials in total, and lasted about five minutes. The task was repeated twice or thrice per participant to serve as practice for the main task and to average the resulting contrast values for a more accurate result. We plotted orientation test

values over trials, and if staircases did not converge to a stable value they were excluded from the average. The resulting averaged contrast value was used for the target gratings presented in the main task.

The main task consisted of two alternating blocks: an “adaptation phase” (see Figure 2.2a) followed by 12 orientation discrimination trials (see Figure 2.2b). The adaptation phase was announced on screen with the words “attention shifts” (27 out of 34 blocks) or “fixation” (7 out of 34 blocks). In the first case, participants covertly shifted their attention from central fixation to a cued peripheral location and back, every second for 40 seconds. Brightening of one quarter of the central circle instructed participants to covertly shift their attention to the indicated location. Disappearance of this cue instructed participants to shift their attention back to the center. In the second case, participants fixated for 40 seconds without making covert attention shifts, thereby serving as the baseline condition. In principle, no responses were required during the adaptation phases, but in six “attention shifts” blocks (two blocks per peripheral location) we still presented a grating stimulus at the cued location. If a grating was presented during the adaptation phase, participants were required to respond as quickly and as accurately as possible, using the same keys as in the stimulus calibration task. These trials were included to ensure that participants were paying attention and complying with task instructions, and all participants indeed responded to these catch stimuli.

After each adaptation phase, participants performed 12 trials of the endogenous cueing task described above. The exact duration of these 12 attention task trials depended on participants’ reaction times, but was on average approximately 25 seconds. The number of trials was based on previously reported adaptation effect durations, which lasted at least 30-35 seconds, with some reports of durations up to 120 seconds (Z. Cattaneo and Silvanto, 2008b; Guzman-Lopez et al., 2011; Silvanto, Muggleton, and Walsh, 2008). In this 2AFC orientation discrimination task, half of the cues was valid, and the other half was neutral (brightening of the entire central circle), the latter providing a temporal but not a spatial cue. Each block contained four trials per peripheral location in random order. Half of the gratings were oriented horizontally, the other half vertically. We recorded both response accuracy (proportion of trials in which target grating orientation was correctly reported) and reaction time in msec (RT; defined as the time between stimulus onset and the participant’s button press). The task consisted

of 408 trials, divided over 34 blocks, with self-paced breaks after each three blocks, and lasted about 45 minutes in total. One session lasted approximately 1.5 hours and participants took part in two identical sessions, leading to a total of 916 trials per participant and at least 28 trials per condition.

## Analyses

Behavioral data were analyzed using MATLAB Version 2017a, Python 3 and SPSS Version 24 (IBM Corp., Armonk, New York, United States). The EyeLink1000 system automatically detects onsets and offsets of saccades and blinks. We only took into account saccades with an amplitude of minimally 1 DVA and blinks with a duration of at least 50 msec. Trials containing blinks and/or saccades during presentation of the cue and/or target stimulus were excluded (number of removed trials:  $M = 26$ ,  $median = 13$ ,  $SD = 33.14$ ). The dependent variable of interest was inverse efficiency (IE), defined by dividing RT by the proportion of correct trials, thereby providing a combined measure of performance (Bruyer and Brysbaert, 2011; Vandierendonck, 2018). For completeness and transparency, we also included RT and the proportion of correct trials as dependent variables. We excluded participants from the analysis if the remaining number of trials and/or overall performance (on any dependent variable) was more than two standard deviations away from the mean. Using this outlier removal criterion, 19 participants were included in the analyses. The condition means of the three dependent variables were compared with three-way repeated measures ANOVAs with the factors “Stimulus Location” (lower left, upper left, upper right), “Cue Type” (valid, neutral) and “Adaptation Condition” (adapted, other-adapted, baseline). Significant interactions were followed by simple effects analyses, and Bonferroni-corrected pairwise comparisons were conducted where necessary.

Since the current study aimed to adapt covert visuospatial attention systems, it is important to assess whether participants were fixating properly during the adaptation phase. Fixation stability should not significantly differ between adaptation phases in which participants were making covert attention shifts (i.e., to the lower left, upper left, and upper right locations) versus adaptation phases in which participants were instructed to not make any attention shifts (fixation/baseline). Several fixation stability measures have been reported in the literature and there is no consensus yet about the most valid or sensitive measure

(Castet and Crossland, 2012; Holmqvist et al., 2011; Thaler et al., 2013). We therefore calculated three different fixation stability metrics and compared these across the different adaptation phases using separate one-way repeated measures ANOVAs. As a first metric for fixation stability, we calculated the number of saccades in each 40-second adaptation phase. We furthermore calculated the standard deviation of eye gaze position on the horizontal and vertical meridian across eyetracking samples, excluding saccades. Lastly, we calculated the proportion of samples in which eye gaze position was within 1 degree of central fixation, excluding saccades.

As anticipated in the Introduction, we furthermore investigated whether manipulation of covert visuospatial attention (during the “adaptation” phase) could affect subsequent overt visuospatial attention metrics (during the “trials” phase). If adaptation of covert attention would indeed influence overt attention, this would provide evidence for shared underlying neuronal mechanisms. To this aim, we used one-way repeated measures ANOVAs to assess whether fixation stability during the trials phase depended on the preceding adaptation phase (lower left, upper left, upper right, or fixation/baseline). Note that we did not use the number of saccades as a fixation stability metric in these analyses, since most trials contained no saccades.

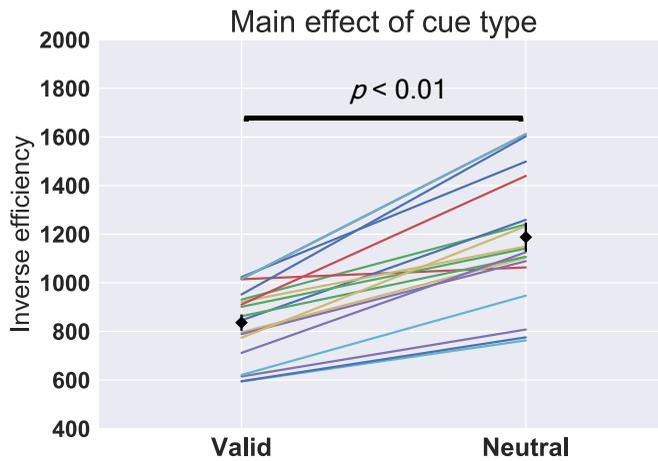
## 2.4 Experiment 1: Results

In a “Stimulus Location” (lower left, upper left, upper right) by “Cue Type” (valid, neutral) by “Adaptation Condition” (“adapted”: adaptation location and stimulus location are the same, “other-adapted”: adaptation location and stimulus location are different, “baseline”: no adaptation but fixation) within-subjects design, participants repeatedly performed a 40-second adaptation phase followed by 12 orientation discrimination trials. Dependent variables were inverse efficiency (IE), reaction times (RT), and the proportion of correct trials, each reported separately below.

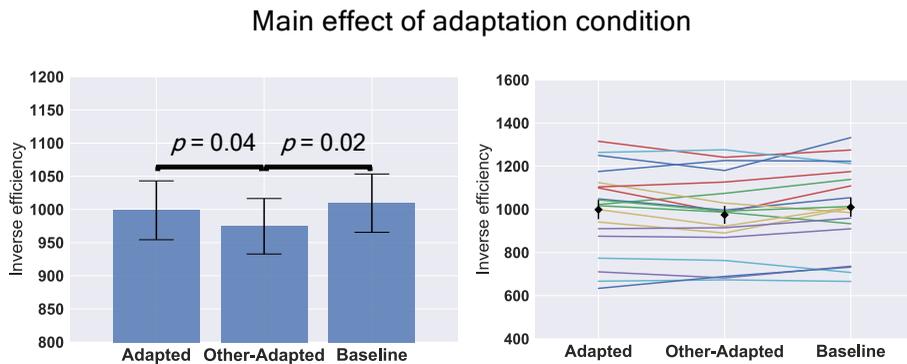
### Inverse efficiency

A  $3 \times 2 \times 3$  repeated-measures ANOVA did not show any significant interaction effects (all  $p$ 's  $> 0.10$ ). There was a significant main effect of “Cue Type” ( $F(1,18) = 88.75$ ,  $p < .001$ ,  $\eta_p^2 = 0.83$ ). Figure 2.3 shows the individual and mean IE scores over cue types. Participants performed significantly better (i.e., had lower IE scores) in valid trials ( $M = 855.64$ ,  $SD = 164.16$ ) as compared to neutral trials ( $M = 1227.95$ ,  $SD = 280.81$ ), replicating the well-established attention benefits effect (Posner, 1980; Posner et al., 1980). This indicates that, in our novel paradigm, participants were able to use the central symbolic cue to covertly shift their attention to the indicated location, thereby performing better compared to when no spatial cue was provided.

There was a significant main effect of “Adaptation Condition” ( $F(2,17) = 6.48$ ,  $p = .010$ ,  $\eta_p^2 = 0.43$ ). We expected decreased 2AFC orientation discrimination performance (higher IE scores) after adaptation as compared to baseline. Contrary to our hypothesis, Bonferroni-corrected paired t-tests showed better performance in other-adapted trials ( $M = 1013.58$ ,  $SD = 204.62$ ) as compared to baseline ( $M = 1059.09$ ,  $SD = 214.56$ ,  $t(18) = 2.73$ ,  $p = .040$ , two-tailed) and adapted trials ( $M = 1052.72$ ,  $SD = 229.91$ ,  $t(18) = 3.03$ ,  $p = .020$ , two-tailed). In other words, after adapting attention to a specific location, participants performed better at the other locations (see Figure 2.4).



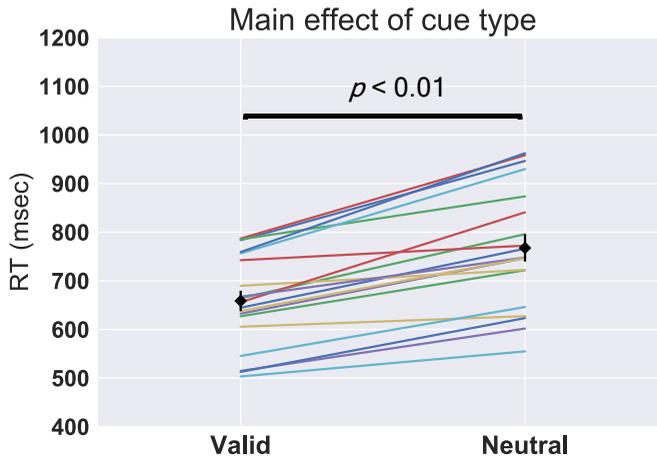
**Figure 2.3: Individual and mean inverse efficiency (IE) scores over cue types.** Error bars are standard errors of the mean (SEM),  $p$ -value is two-tailed.



**Figure 2.4: Mean and individual inverse efficiency scores (IE) over adaptation conditions.** Error bars are standard errors of the mean (SEM).  $P$ -values are two-tailed and Bonferroni-corrected.

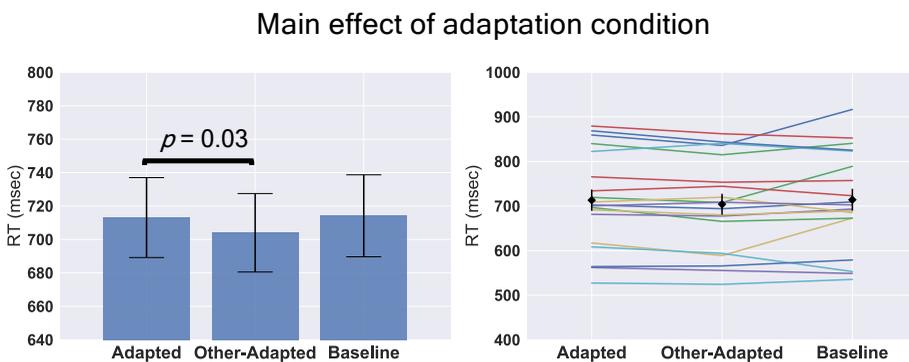
### Reaction times

A three-way repeated measures ANOVA showed no significant interaction effects (all  $p$ 's  $> 0.10$ ). There was a significant main effect of "Cue Type" ( $F(1,18) = 80.29$ ,  $p < .001$ ,  $\eta_p^2 = 0.82$ ). As expected, participants were significantly faster in valid ( $M = 663.54$ ,  $SD = 96.92$ ) as compared to neutral trials ( $M = 771.31$ ,  $SD = 126.30$ ) (see Figure 2.5).



**Figure 2.5: Individual and mean reaction time (RT) scores over cue types.** Error bars are standard errors of the mean (SEM),  $p$ -value is two-tailed.

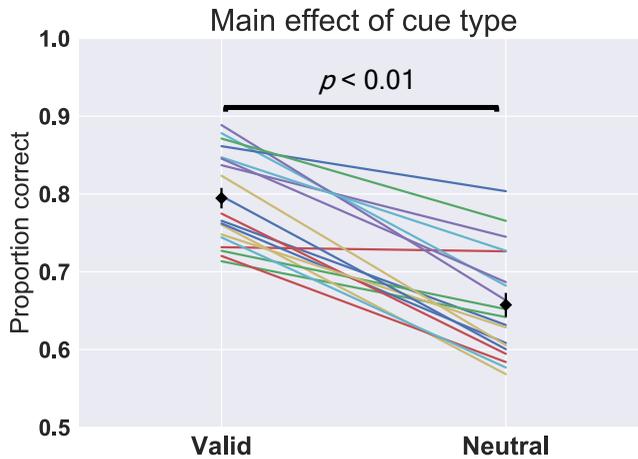
Furthermore, a significant main effect of “Adaptation Condition” was found ( $F(2,17) = 4.17, p = .030, \eta_p^2 = 0.33$ ). RTs were significantly lower in other-adapted ( $M = 720.21, SD = 111.73$ ) as compared to adapted trials ( $M = 710.81, SD = 108.56, t(18) = 2.94, p = .030$ , two-tailed) (see Figure 2.6), which is in line with the IE results described above.



**Figure 2.6: Mean and individual reaction time (RT) scores over adaptation conditions.** Error bars are standard errors of the mean (SEM). The  $p$ -value is two-tailed and Bonferroni-corrected.

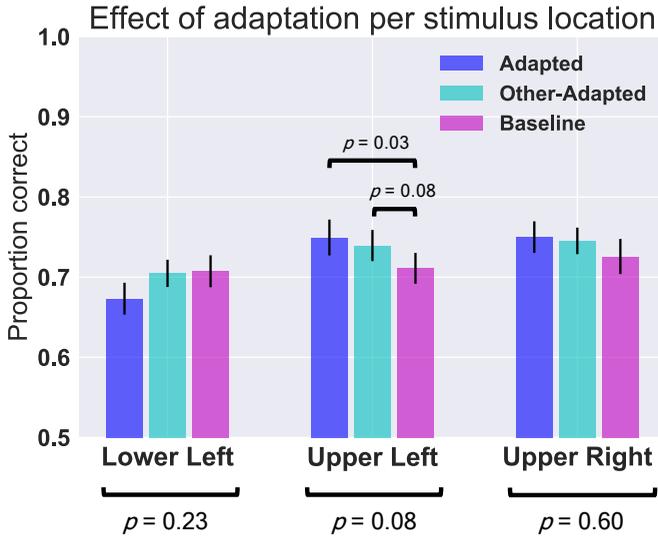
### Proportion of correct trials

A  $3 \times 2 \times 3$  repeated-measures ANOVA again showed a significant main effect of “Cue Type” ( $F(1,18) = 102.96, p < .001, \eta_p^2 = 0.85$ ). Attention benefits were again present, since participants responded more accurately in valid ( $M = 0.79, SD = 0.06$ ) as compared to neutral trials ( $M = 0.66, SD = 0.07$ ) (see Figure 2.7).



**Figure 2.7: Individual and mean proportion correct over cue types.** Error bars are standard errors of the mean (SEM), p-value is two-tailed.

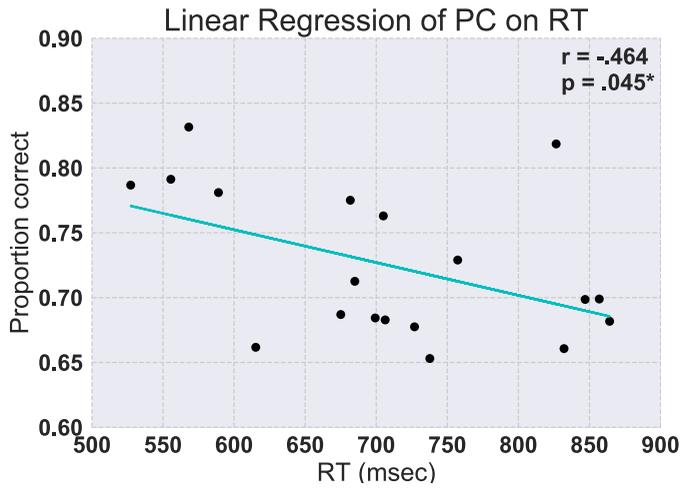
Furthermore, a significant “Stimulus Location”  $\times$  “Adaptation Condition” interaction was present ( $F(4,15) = 4.04, p = .020, \eta_p^2 = 0.52$ ). This indicates that the effect of “Adaptation Condition” differed across stimulus locations. Simple effects analyses showed that, after Bonferroni correction, the effect of “Adaptation Condition” only approached significance for the upper left location ( $F(2,17) = 4.61, p = .080, \eta_p^2 = 0.35$ ). At this location, participants were more accurate at adapted locations, and tended to be more accurate at other-adapted locations, compared to baseline performance (see Figure 2.8). In contrast to the previously reported results, there was no significant difference between the adapted and other-adapted locations. Note that exclusion of the participant showing only minor attention benefits (see Figures 2.3, 2.5, and 2.7: nearly flat line) did not change any of the reported conclusions.



**Figure 2.8: Effect of adaptation condition on mean proportion correct per stimulus location.** Errors are standard errors of the mean (SEM). P-values are two-tailed and Bonferroni-corrected.

### Inverse efficiency validity check

Some reports suggest that IE might only be a valid measure if RT and proportion correct point in the same direction (Bruyer and Brysbaert, 2011; Vandierendonck, 2018). In other words, there should be no speed-accuracy tradeoff. This means that if participants are worse in terms of RT (higher scores), participants should also be worse in terms of the proportion of correct trials (lower scores). Linear regression of the proportion of correct trials on RT scores indeed confirmed that such a negative association was present in our data ( $r = -0.46$ ,  $p = 0.045$ ) (see Figure 2.9).

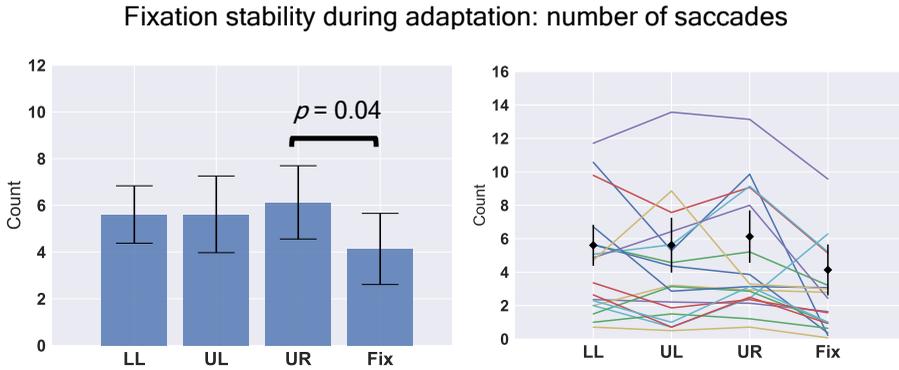


**Figure 2.9: Linear regression of the proportion of correct trials (PC) on reaction time scores (RT).** Pearson correlation is shown. The asterisk indicates  $p < 0.05$ .

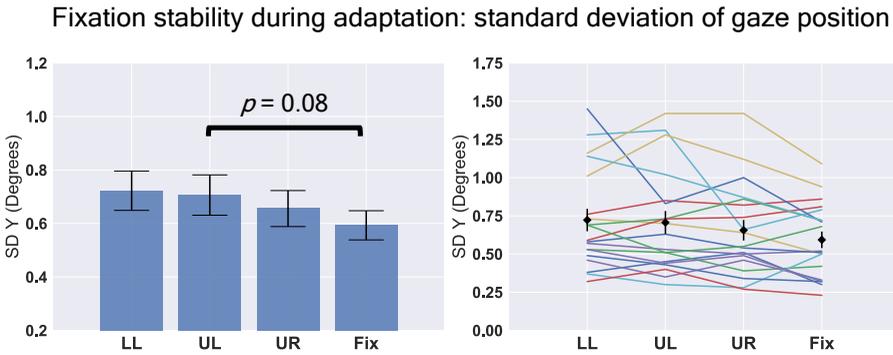
### Fixation stability during the adaptation phase

A one-way repeated measures ANOVA with the factor “Adaptation Condition” (levels: “Lower Left”, “Upper Left”, “Upper Right”, and “Fixation”) showed that the number of saccades differed across adaptation phases ( $F(3,16) = 3.16$ ,  $p = .050$ ,  $\eta_p^2 = 0.37$ ). Bonferroni-corrected follow-up tests showed that the number of saccades during the 40 second “Fixation” period ( $M = 6.13$ ,  $SD = 0.37$ ) was significantly lower than during adaptation of attention to the “Upper Right” location ( $M = 4.14$ ,  $SD = 0.36$ ,  $t(18) = 3.15$ ,  $p = .040$ , two-tailed). Note that the exclusion of one outlier participant (see Figure 2.10, uppermost line) did not change this conclusion.

We did not find a significant effect of “Adaptation Condition” on the standard deviation of gaze position on the horizontal meridian ( $F(3,16) = 2.38$ ,  $p = .110$ ,  $\eta_p^2 = 0.31$ ), but we did find a trending effect on the standard deviation of gaze position on the vertical meridian ( $F(3,16) = 2.65$ ,  $p = .080$ ,  $\eta_p^2 = 0.33$ ). More specifically, the standard deviation in the “Fixation” phase ( $M = 0.59$ ,  $SD = 0.24$ ) was lower than in the “Upper Left” phase ( $M = 0.71$ ,  $SD = 0.33$ ) (see Figure 2.11).



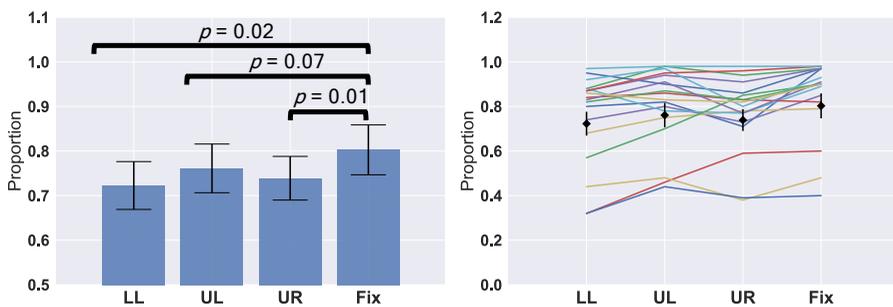
**Figure 2.10: Mean and individual number of saccades during different types of adaptation phases.** LL = adapt attention to lower left, UL = upper left, UR = upper right, Fix = no adaptation / fixation baseline. Error bars represent standard errors of the mean (SEM). The p-value is two-tailed and Bonferroni-corrected.



**Figure 2.11: Mean and individual standard deviation of gaze position on the vertical meridian across adaptation phases.** The x-axis shows the different attention adaptation phases, where LL = lower left, UL = upper left, UR = upper right, Fix = no adaptation / fixation baseline. Error bars represent standard errors of the mean (SEM). The p-value is two-tailed and Bonferroni-corrected.

The proportion of eye gaze samples within one visual degree of central fixation differed significantly across adaptation phases ( $F(3,16) = 6.00$ ,  $p = .010$ ,  $\eta_p^2 = 0.53$ ). The proportion of samples within one degree was significantly larger for the “Fixation” phase ( $M = 0.80$ ,  $SD = 0.25$ ) as compared to all other adaptation conditions (“Lower Left”:  $M = 0.72$ ,  $SD = 0.24$ ,  $t(18) = 3.38$ ,  $p = .020$ , two-tailed; “Upper Left”:  $M = 0.76$ ,  $SD = 0.24$ ,  $t(18) = 2.67$ ,  $p = .070$ , two-tailed; “Upper Right”:  $M = 0.74$ ,  $SD = 0.25$ ,  $t(18) = 3.61$ ,  $p = .010$ , two-tailed). This result was not affected by exclusion of three outlier participants (see Figure 2.12, lowest lines).

#### Fixation stability during adaptation: proportion of eye gaze samples < 1 degree



**Figure 2.12: Mean and individual proportion of eye gaze samples within 1 visual degree of central fixation.** LL = adapt attention to lower left, UL = upper left, UR = upper right, Fix = no adaptation / fixation baseline. Error bars represent standard errors of the mean (SEM). P-values are two-tailed and Bonferroni-corrected.

We furthermore created two-dimensional histograms/heatmaps showing eye gaze position on the horizontal and vertical meridian for all samples across all adaptation conditions, per participant (see Figure 2.13). These plots give a better impression of the difference in overall fixation stability across participants. Importantly, although there are clear differences in the hotspot and spread of the cloud of eye gaze positions across participants, the majority of eye gaze positions fall within 1 degree of central fixation.

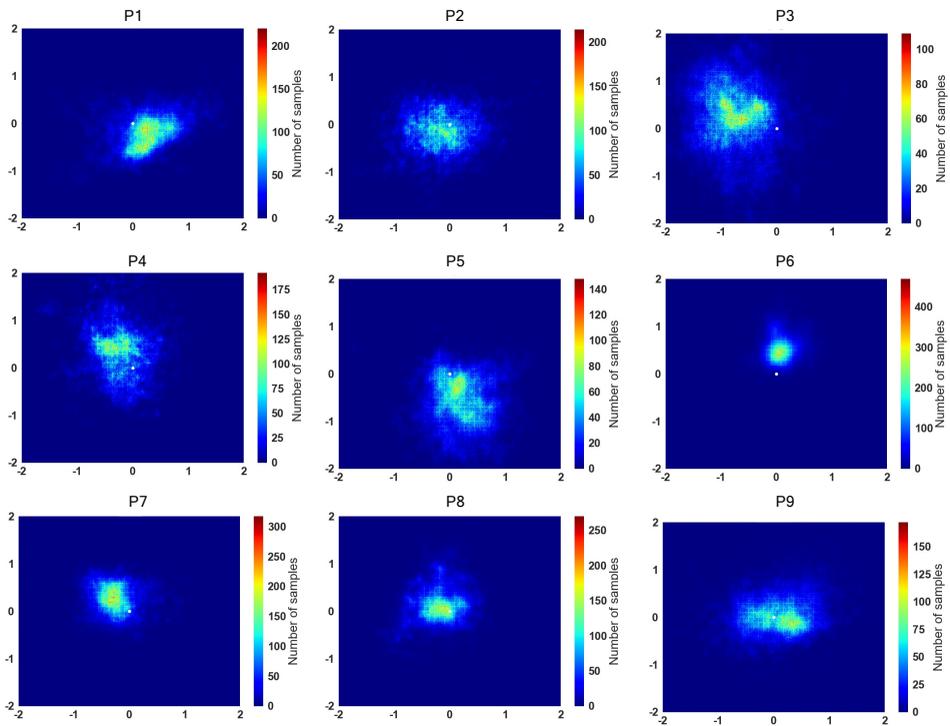
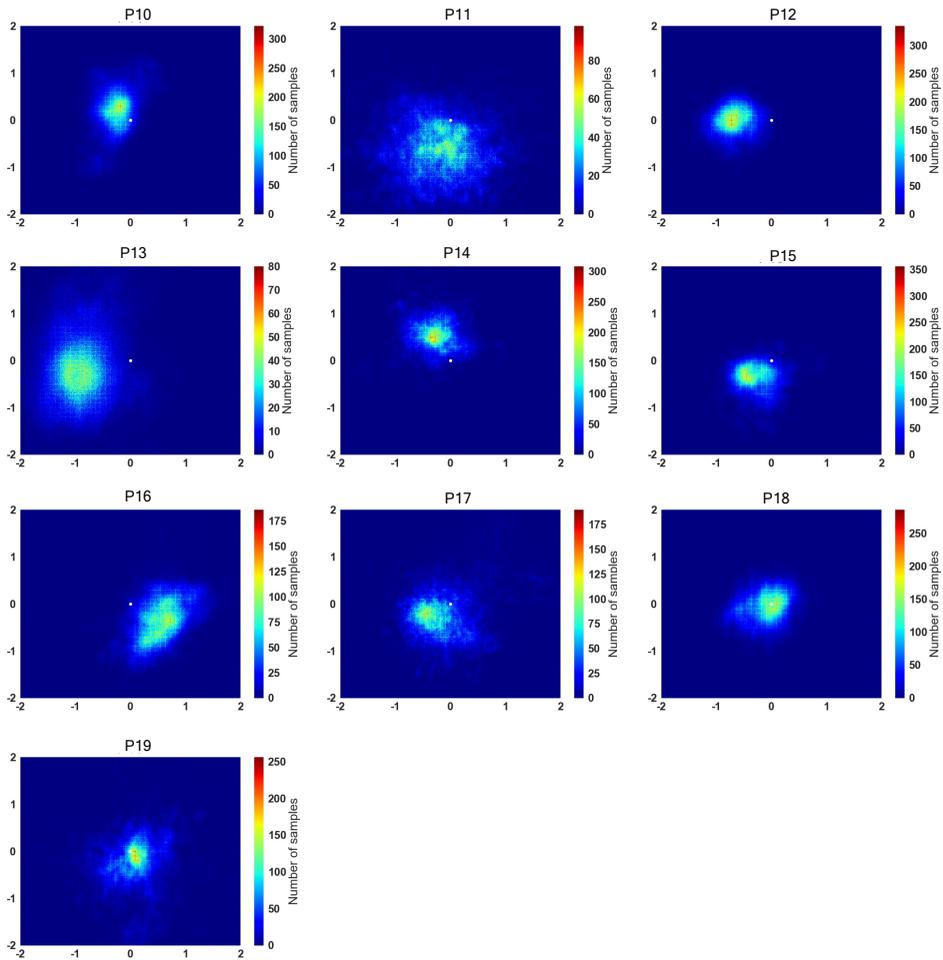


Figure 2.13: Eye gaze positions on the horizontal and vertical meridian per participant.

*Continued on the next page.*



**Figure 2.13: Eye gaze positions on the horizontal and vertical meridian per participant.** Two-dimensional histograms show eye gaze positions on the horizontal and vertical meridian across all adaptation phases. X- and y-axes are indicated in degrees visual angle. The color code indicates the number of samples at a certain location on the computer screen. The fixation dot is shown in white at the origin (screen center).

### Covert attention versus overt attention

We used one-way repeated measures ANOVAs to assess whether “Adaptation Condition” (levels: “Lower Left”, “Upper Left”, “Upper Right”, “Fixation/Baseline”) affected fixation stability during the 2AFC orientation discrimination task. We did not find a significant effect of “Adaptation Condition” on the standard deviation of eye gaze on the horizontal or vertical meridian, or on the proportion of eye gaze samples within 1 degree of central fixation (all  $p$ 's > 0.10). It thus seems that our manipulation of covert visuospatial attention did not affect subsequent overt visuospatial attention metrics.

## 2.5 Experiment 1: Interim Discussion

In the current study, an experimental paradigm was applied to endogenous covert visuospatial attention. An orientation discrimination task was used to assess if the underlying neuronal substrates were indeed adapted. If performance would be decreased compared to baseline at specifically the adapted spatial location, this would provide evidence that our newly developed paradigm was successful. Unexpectedly, we found increased performance (i.e., faster RTs and decreased IE scores) at the locations that were not adapted, compared to baseline performance. This finding could possibly be the result of successful adaptation, since it could involve a compensation mechanism. For instance, it has been shown previously that adaptation can lead not only to reductions in perception of adapted properties, but also to enhancements in perception of the opposite properties (Z. Cattaneo and Silvanto, 2008a). However, the results were more complicated when using the proportion of correct trials as a dependent variable, since the effect of adaptation condition then seemed to depend on the target stimulus location.

Our paradigm was essentially based on the classic Posner task, while incorporating multiple target locations and a new type of central symbolic cue (Posner, 1980; Posner et al., 1980). Importantly, we found better performance in valid as compared to neutral trials on all three dependent variables, thus replicating the often reported attention benefits effect (Duecker et al., 2013; Duecker et al., 2019; Duecker and Sack, 2015). This indicates that participants could effectively make use of the cue to shift their attention to the indicated

location. Furthermore, trials with eye movements (or blinks) during presentation of the cue and/or target stimulus were excluded, thereby ensuring that our results purely reflect covert attention task performance. However, we did find differences in fixation stability between adaptation phases in which covert attention shifts were made compared to the 40-second baseline/fixation periods. This implies that our adaptation paradigm not only affected covert attention, but also affected overt attention. Such limitations in the specificity of our paradigm complicate matters, for instance making it impossible to investigate whether covert and overt attention rely on the same neuronal substrates. Nevertheless, it seemed that overall, participants were able to fixate well throughout the adaptation phases (see Figure 2.13), with most eyetracking samples falling within 1 DVA from the fixation point.

In sum, we found a significant but unexpected effect of adaptation condition, which was not entirely consistent across individuals and dependent variables. It could possibly be explained by a real, neuronal adaptation effect, but at the same time, the behavioral effect might be confounded by differences in overt attention across adaptation phases. We therefore performed Experiment 2 in a direct attempt to replicate our results in an independent sample.

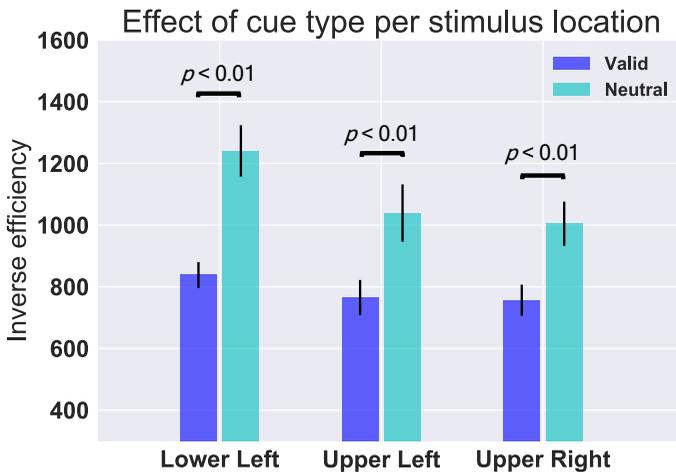
## 2.6 Experiment 2: Materials and Methods

Since Experiment 2 was a direct replication of Experiment 1, all procedures were identical except that a new 24.5-inch monitor was used (resolution 1920  $\times$  1080 pixels). Twenty-three participants were recruited (5 males, ages 19 – 28) for the experiment. Using the same outlier removal criterion as in Experiment 1, 18 participants were included in the analyses.

## 2.7 Experiment 2: Results

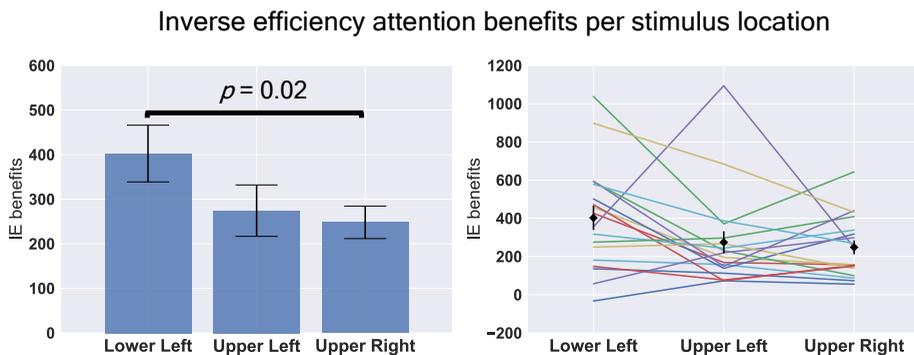
### Inverse efficiency

A three-way repeated-measures ANOVA showed a significant “Stimulus Location”  $\times$  “Cue Type” interaction ( $F(2,16) = 6.40$ ,  $p = .010$ ,  $\eta_p^2 = 0.45$ ). This indicates that the effect of “Cue Type” differed across stimulus locations. Using paired t-tests, we first validated that there was an effect of “Cue Type” for each stimulus location (see Figure 2.14).



**Figure 2.14: The effect of cue type on mean inverse efficiency (IE) scores per stimulus location.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.

To assess how the effect of “Cue Type” differed across stimulus locations, we calculated attention benefits by subtracting IE scores in valid trials from IE scores in neutral trials (such that a larger score indicates a larger attention benefit). We then used paired t-tests to compare these IE benefits across the three stimulus locations. IE benefits were significantly higher at the lower left ( $M = 402.37$ ,  $SD = 277.81$ ) as compared to the upper right location ( $M = 248.08$ ,  $SD = 159.31$ ,  $t(17) = 3.17$ ,  $p = .020$ , two-tailed, see Figure 2.15). Attention benefits might have been higher at the lower left location since participants on average performed worse at that location, thus leaving more room for improvement when a valid cue was provided (Lower Left:  $M = 619.87$ ,  $SD = 273.09$ ; Upper Left:  $M = 528.51$ ,  $SD = 295.19$ ; Upper Right:  $M = 505.91$ ,  $SD = 261.67$ ). There were no significant main or interaction effects including the factor “Adaptation Condition”. Note that none of these results changed after exclusion of three seemingly deviating participants (see Figure 2.15, highest lines).

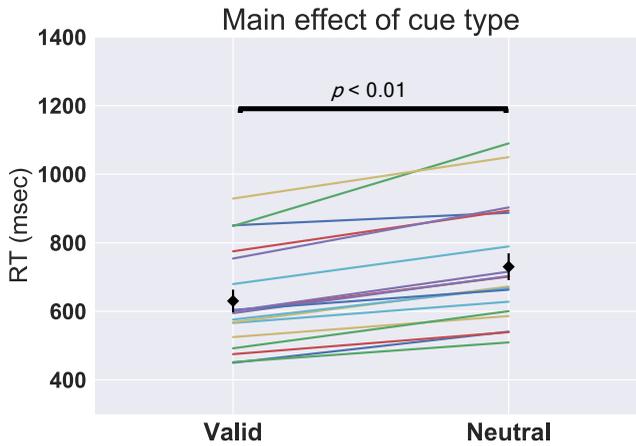


**Figure 2.15: Mean and individual inverse efficiency (IE) benefits across stimulus locations.** IE benefits were calculated as follows: IE neutral – IE valid, a larger score thus indicating larger attention benefits. Error bars are standard errors of the mean (SEM), the p-value is two-tailed and Bonferroni-corrected.

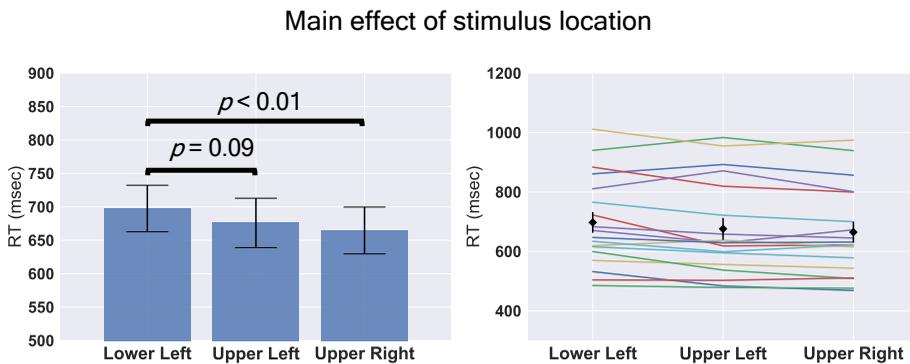
## Reaction times

A three-way repeated measures ANOVA revealed significant main effects of “Cue Type” ( $F(1,17) = 89.92$ ,  $p < .001$ ,  $\eta_p^2 = 0.84$ ) and “Stimulus Location” ( $F(2,16) = 7.30$ ,  $p = .010$ ,  $\eta_p^2 = 0.48$ ). Reaction times were significantly faster in valid ( $M = 630.14$ ,  $SD = 143.48$ ) as compared to neutral trials ( $M = 734.32$ ,  $SD = 171.25$ , see Figure 2.16). Moreover, participants responded slower at the lower left ( $M = 702.99$ ,

$SD = 156.20$ ) as compared to the upper left ( $M = 677.14$ ,  $SD = 162.86$ ,  $t(17) = 2.36$ ,  $p = .090$ , two-tailed) and upper right locations ( $M = 666.55$ ,  $SD = 154.54$ ,  $t(17) = 3.83$ ,  $p < .001$ , two-tailed, see Figure 2.17). There were no significant effects including the factor “Adaptation Condition”.



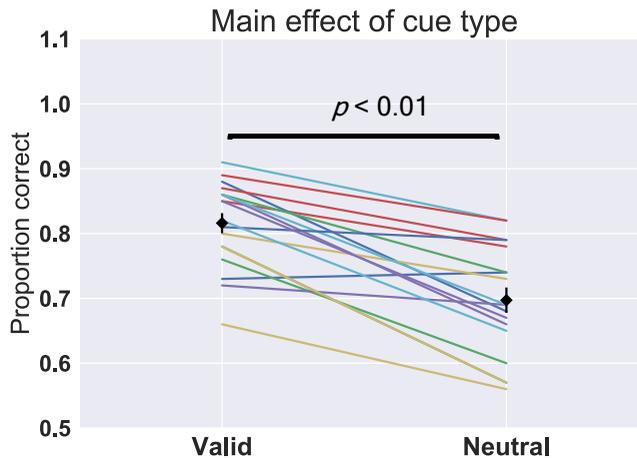
**Figure 2.16: Individual and mean inverse efficiency (IE) scores over cue types.** Error bars are standard errors of the mean (SEM), p-value is two-tailed.



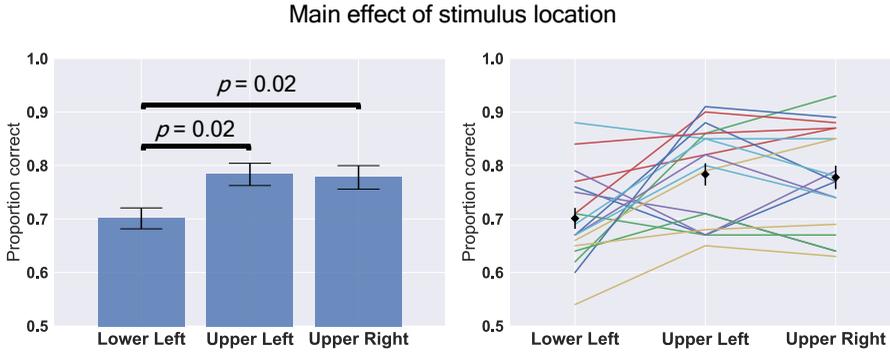
**Figure 2.17: Mean and individual reaction times (RTs) across stimulus locations.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.

### Proportion of correct trials

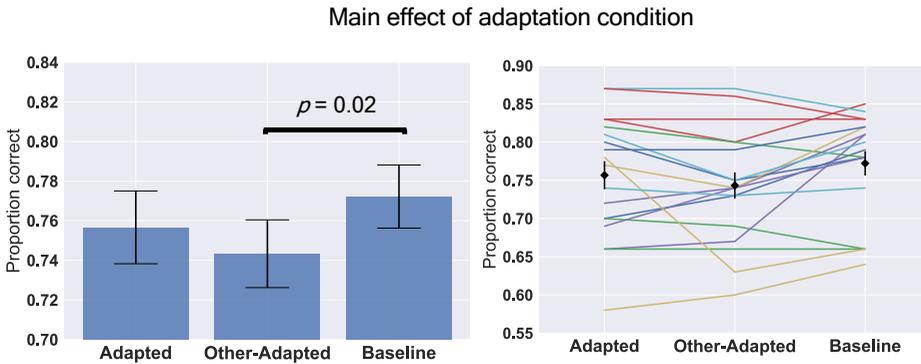
A three-way repeated measures ANOVA showed a significant main effect of “Cue Type” ( $F(1,17) = 44.11, p < .001, \eta_p^2 = 0.72$ ), “Stimulus Location” ( $F(2,16) = 5.26, p = .020, \eta_p^2 = 0.40$ ), and “Adaptation Condition” ( $F(2,16) = 5.23, p = .020, \eta_p^2 = 0.40$ ). Follow-up tests showed that participants responded more accurately in valid ( $M = 0.82, SD = 0.07$ ) as compared to neutral trials ( $M = 0.70, SD = 0.08$ , see Figure 2.18). Furthermore, participants performed worse at the lower left ( $M = 0.71, SD = 0.08$ ) as compared to the upper left ( $M = 0.79, SD = 0.09, t(17) = 3.19, p = .020$ , two-tailed) and upper right locations ( $M = 0.79, SD = 0.09, t(17) = 3.20, p = .020$ , two-tailed, see Figure 2.19). Lastly, participants were less accurate in other-adapted trials ( $M = 0.75, SD = 0.07$ ) as compared to baseline trials ( $M = 0.78, SD = 0.07, t(17) = 3.00, p = .020$ , two-tailed, see Figure 2.20).



**Figure 2.18: Individual and mean proportion correct over cue types.** Error bars are standard errors of the mean (SEM), p-value is two-tailed.



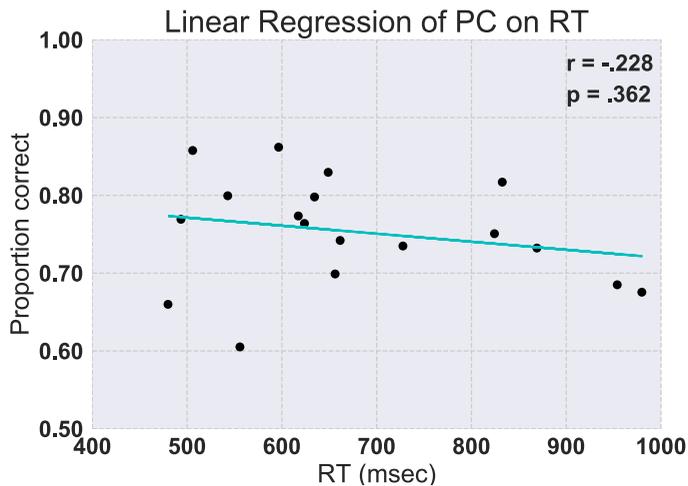
**Figure 2.19: Mean and individual proportion correct per stimulus location.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.



**Figure 2.20: Mean and individual proportion correct per adaptation condition.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.

### Inverse efficiency validity check

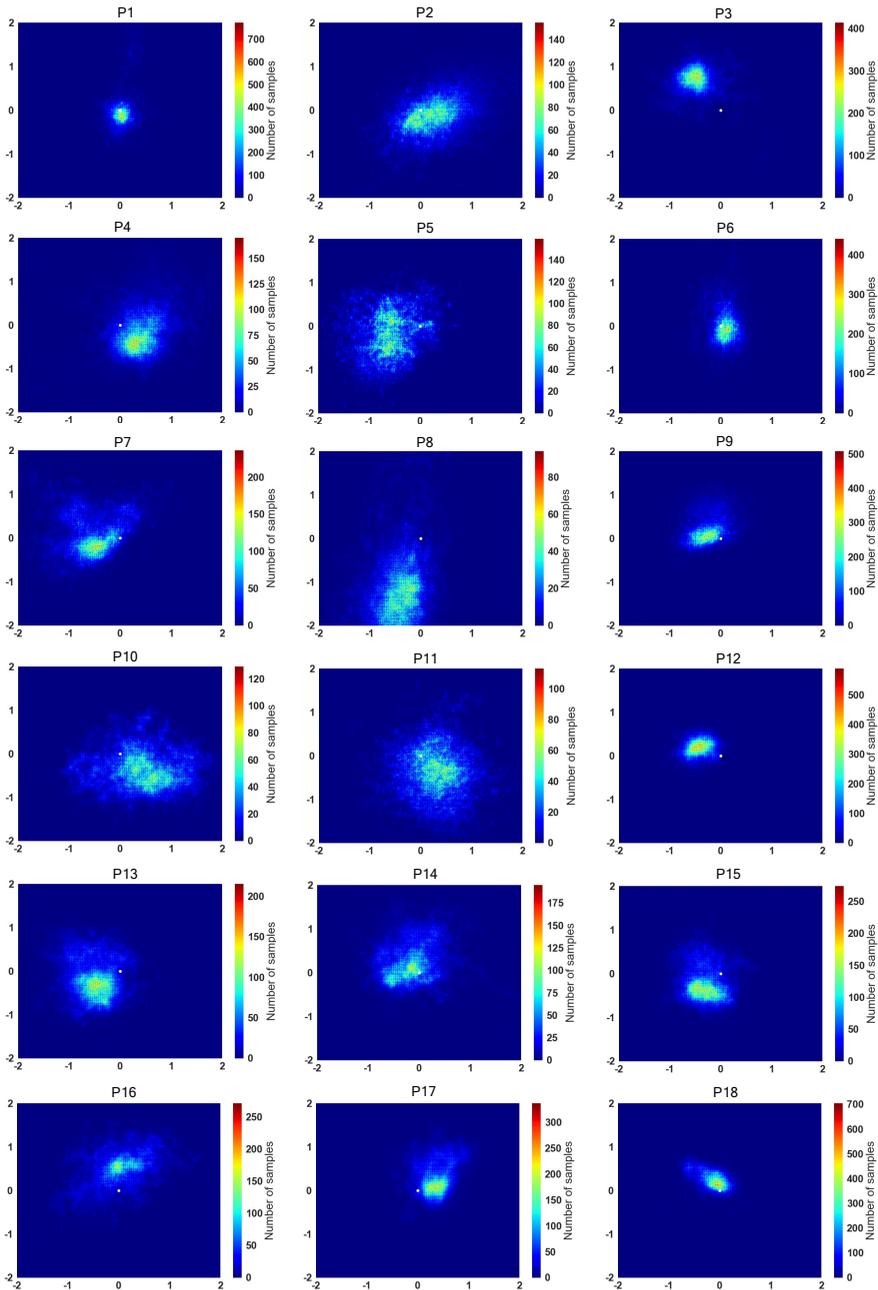
In contrast to Experiment 1, we did not find a significant linear correlation between the proportion of correct trials and RT scores in Experiment 2 ( $r = -0.23$ ,  $p = 0.36$ , see Figure 2.21). This result does not point to the existence of a speed-accuracy tradeoff, since we did not find a significant positive association between the proportion correct and RT. Nevertheless, the IE results should be interpreted with caution due to the absence of a significant negative association in the current dataset (Bruyer and Brysbaert, 2011; Vandierendonck, 2018).



**Figure 2.21:** Linear regression of the proportion of correct trials (PC) on reaction time scores (RT). Pearson correlation is shown.

### Fixation stability during the adaptation phase

We did not find a significant effect of “Adaptation Condition” (levels: “Lower Left”, “Upper Left”, “Upper Right”, and “Fixation”) on the number of saccades during the adaptation phases ( $p > 0.10$ ). There was also no effect of “Adaptation Condition” on the standard deviation of gaze position on the horizontal or vertical meridian ( $p > 0.10$ ). The proportion of eye gaze samples within one degree of central fixation differed significantly across adaptation phases ( $F(3,15) = 4.03$ ,  $p = .030$ ,  $\eta_p^2 = 0.45$ ). However, follow-up pairwise comparisons were all non-significant. It thus seems that in Experiment 2, the differences in fixation stability across adaptation conditions were either absent or less strong compared to Experiment 1. Overall, participants were fixating well, with the majority of eye gaze positions falling within 1 degree of central fixation (see Figure 2.22).



**Figure 2.22: Eye gaze positions on the horizontal and vertical meridian per participant.** Two-dimensional histograms show eye gaze positions on the horizontal and vertical meridian across all adaptation phases. X- and y-axes are indicated in degrees visual angle. The color code indicates the number of samples at a certain location. The fixation dot is shown in white at the origin.

### Covert attention versus overt attention

We used one-way repeated measures ANOVAs to assess whether “Adaptation Condition” (levels: “Lower Left”, “Upper Left”, “Upper Right”, “Fixation/Baseline”) affected fixation stability during the 2AFC orientation discrimination task. There was no significant effect of “Adaptation Condition” on the standard deviation of eye gaze on the horizontal or vertical meridian, or on the proportion of eye gaze samples within 1 degree of central fixation (all  $p$ 's > 0.10). As in Experiment 1, our manipulation of covert visuospatial attention seemed to have no effect on over visuospatial attention metrics.

## 2.8 Experiment 2: Interim Discussion

Experiment 1 served to test whether the neuronal systems underlying covert visuospatial attention could be adapted. As the results were unexpected and inconclusive, we attempted to replicate these findings in Experiment 2. In contrast to Experiment 1, we did not find an effect of “adaptation condition” on IE or RT scores, but we did find an effect on the proportion of correct trials. Here, performance in other-adapted trials was worse compared to baseline performance, which is in direct opposition with the results from Experiment 1. We thus did not find convincing evidence that our novel paradigm could successfully adapt covert visuospatial attention.

The results of Experiment 1 might have been confounded by differences in fixation stability across adaptation phases. By contrast, there were no significant differences in overt attention between adaptation phases in Experiment 2. It is unclear why this change occurred; possibly, the participants in the second subject sample were more proficient at fixation tasks. It is unlikely that the change in monitor affected task performance, as the luminance and sizes of all stimuli were kept constant across studies. Overall, though, fixation stability was good and fairly similar in both studies (standard deviation of eye gaze position on the horizontal meridian:  $M = 0.81$  versus  $M = 0.90$ , vertical meridian:  $M = 0.67$  versus  $M = 0.86$ , number of saccades:  $M = 5.37$  versus  $M = 7.45$ , proportion of trials within 1 visual degree of fixation:  $M = 0.76$  versus  $M = 0.73$ ).

One of the aims of Experiments 1 and 2 was to exploit the adaptation paradigm to investigate whether covert and overt attention share the same underlying neuronal mechanisms. However, since we were unable to reliably demonstrate that our paradigm could adapt covert visuospatial attention, we could not draw any conclusions about this issue. In Experiment 3, we improved the adaptation task design in a final attempt to demonstrate its efficacy, and to assess how attention moves across the visual field.

## 2.9 Experiment 3: Materials and Methods

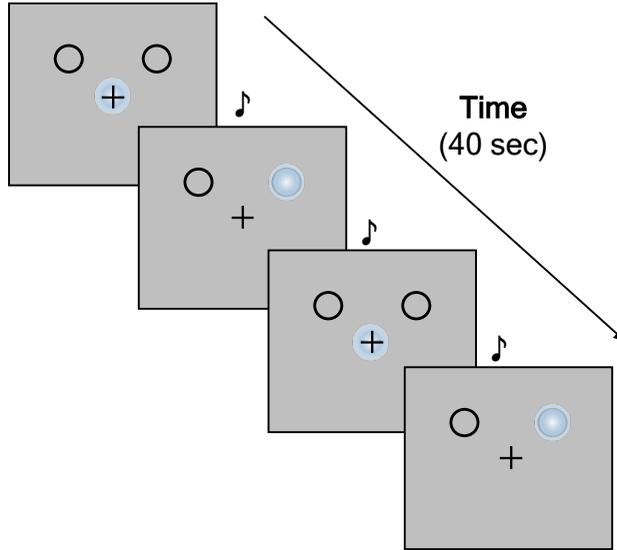
### Participants

Twenty healthy volunteers participated in this experiment (8 males, ages 18 – 30). The local ethics committee approved the experiment. Participants had (corrected-to-)normal vision, provided written informed consent, and were compensated with either 1 participation credit or 7.50 euros per hour.

### Stimuli, Tasks and Design

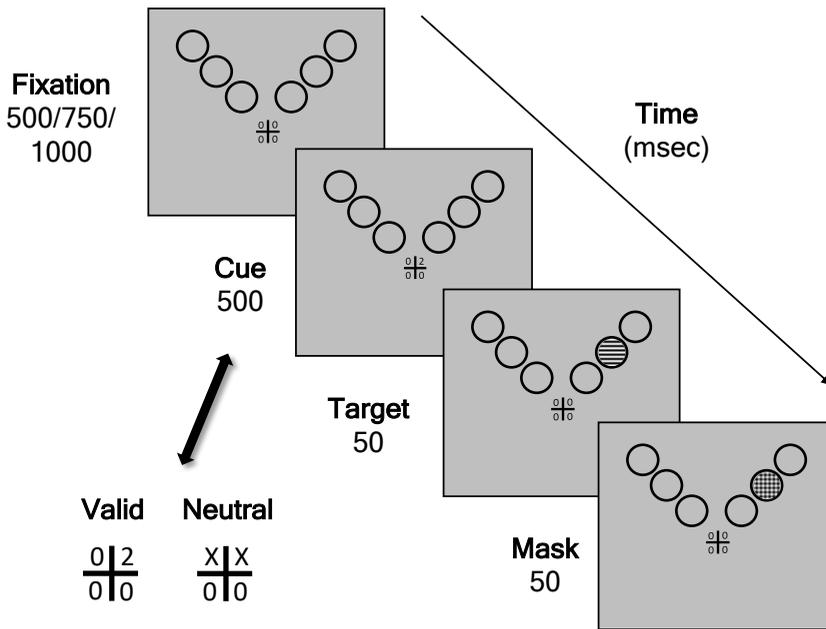
The aim of Experiment 3 was to investigate how covert visuospatial attention moves across space. As described in the Introduction, attention might jump between locations, spread along a path, or enhance an entire directional axis (see Figure 2.1b). To distinguish between these hypotheses, we employed a modified version of the “attention adaptation” paradigm described previously, with six possible target stimulus locations. The three hypotheses lead to different predictions in terms of how the attention adaptation paradigm should affect behavioral performance (see Figure 2.1c). The first hypothesis predicts that performance should decrease as compared to baseline specifically at the adapted (middle) location. The second hypothesis predicts that both the closest and the middle location should show decreased performance as compared to baseline. Lastly, the third hypothesis predicts that all three locations in the same hemifield as the adapted location should be affected. Importantly, all hypotheses predict that the effects should be specific to the hemifield of the adapted location.

During the adaptation phase, only the two circles in the middle of each hemifield were shown (see Figure 2.23). Participants were shortly presented with the text “LEFT”, “RIGHT”, or “CENTER”, indicating that they should covertly shift their attention from central fixation to the upper left or upper right location and back, or not at all (fixation/baseline), respectively (factor “adaptation condition” with three levels: left, right, and fixation/baseline). During the 40-second adaptation phase, an auditory stimulus was used to instruct participants to shift their attention.



**Figure 2.23: Attention adaptation paradigm: example adaptation phase.** Participants covertly shifted their attention from central fixation to a peripheral location and back for 40 seconds. A tone served as a cue to shift attention. At the beginning of each adaptation phase, instructions were presented on screen: “LEFT”, “RIGHT” or “CENTER”, indicating that covert attention shifts should be directed towards the upper left or upper right location, or not at all (fixation/baseline), respectively. The blue circle represents the locus of covert spatial attention.

After each adaptation phase, participants performed 12 two-alternative forced-choice (2AFC) orientation discrimination trials (see Figure 2.24). In each trial, a valid or a neutral cue was presented for 500 msec (factor “cue type” with two levels: valid and neutral). A horizontally or vertically oriented target grating was then presented for 50 msec at one out of six possible locations (factor “hemifield” with two levels: left and right, and factor “eccentricity” with three levels: close, middle, far). Participants reported the grating orientation as quickly and as accurately as possible by button press. Response correctness, reaction times and eye movement data were recorded as in Experiment 1 and 2.



**Figure 2.24: Attention adaptation paradigm: example orientation discrimination trial.** After each adaptation phase, participants performed 12 orientation discrimination trials. After a randomly varied inter-trial fixation period, a cue appeared for 500 msec. This cue could either be valid, indicating where the target would appear (as in this example), or neutral, providing temporal but not spatial information. For valid cues, the side on which the digit appeared indicated the target hemifield and the value indicated the position (1 = inner circle, 2 = middle circle, 3 = outer circle). A horizontally or vertically oriented target grating was then presented for 50 msec. A mask stimulus was presented for 50 msec. Participants reported target orientation as quickly and as accurately as possible.

## Procedures

Participants had their heads stabilized in a chin rest at 65 cm distance from the screen and they fixated throughout the task. Equipment and software were as described for Experiment 1. A black fixation cross of 0.15 degrees visual angle (DVA) was presented on a gamma-corrected uniform grey background of  $107 \text{ cd/m}^2$ . Participants were informed about an upcoming adaptation phase by the text “LEFT”, “RIGHT” or “CENTER”, instructing them to covertly shift their attention from central fixation to the left location, to the right location, or not at all (baseline/fixation), respectively. During the 40-second adaptation phase, two placeholder circles with a diameter of 2.1 DVA were centered at 6 DVA eccentricity diagonally from the screen center. Attention shifts were cued by a 350 Hz tone played for 100 msec every second.

After each adaptation phase, 12 orientation discrimination trials were presented. During these trials, placeholder circles with 2.1 DVA diameter were presented at 3, 6, and 9 DVA eccentricity diagonally from the screen center in both hemifields. Furthermore, four zeros of 0.2 DVA were presented in each corner of the fixation cross (see Figure 2.24). After a variable inter-trial fixation period of 500, 750 or 1000 msec, a valid or a neutral cue was presented for 500 msec. To create a valid cue, the upper left or upper right “0” was replaced with a “1”, “2” or “3”, to announce that the target stimulus would appear at the closest, middle or farthest eccentricity, respectively. To create a neutral cue, the upper left and upper right “0”s were replaced with an “X”, providing a temporal but not a spatial cue. After the cue, a horizontally or vertically oriented sinusoidal grating with 0.4 Michelson contrast, a diameter of 1.5 DVA and a spatial frequency of 2.5 cycles/DVA was presented for 50 msec at one of the six possible locations. Target location was pseudo-randomized such that each location occurred twice during each block of 12 trials. A mask stimulus was presented for 50 msec after target presentation to prevent the appearance of an afterimage. Participants reported target orientation as quickly and as accurately as possible using the “left arrow” button for horizontal and “down arrow” button for vertical stimuli.

In each of two identical sessions, participants went through 30 adaptation phases and 360 orientation discrimination trials. Participants could take a break after each three adaptation phases. Every orientation discrimination block of 12 trials contained six valid and six neutral trials in random order. Half of the gratings were oriented horizontally, the other half vertically (randomly selected). RTs were recorded in msec. The task lasted approximately 1 hour, and an entire session lasted approximately 1 hour and 15 minutes in total.

## Analyses

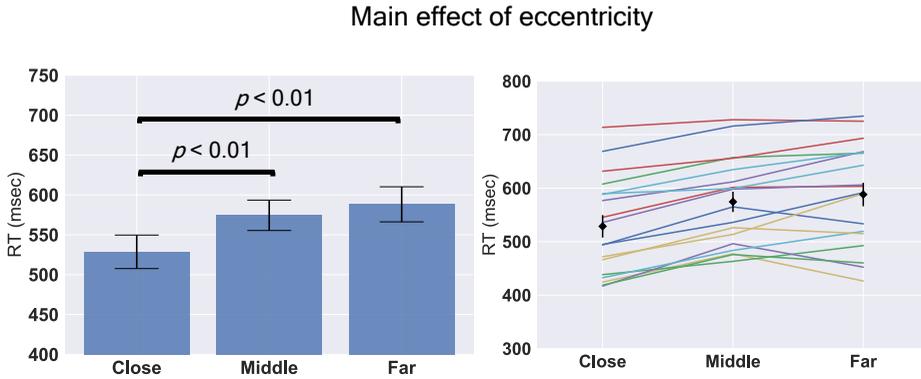
Eyetracking analyses were as described for Experiments 1 and 2. Since Experiment 3 involved high contrast gratings and therefore a high proportion of correct trials, the dependent variable of interest was RT in msec. Two participants were excluded from the analyses since their remaining number of trials and/or overall performance was more than two standard deviations (SDs) away from the mean. Thus, 18 participants were included in the analyses. The mean RTs were compared across conditions using a four-way repeated measures ANOVA with the factors “Adaptation Condition” (left,

right, baseline/fixation), “Cue Type” (valid, neutral), “Hemifield” (left, right) and “Eccentricity” (close, middle, far). Bonferroni-corrected pairwise comparisons were conducted where necessary.

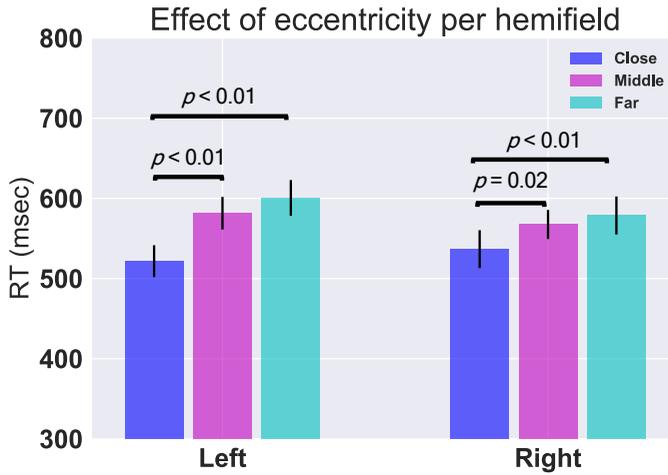
## 2.10 Experiment 3: Results

### Reaction times

A  $3 \times 2 \times 2 \times 3$  repeated-measures ANOVA showed a trending “Hemifield”  $\times$  “Eccentricity” interaction ( $F(2,16) = 3.49$ ,  $p = .060$ ,  $\eta_p^2 = 0.30$ ) and a significant main effect of “Eccentricity” ( $F(2,16) = 86.40$ ,  $p < .001$ ,  $\eta_p^2 = 0.92$ ). Overall, participants responded faster to targets presented at the closest eccentricity ( $M = 529.19$ ,  $SD = 91.37$ ) as compared to the middle ( $M = 574.52$ ,  $SD = 82.85$ ,  $t(17) = 9.96$ ,  $p < .001$ , two-tailed) and the farthest ( $M = 590.05$ ,  $SD = 95.66$ ,  $t(17) = 8.43$ ,  $p < .001$ , two-tailed) eccentricities (see Figure 2.25). Simple effects analyses showed that this effect was present in both hemifields, but seemed to be slightly stronger in the left hemifield ( $F(2,16) = 39.34$ ,  $p < .001$ ,  $\eta_p^2 = 0.83$ ) as compared to the right hemifield ( $F(2,16) = 12.00$ ,  $p < .001$ ,  $\eta_p^2 = 0.60$ ) (see Figure 2.26).

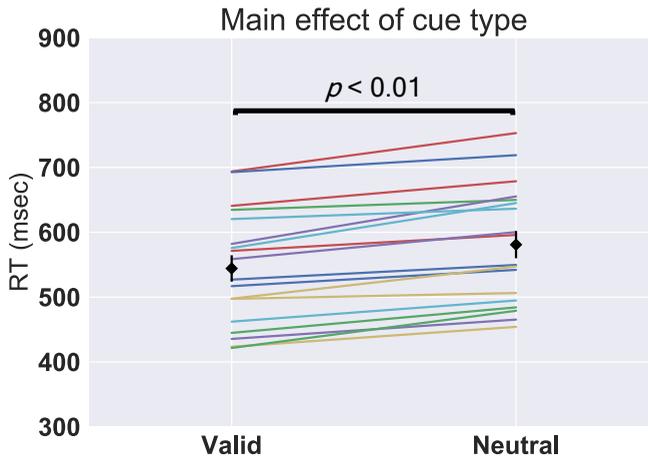


**Figure 2.25: Mean and individual reaction times (RT) per eccentricity.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.

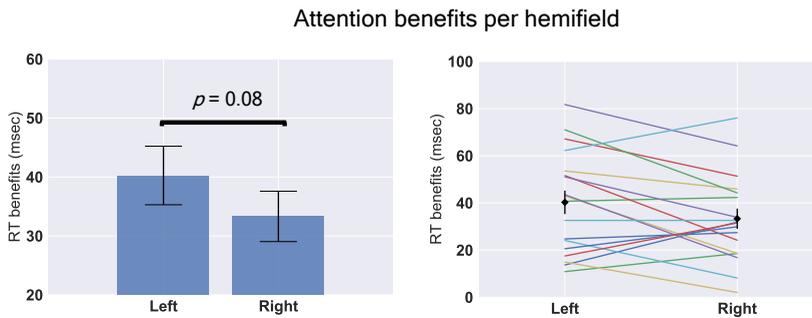


**Figure 2.26: Mean and individual reaction times (RT) per eccentricity, separately for the left and right hemifield.** Error bars are standard errors of the mean (SEM), p-values are two-tailed and Bonferroni-corrected.

We furthermore found a trending “Hemifield”  $\times$  “Cue Type” interaction ( $F(1,17) = 3.30$ ,  $p = .090$ ,  $\eta_p^2 = 0.16$ ) and a significant main effect of “Cue Type” ( $F(1,17) = 70.88$ ,  $p < .001$ ,  $\eta_p^2 = 0.81$ ). Participants responded significantly faster in valid ( $M = 545.01$ ,  $SD = 87.79$ ) as compared to neutral trials ( $M = 583.16$ ,  $SD = 90.05$ , see Figure 2.27). Thus, even though we developed a new type of cue, attention benefits were present in our data. This shows that participants were able to use the valid cues to shift their attention to the indicated location. To further investigate the interaction with the factor “Hemifield”, we calculated attention benefits by subtracting the RT in valid cue trials from the RT in neutral cue trials (a higher score thus indicating higher attention benefits). Attention benefits were present for both the left ( $t(17) = 7.88$ ,  $p < .001$ , two-tailed) and right hemifield ( $t(17) = 7.58$ ,  $p < .001$ , two-tailed), but on average seem to be slightly larger in the left hemifield ( $M = 40.26$ ,  $SD = 21.68$  versus  $M = 33.32$ ,  $SD = 18.65$ ). However, this effect was not very consistent across participants (see Figure 2.28). There were no other significant main or interaction effects (all  $p$ 's  $> 0.10$ ).



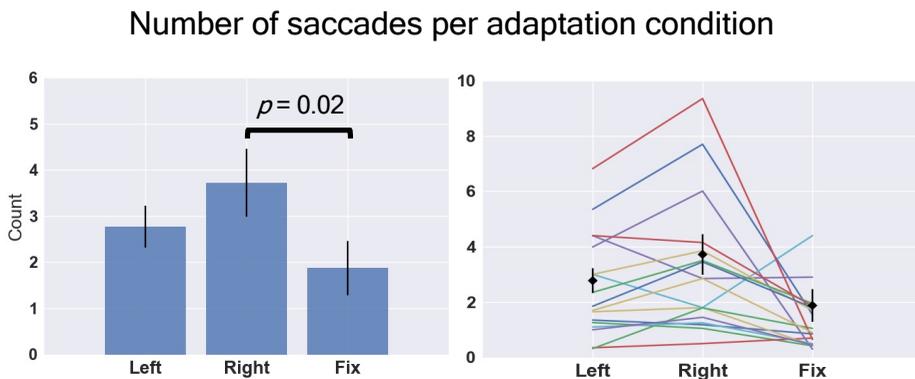
**Figure 2.27: Individual and mean reaction time (RT) scores over cue types.** Error bars are standard errors of the mean (SEM), p-value is two-tailed.



**Figure 2.28: Mean and individual attention benefits in reaction times (msec).** Attention benefits are calculated as follows: RT neutral – RT valid, a larger score thus indicating larger attention benefits. Error bars are standard errors of the mean (SEM), the p-value is two-tailed and Bonferroni-corrected.

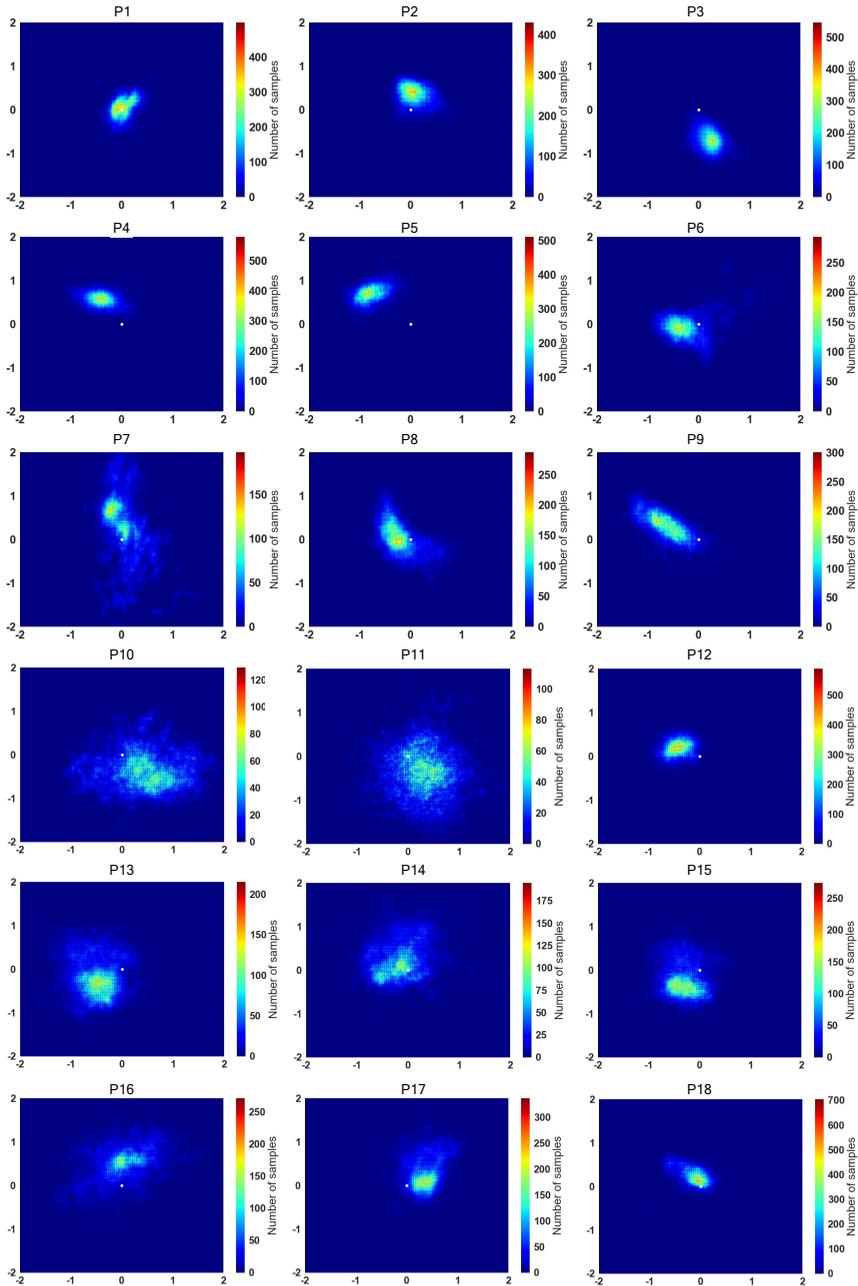
### Fixation stability assessment

As for Experiments 1 and 2, we investigated whether participants managed to keep fixating during adaptation. There was a significant effect of “Adaptation Condition” on the number of saccades during the adaptation phase ( $F(2,16) = 6.70$ ,  $p = .030$ ,  $\eta_p^2 = 0.37$ ). More saccades were made during adaptation of attention to the right location ( $M = 3.72$ ,  $SD = 3.23$ ) as compared to the 40-second fixation/baseline period ( $M = 1.87$ ,  $SD = 2.57$ ,  $t(17) = 3.00$ ,  $p = .020$ , two-tailed). This conclusion was not changed after excluding two seemingly deviating participants (see Figure 2.29). There was no significant effect of “Adaptation Condition” on the standard deviation of gaze position on the horizontal or vertical meridian, or on the proportion of eye gaze samples within 1 DVA of central fixation. Overall, participants seemed to be fixating well, since the majority of eye gaze positions fell within 1 degree of central fixation (see Figure 2.30).



**Figure 2.29: Mean and individual number of saccades during the different 40-second adaptation periods.** Left = adapt attention to the left location, Right = adapt attention to the right location, Fix = 40 second fixation/baseline period. Error bars are standard errors of the mean (SEM), the p-value is two-tailed and Bonferroni-corrected.

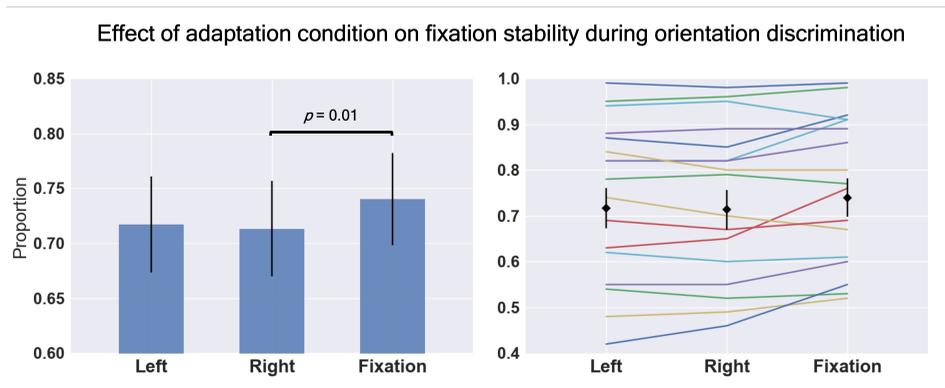
Note that Participant 11 and possibly Participant 7 show two hotspots. This indicates that they might have shifted their central fixation in between adaptation phases. The results were not changed significantly after excluding these participants from the analyses.



**Figure 2.30: Eye gaze positions on the horizontal and vertical meridian per participant.** Two-dimensional histograms show eye gaze positions on the horizontal and vertical meridian across all adaptation phases. X- and y-axes are indicated in degrees. The color code indicates the number of samples at a certain location. The fixation dot is shown in white at the origin.

### Covert attention versus overt attention

One-way repeated measures ANOVAs were used to assess whether “Adaptation Condition” (levels: “Left”, “Right”, “Fixation”) influenced fixation stability during the subsequent 2AFC orientation discrimination task. “Adaptation Condition” did not significantly affect the standard deviation of eye gaze on the horizontal or vertical meridian (all  $p$ 's > 0.10). However, “Adaptation Condition” did affect the proportion of eye gaze samples within 1 degree of central fixation ( $F(2,16) = 5.63$ ,  $p = .010$ ,  $\eta_p^2 = 0.41$ ). The proportion of eye gaze samples within 1 degree of central fixation was significantly higher during orientation discrimination trials following a 40-second fixation/baseline period ( $M = 0.74$ ,  $SD = 0.18$ ) as compared to a 40-second attention adaptation towards the right location ( $M = 0.72$ ,  $SD = 0.19$ ) (see Figure 2.31). It thus seems that, in contrast to the results of Experiment 1 and 2, our covert attention adaptation paradigm influenced subsequent overt visuospatial attention.



**Figure 2.31:** Effect of adaptation condition on average and individual proportion of eye gaze samples within 1 visual degree of central fixation during orientation discrimination trials. Error bars represent standard errors of the mean (SEM). The  $p$ -value is two-tailed and Bonferroni-corrected.

## 2.11 Experiment 3: Interim Discussion

In Experiment 3, we modified our attention adaptation paradigm in a final attempt at adapting covert visuospatial attention. The paradigm was improved by using an auditory instead of a visual cue to instruct covert attention shifts during the

adaptation phase, which might help participants to keep their central fixation. Furthermore, we used high contrast gratings and focused on reaction time as a dependent variable, instead of individually calibrating grating contrast and including response accuracy and inverse efficiency as dependent variables. This change was implemented because response accuracy (and, consequently, inverse efficiency scores) can be strongly affected in designs with relatively few trials, which can be problematic for instance when participants accidentally press a wrong key. Reaction times suffer less from this problem, since they are calculated by taking an average score instead of a proportion (as for response accuracy). With these adjustments, we again investigated the efficacy of our adaptation paradigm, and applied it to an unresolved question: how does attention move through visual space? By including three spatial locations with different eccentricities within each hemifield, we explored whether attention jumps between spatial locations, moves along a path, or enhances an entire directional axis. Unfortunately, we did not find any significant effects of our adaptation manipulation on subsequent endogenous visuospatial attention task performance. We therefore could not demonstrate the efficacy of our adaptation paradigm and could not resolve how attention moves through visual space.

The use of three spatial locations within each hemifield necessitated the development of a new type of symbolic cue. The cue duration (which was also the cue-target interval) was the same as in Experiments 1 and 2, even though the valid cue used in Experiment 3 was more cognitively demanding. Specifically, besides pointing to the hemifield, a valid cue also informed about the eccentricity of the upcoming target stimulus. Participants thus had to “translate” the appearance of the number “1”, “2” or “3” into the specific location within the indicated hemifield that they should covertly attend to. Importantly, participants were able to use this cue to shift their attention to the indicated location, as evidenced by the significantly faster reaction times in valid cue trials compared to neutral cue trials. These attention benefits were on average slightly larger in the left hemifield, an effect which has been observed previously (Duecker et al., 2013), but does not seem to be a consistent finding (Duecker et al., 2017). In any case, the presence of attention benefits in our data validates our novel symbolic cue, and shows the robustness of cue validity effects (Posner, 1980; Posner et al., 1980).

## 2.12 Discussion

This chapter describes three behavioral experiments in which an experimental adaptation paradigm was applied to a novel domain. Though the adaptation paradigm has already been successfully applied to higher-order cognitive functions (Z. Cattaneo et al., 2012; Kadosh et al., 2010; Webster et al., 2004), it had yet to be investigated whether this paradigm can also be applied to complex cognitive functions that are entirely voluntary. To the best of our knowledge, we were the first to explore this, investigating whether it is possible to adapt the neuronal systems underlying endogenous visuospatial attention. If successful, adaptation of attention to a specific location in space should lead to a deterioration in performance at the adapted location as compared to locations that were not adapted, and as compared to baseline performance. This hypothesis was tested by having participants perform several endogenous cueing task trials after each adaptation phase (Posner, 1980; Posner et al., 1980). All experiments were designed in a way that, if adaptation proved successful, it was possible to answer an additional research question that related to a longstanding debate in cognitive neuroscience. The first question was whether overt and covert spatial attention share the same neuronal mechanisms, and this question could be addressed in all three experiments. The second question was how attention moves through visual space, and could be addressed in Experiment 3. The presented behavioral experiments thus had multiple goals, since we developed and tested a novel experimental task, and simultaneously showed its potential applicability by posing several highly relevant research questions.

First and foremost, our aim was to test whether the 40-second adaptation manipulation could successfully affect attention task performance at specific locations in space. In Experiment 1, we found evidence that performance improved at locations that were not adapted, as compared to the adapted location and baseline performance. This effect was specific to those analyses in which inverse efficiency scores and reaction times were used as dependent variables. We were unable to replicate this effect in Experiment 2. Instead, we found decreased performance at locations that were not adapted when using the proportion of correct trials as a dependent variable. These two (nearly) identical studies thus led to opposite results, both in terms of the direction of the behavioral effect, and in terms of the dependent variable(s) that showed the effect. This finding is

instructive in itself, since it highlights the importance of replication and reproducibility, regardless of whether a certain finding is expected or unexpected, even if a finding is statistically strong. Although it is not entirely clear whether we are facing a real reproducibility crisis in science (Fanelli, 2018), failed replication of research findings is not uncommon – even when replication is attempted by the same experimenters (see, for example, Veniero et al., 2017). Failed replication occurs in many domains of science, but cognitive neuroscience might be especially vulnerable to this problem, as its data are generally noisy (Huber et al., 2019). In order to establish whether an effect is “real” or not, it is therefore essential to perform direct replication studies, to report/publish both positive and negative (null) findings, and to assess the consistency/reliability of findings by visualizing single-subject data.

Considering the inconsistencies between Experiments 1 and 2, we attempted to improve the adaptation paradigm in Experiment 3. The first modification was that attention shifts were cued through means of auditory rather than visual cues during the adaptation phase, which might facilitate central fixation. The second modification was that high contrast gratings were used in the endogenous attention task trials, such that reaction times could be used as the sole dependent variable. Reaction times might be a more sensitive measure compared to response accuracy, in the sense that smaller differences can be detected, while at the same time being less susceptible to large changes due to (accidentally) erroneous responses. Also inverse efficiency scores suffer from various limitations, and can only be used if reaction times and response accuracy are negatively correlated (Bruyer and Brysbaert, 2011; Vandierendonck, 2018). But even with these improvements, the adaptation paradigm did not lead to detectable changes in discrimination performance in Experiment 3. In sum, our three behavioral experiments led to two opposite positive effects and one null finding. We could thus not provide conclusive evidence for the possibility to adapt covert visuospatial attention.

One factor that complicates the interpretability of our findings is participants' fixation stability during the adaptation phase. Since the aim of our experiments was to adapt the neuronal systems underlying covert visuospatial attention, it should be assessed whether our participants managed to centrally fixate throughout the 40-second adaptation phases. Thus far, though, there is no gold standard for measuring fixation stability (Castet and Crossland, 2012; Holmqvist et al., 2011;

Thaler et al., 2013), which is why we selected three commonly used metrics. Here we also found opposing results, since all metrics differed between adaptation phases in Experiment 1, but none differed in Experiment 2 – even though the experimental procedures were identical. It is unclear why this might have occurred. Perhaps, participants in Experiment 2 were more skilled at keeping central fixation. The difficulty lies in the fact that it is impossible to perfectly maintain central fixation for extended periods of time, and that it is unclear what would constitute “good” or “sufficient” fixation stability, or what duration/amount of “truly” covert attention shifts would be necessary in order to cause neuronal adaptation. The heat maps seemed to indicate relatively stable fixation over time in both experiments, but again, it is difficult to develop an objective and valid measure. Notably, in Experiment 2, there were two participants that seemed to have two clusters in their heat map of eyetracking samples. Future studies could prevent this by calibrating the eyetracker multiple times during a session, for instance after every break in the task, or by automatically re-calibrating the eyetracker after detecting a certain amount of shift in average eye position. Another problem is that different fixation stability metrics did not always agree with one another. To name one example, some participants made a lot of saccades, but overall showed relatively low standard deviations and high proportion of eyetracking samples within 1 DVA of central fixation. It is therefore important to further investigate which measure is most accurate, or possibly even combine multiple fixation stability metrics into a single score. Lastly, in experiments that require fixation such as the ones presented here, it is advisable to train participants in central fixation, and possibly to provide them with feedback if they are becoming less accurate in fixating.

As stated previously, these studies constituted the first attempt at adapting covert visuospatial attention, and the parameters of the adaptation paradigm might not have been optimal. For instance, it could be the case that the adaptation phase needs to be longer than 40 seconds in order to achieve any effect. The attention shift interval was set to 1 second, but this might not have been ideal because attention shifts are much faster in naturalistic settings (Baloh et al., 1975). Moreover, participants might not be shifting their attention as often as we want, or they might not shift their attention exactly to the intended location – which are both difficult to control. We did include catch trials to make sure that participants were attentive, but that does not guarantee that they *always* complied with task instructions. To gain some control over participants’ covert attention shifts, future

studies could measure electroencephalography (EEG) data (Sauseng et al., 2005), which should at least be able to show when and to what hemifield attention shifts are being made. Given the limited spatial resolution of EEG (Light et al., 2010), tracking covert attention shifts to several locations within the same hemifield seems difficult; but it is not impossible (Fahrenfort et al., 2017). It would furthermore be interesting to investigate whether microsaccade tracking could provide sufficient information about the accuracy of covert attention shifts (Lowet et al., 2018; Meyberg et al., 2017).

It could be worthwhile to further pursue the attention adaptation paradigm, since it could have many interesting applications if successful. Two unresolved research questions were previously mentioned in this chapter, namely the relation between overt and covert attention systems, and the question as to how attention moves across visual space. Another fruitful direction for future research is to combine the adaptation paradigm with transcranial magnetic stimulation (TMS) (Hallett, 2000; Pascual-Leone et al., 2000; Ziemann, 2010). TMS essentially reactivates the adapted neuronal population and thereby causes an improvement in behavioral performance (Silvanto and Cattaneo, 2017; Silvanto et al., 2007; Silvanto, Muggleton, Kwong, et al., 2008). This has already been proven successful for higher-level cognitive functions such as the processing of affective body movements (Mazzoni et al., 2017), number processing (Kadosh et al., 2010), and language processing (Pattamadilok et al., 2019). Being able to selectively reactivate specific sub-populations of neurons greatly improves the spatial resolution of TMS, by making it possible to selectively target neuronal sub-populations that are intermixed within a single brain region (Silvanto, Muggleton, Kwong, et al., 2008). Such methodological advances are highly relevant, as they allow increasingly detailed and complex questions to be answered, paving the way to a better understanding of the human brain.

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# Chapter 3

## Spontaneous fluctuations in oscillatory brain state cause differences in TMS effects within and between individuals

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### 3.1 Abstract

Transcranial magnetic stimulation (TMS) can cause measurable effects on neural activity and behavioral performance in healthy volunteers. In addition, TMS is increasingly used in clinical practice for treating various neuropsychiatric disorders. Unfortunately, TMS-induced effects often show large intra- and inter-subject variability, hindering its reliability and efficacy. One possible source of this variability may be the spontaneous fluctuations of neuronal oscillations. We present recent studies using multimodal TMS including combined TMS-EMG (electromyography), TMS-tACS (transcranial alternating current stimulation), and the pioneering approach of concurrent TMS-EEG-fMRI (electroencephalography, functional magnetic resonance imaging), to study how individual oscillatory brain state affects TMS signal propagation within targeted networks. We demonstrate how the spontaneous oscillatory brain state at the time of TMS influences both immediate TMS effects (reactivity and signal propagation) and TMS aftereffects (modulation of neuroplasticity). These findings clearly indicate that at least part of the variability in TMS efficacy may be attributable to the current practice of ignoring (spontaneous) fluctuations in neuronal oscillations during TMS. Ignoring this (oscillatory) state-dependent spread of activity, however, may cause great individual variability which so far is poorly understood and has proven impossible to control. We therefore also compare two technical solutions to directly account for oscillatory state during TMS, namely, to use either (a) tACS to externally 'entrain' and control these oscillatory states and then apply TMS at the optimal (controlled) brain state, or (b) oscillatory state-triggered TMS protocols (closed-loop TMS). The described multimodal TMS approaches are paramount for establishing more robust TMS effects, and to allow enhanced control over the individual outcome of TMS interventions aimed at modulating information flow in the brain to achieve desirable changes in cognition, mood, and behavior.

#### *Key words*

Transcranial magnetic stimulation (TMS); inter- and intra-subject variability; neuronal oscillations; multimodal TMS; closed-loop TMS.

## 3.2 Introduction

In 1985, Anthony Barker and colleagues were the first to show that the human brain could be stimulated non-invasively using rapidly changing magnetic fields (Barker et al., 1985). This transcranial magnetic stimulation (TMS) method was virtually painless, required minimal preparation, and offered a flexible stimulation coil which could be rapidly and easily moved between scalp locations (i.e., brain areas). When the TMS coil was placed on the scalp above the motor cortex, movements could be induced in contralateral body parts, and the muscles' responses could be measured using electromyography (EMG) (Hallett, 2000, 2007; Rothwell et al., 1999). These so-called "motor-evoked potentials" (MEPs) are caused by the excitation of corticospinal neurons (Berardelli et al., 1990; Burke et al., 1993; Lazzaro et al., 1998), and MEPs are still used in contemporary research as a measure of motor cortex excitability (Boroojerdi et al., 2002; Rossini et al., 2015).

Given its ability to directly influence brain processing (Romero et al., 2019), TMS can serve several purposes. It can be used to investigate whether and when a brain area is causally relevant for a cognitive function (de Graaf et al., 2015; de Graaf et al., 2009; Jacobs et al., 2012; Sack, 2006; Sack et al., 2006; Schuhmann et al., 2009), and to map the brain's functional connectivity profile (Arai et al., 2012; Bäumer et al., 2009; de Graaf et al., 2012; de Graaf et al., 2009; Pascual-Leone et al., 2000; Reithler et al., 2011; Sack et al., 2007; Sack and Linden, 2003). Since its development, TMS has therefore been widely used in cognitive neuroscience research (O'Shea and Walsh, 2007; Walsh and Cowey, 2000), not only to map the motor cortex (Gunduz et al., 2020), but also to study domains such as visual perception (Amassian et al., 1989; de Graaf et al., 2014; de Graaf and Sack, 2014; Jacobs et al., 2012; Jacobs et al., 2014; Janssens, Sack, Jessen, et al., 2020; Kammer, 2007), attention (Ashbridge et al., 1997; Duecker and Sack, 2015; Ronconi et al., 2014; Rushworth and Taylor, 2006; Sack et al., 2007; Sack et al., 2002), imagery (Cattaneo et al., 2012; Sack et al., 2005; Sack et al., 2002), language (Acheson and Hagoort, 2013; Pascual-Leone et al., 1991; Schuhmann et al., 2012; Tarapore et al., 2013), learning (de Weerd et al., 2012; Platz, Roschka, Christel, et al., 2012; Platz, Roschka, Doppl, et al., 2012), and memory (Bonni et al., 2015; Ferrari et al., 2018; Osaka et al., 2007; Rademaker et al., 2017; van de Ven et al., 2012; van de Ven and Sack, 2013). In addition, TMS is increasingly used in clinical practice for treating various neuropsychiatric disorders

(de Graaf, Janssens, et al., 2021; de Graaf, Thomson, et al., 2021; Lefaucheur et al., 2020; Lefaucheur et al., 2014). TMS is used during stroke rehabilitation (Di Pino et al., 2014; Hummel and Cohen, 2006; Wessel et al., 2015), and as treatment for depression (Baeken et al., 2019; Donse et al., 2018; Loo and Mitchell, 2005; Perera et al., 2016; Sonmez et al., 2019) and schizophrenia (Cole et al., 2015).

### 3.3 Immediate and aftereffects of TMS show high inter- and intra-subject variability

Given the widespread use of TMS in research and clinical settings, one might assume that TMS generally leads to positive and consistent findings. Yet, the effects of TMS are not always robust and reliable. Inconsistent TMS effects between experiments or clinical trials could partially be due to methodological factors, such as differences in the coil placement method (Beam et al., 2009; Gomez et al., 2021; Rusjan et al., 2010). But even if methodological factors are kept constant, TMS effects can show substantial variability. There are two types of variability in the effects of TMS: different individuals may respond differently to TMS (*inter-subject variability*), and the effect of TMS may differ within the same individual over time (*intra-subject variability*). We should furthermore distinguish between two types of TMS effects: the *immediate* effects of single-pulse TMS, and the *aftereffects* of repetitive TMS (“rTMS”). Below, we present evidence that suggests that both the immediate and aftereffects of TMS show substantial inter- and intra-individual variability.

The *immediate* effects of single-pulse TMS to the primary motor cortex are often measured with MEPs, which provide a measure of the momentary TMS reactivity (Rossini et al., 2015). Within the same individual, TMS-MEP amplitudes vary over trials (Burke et al., 1995; Goetz et al., 2014; Goldsworthy, Hordacre, et al., 2016; Kiers et al., 1993; Rösler et al., 2008; Wassermann, 2002). Interestingly, optimization of TMS target localization does not necessarily improve the variability and reproducibility of TMS-induced MEPs (Jung et al., 2010). This finding already suggests that factors beyond the TMS parameters may contribute to immediate TMS reactivity. Such variability in immediate TMS effects is not limited to the motor network. When stimulating early visual cortex, some individuals can perceive ‘phosphenes’ (an illusory percept). The “phosphene threshold” (the

minimal TMS intensity required to perceive a phosphene in half of the cases) is often used as a measure of visual cortex excitability (Bestmann et al., 2007; Borojerdj et al., 2002; de Graaf et al., 2017). The probability of inducing phosphenes within the same participant can vary over time (Dugué et al., 2011; Gerwig et al., 2003; Romei, Brodbeck, et al., 2008; Romei, Rihs, et al., 2008).

Variability in TMS *aftereffects* can be illustrated by evaluating individual responses to rTMS protocols that were designed to modulate synaptic plasticity beyond the duration of stimulation (Pascual-Leone et al., 1998; Ridding and Ziemann, 2010). Low (<1 Hz) and high (>1 Hz) frequency rTMS were originally reported to decrease and increase the excitability of the human motor cortex, respectively (Wassermann et al., 1998). This may indeed be the case on average, but when inspecting individual responses, not all participants showed these effects (Maeda et al., 2000). Similarly, intermittent and continuous theta burst stimulation (iTBS and cTBS, two forms of patterned rTMS) were reported to enhance and suppress motor cortex excitability for ~30 minutes after stimulation, respectively (Y. Huang et al., 2005). These findings have not always been replicated in another subject sample (Goldsworthy et al., 2012; Hordacre et al., 2017), and even if they are present at the group level, not all individuals show these effects (Cheeran et al., 2008; Nettekoven et al., 2015; Schilberg et al., 2017). In fact, one study reported that only 1 in 4 participants showed the expected pattern of results (Hamada et al., 2013). Another TMS procedure aimed at modulating neuroplasticity is called “paired associative stimulation” (PAS). Originally, PAS involved peripheral nerve stimulation that was paired with single-pulse TMS to primary motor cortex in order to enhance corticomotor excitability (Stefan et al., 2000), but PAS has also been employed to facilitate communication between the motor cortex and interconnected cortical areas (Veniero et al., 2013). As for the other plasticity-inducing TMS protocols, there is high inter-subject variability in the effects of PAS (Florian et al., 2008; López-Alonso et al., 2014; Sale et al., 2007), with a recent study reporting that only 61% of participants responded to PAS (Minkova et al., 2019).

Besides inter-subject variability, TMS aftereffects also show significant intra-subject variability. Some reports indicated that the aftereffects of iTBS and cTBS were relatively stable within the same individuals (Hinder et al., 2014; Vernet et al., 2014), but a recent study showed the opposite (Schilberg et al., 2017).

Schilberg and colleagues (2017) further investigated the within-subject reliability of iTBS effects over the course of 60 minutes, and across two experimental sessions that were scheduled ~8 days apart. They found that the effect of iTBS on corticospinal excitability (as measured with MEP amplitude) differed between sessions. The average increase in MEP amplitude was approximately 23% in the first session, but only approximately 6% during the second visit.

From these examples, it becomes clear that TMS effects show considerable inter- and intra-subject variability, for both the immediate effects of single-pulse TMS (MEP amplitudes, phosphene induction) and the longer-lasting plasticity effects as induced by rTMS, TBS, or PAS. The limited consistency of TMS effects can have negative consequences in research and clinical settings, because TMS effects are not always predictable or optimized. If TMS effects are not sufficiently reliable, they thus have limited use as a biomarker for individual changes in neuroplasticity and concomitant desirable changes in cognition and behavior (Schambra et al., 2015). It is therefore important to identify the factors that contribute to the variability of TMS effects (Corp et al., 2020, 2021), such that the consistency and efficacy of TMS can be improved. We here discuss one possible source of this variance, namely, spontaneous fluctuations in neuronal oscillations (Bergmann, 2018; Buzsáki and Draguhn, 2004; Iscan et al., 2016; Pasley et al., 2009). Below, we explain how spontaneous fluctuations in oscillatory brain state contribute to variability both in the immediate effects of TMS and in TMS-induced plasticity effects.

### 3.4 Spontaneous fluctuations in neuronal oscillations contribute to variations in immediate TMS effects

To investigate the link between TMS effect variability and ongoing neuronal oscillations, TMS can be combined with magneto- or electroencephalography (M/EEG). Specific characteristics of neuronal oscillations (i.e., their frequency, power, or phase; Palva and Palva, 2007) might be correlated with the immediate responsivity to single-pulse TMS. Indeed, the probability of inducing phosphenes when applying TMS to early visual cortex was negatively correlated with EEG alpha power prior to TMS (Romei, Brodbeck, et al., 2008; Romei, Rihs, et al., 2008). The probability of perceiving TMS-induced phosphenes was also associated

with the phase of ongoing EEG alpha oscillations (Dugué et al., 2011). Results have been less clear for the motor system. Some studies reported a negative association between pre-TMS EEG alpha power and TMS-induced MEP amplitude (Sauseng et al., 2009; Zarkowski et al., 2016). Others reported a negative association between TMS-MEP amplitude and oscillatory beta power (Lepage et al., 2008; Mäki and Ilmoniemi, 2010; Schulz et al., 2014), or no relation with oscillatory power in any frequency band (Berger et al., 2014; Mitchell et al., 2007). Spontaneous fluctuations in the phase of ongoing beta (Keil et al., 2014) and alpha (Bergmann et al., 2019; Schaworonkow et al., 2018; Schaworonkow et al., 2019) oscillations may also play a role in TMS-MEP variability. Note that inconsistencies across studies may in part be explained by methodological differences, such as differences in TMS intensity (Pellegrini et al., 2018).

Schilberg and colleagues (2021) recently assessed the relation between the power and phase of ongoing EEG alpha and beta oscillations with motor cortex TMS reactivity. They found that TMS-MEP amplitude correlated positively with pre-TMS oscillatory power in the alpha and beta bands. The authors also reported a significant effect of alpha phase on TMS-MEP amplitude, but there was no consistent alpha phase that led to high TMS-MEP amplitudes across participants. The latter is in contrast with previous reports showing that higher TMS-induced MEP amplitudes are mostly induced during alpha troughs instead of peaks (Schaworonkow et al., 2018; Schaworonkow et al., 2019; Zrenner et al., 2018). Interestingly, a standard FFT analysis did not reveal a significant correlation between pre-TMS beta phase and TMS-MEP amplitude, while a Hilbert transform did show an effect (Schilberg et al., 2021). This discrepancy between analyses may be partially explained by the variability in individual beta frequency (IBF), which is larger than the variability in individual alpha frequency (IAF) (Haegens et al., 2014). The Hilbert transform is less affected by frequency variations compared to the FFT approach, since the former can be used for non-stationary time series (Schilberg et al., 2021). Another contributing factor might be that participants were not involved in any active motor task. Ongoing beta power was therefore naturally low, making it more difficult to reliably estimate beta phase. When TMS is applied at high beta power, the relation between beta phase and TMS-MEP amplitude indeed becomes evident (Torrecillos et al., 2020). In any case, most of the evidence presented above is of correlational nature, because oscillations were measured rather than experimentally manipulated.

### 3.5 Direct evidence for a causal link between (controlled) oscillatory state and variations in immediate TMS effects

Transcranial alternating current stimulation (tACS) can be used to establish the causal relevance of neuronal oscillations (Herrmann et al., 2016). TACS is a form of non-invasive brain stimulation (NIBS) that involves electrical stimulation with a sinusoidal waveform (Antal and Paulus, 2013). It can be used to enhance the power of oscillations of a certain frequency within the stimulated brain area (Herrmann et al., 2013; Vieira et al., 2020; Vossen et al., 2015), potentially through mechanisms of entrainment (W. Huang et al., 2021; Thut et al., 2011) or spike-timing dependent plasticity (Herrmann et al., 2013; Vossen et al., 2015). The causal relevance of oscillatory phase can then be established by presenting stimuli at certain phases of the tACS waveform (de Graaf et al., 2012). It was previously shown that it is possible to apply TMS at certain tACS phases with high temporal precision (ten Oever et al., 2016), and that it is feasible to use simultaneous tACS-TMS to investigate the causal relation between oscillatory tACS phase and TMS-MEP amplitudes (Raco et al., 2016). The same logic was applied by Schilberg and colleagues (2018), who administered TMS pulses at eight equidistant phases of a tACS waveform, using IBF-, IAF-, or sham tACS to primary motor cortex. The authors found that tACS modulated TMS-MEP amplitude only for the IBF-tACS condition, and this effect seemed to be specific to individuals with lower IBF frequencies (Schilberg et al., 2018). These findings suggest that beta-tACS phase at the time of TMS influences the immediate effects of TMS (*intra-subject variability*), and that this effect interacts with the individual dominant beta frequency (*inter-subject variability*) (Haegens et al., 2014).

### 3.6 Spontaneous fluctuations in neuronal oscillations contribute to the propagation of TMS pulses through functionally connected networks

Simultaneously combining TMS with M/EEG or tACS is an excellent approach to investigate the link between ongoing neuronal oscillations and the variability of TMS effects. However, this approach does not allow an accurate (high-resolution) visualization of the immediate effects of TMS at the level of the brain. Functional magnetic resonance imaging (fMRI) can be used to visualize TMS signal

propagation, given its potential to measure whole-brain activation with good spatial resolution (Bestmann et al., 2008; Reithler et al., 2011; Sack, 2006; Sack and Linden, 2003; Walsh and Cowey, 2000). Simultaneous TMS-fMRI studies have shown that the effects of TMS pulses can extend beyond the targeted brain area, since signals can spread towards interconnected brain areas (Blankenburg et al., 2010; Ruff et al., 2006; Sack et al., 2007). Though the local effects of TMS pulses do not reach deeper than the superficial cortex, remote effects can even be observed in subcortical areas (Bergmann et al., 2021). Nonetheless, to achieve a full understanding of how TMS pulses propagate through functionally connected networks, it is important to investigate whether and how TMS-evoked fMRI responses vary as a function of ongoing neuronal oscillations on a trial-by-trial level. This was made possible with a unique setup, which simultaneously combines TMS, EEG, and fMRI.

This technically challenging experimental triad approach was introduced by our lab in 2013 (Peters et al., 2013). We demonstrated that concurrent TMS-EEG-fMRI is feasible and safe in both phantom and human measurements, and we showed that the EEG and fMRI data were of sufficient quality. Yet, the full potential of this approach only became apparent in a recent publication from our lab, in which we mapped whole-brain TMS signal propagation as a function of the pre-TMS oscillatory state as indexed by simultaneous EEG (Peters et al., 2020). In four healthy individuals, we applied triple-pulse (15 Hz) TMS to the right dorsal premotor area (PMd), while continuously measuring EEG. Triple-pulse TMS was used to probe the motor network with a sufficiently strong stimulus, rather than to modulate neuroplasticity as with typical rTMS protocols (the findings described here thus relate to *immediate* TMS effects).

TMS to PMd evoked both local and remote fMRI activation in a cortico-subcortical motor network, resembling the activations as seen for voluntary movements. It again became evident that different individuals may respond differently to TMS (*inter-subject variability*): two individuals showed fewer/more confined activations in response to TMS compared to the other two individuals. These individuals also showed less engagement of the motor network irrespective of TMS (“low activators”, the others were called “high activators”). It should be noted that the difference in TMS-evoked responses may in part be due to differences in TMS intensity between the “low activators” and “high activators”. In

any case, to evaluate immediate TMS-evoked responses within the cortico-subcortical motor network as a function of oscillatory state, it was crucial that participants showed reliable engagement of the motor network. The EEG-informed analyses were therefore performed only for the two “high activators”.

The main question of interest was whether TMS signal propagation within a cortico-subcortical motor network varies with pre-TMS parietal alpha power. Pre-TMS alpha power was negatively correlated with TMS-evoked fMRI responses in both local and remote (including subcortical) areas of the motor network. This negative association is in line with the supposed inhibitory role of alpha oscillations (Klimesch et al., 2007). From these findings, we can conclude that, within the same individual, TMS pulses may propagate differently throughout the motor network depending on pre-TMS oscillatory state (*intra-subject variability*). Our group has recently also established the feasibility of using simultaneous TMS-EEG-fMRI for non-motor areas (Janssens, Sack, Duecker, et al., 2020). This comes with additional technical challenges, including the determination of the TMS site and intensity, because most non-motor areas are so-called “silent” areas that do not show any overt response to TMS.

### 3.7 Direct evidence for a causal link between (controlled) oscillatory state and variations in TMS aftereffects

Thus far, we focused on within- and between-subject variability in the *immediate* effects of TMS, and how such variability can be linked to ongoing neuronal oscillations. There is reason to believe that changes in oscillatory state also contribute to variations in TMS-induced neuroplasticity (*TMS aftereffects*). Goldsworthy and colleagues (2016) applied cTBS to the primary motor cortex, while phase-aligning the TMS pulses to either the peak or the trough of concurrent alpha-tACS. They investigated whether the response to cTBS, as measured with TMS-induced MEP amplitudes, depended on the alpha-tACS phase. The excitability of the motor cortex was suppressed (i.e., TMS-MEP amplitudes were reduced) when cTBS was aligned with alpha-tACS troughs. Crucially, cTBS did not modulate motor cortex plasticity when cTBS was aligned with alpha-tACS peaks. Furthermore, the effect of tACS-trough-aligned cTBS was greater for individuals

with higher IAFs (Goldsworthy, Vallence, et al., 2016). Thus, TMS-induced neuroplasticity may vary both as a function of the controlled momentary oscillatory state and the intrinsic dominant oscillatory frequency.

Besides oscillatory phase, the power of ongoing neuronal oscillations might be relevant for TMS-induced neuroplasticity as well. Guerra and colleagues (2018) showed that concurrent gamma tACS enhanced and prolonged iTBS-induced increases in TMS-MEP amplitude, in contrast to beta-tACS and sham-tACS (Guerra et al., 2018). This positive effect of simultaneous gamma tACS on iTBS efficacy was later replicated, but it seems that simultaneous gamma tACS *reduced* the efficacy of cTBS (Guerra, Ascii, et al., 2020). These findings are especially relevant in a clinical context, where the goal is to employ rTMS to modulate neuroplasticity for longer periods of time. It would be beneficial to optimize plasticity-inducing TMS protocols based on oscillatory brain state, such that treatment efficacy can be improved.

### 3.8 Accounting for spontaneous fluctuations in neuronal oscillations during TMS

Thus far, we have outlined that immediate and prolonged TMS effects vary considerably within- and between-individuals. We also showed that spontaneous fluctuations in neuronal oscillations can explain at least part of the variability in TMS effects, as can more stable oscillatory characteristics (individual peak frequencies). The question then becomes: how can we incorporate such oscillatory information into our TMS protocols?

The first step is to form a clear hypothesis regarding the to-be-targeted oscillatory frequency, since different frequency bands are associated with different functions (Başar et al., 1999; Clayton et al., 2018; Ward, 2003). Even within the same (e.g., alpha) frequency band, there might be different functionally relevant oscillation generators in the brain, which are not easily disentangled in the M/EEG signal (Bollimunta et al., 2011; Haegens et al., 2015; Sokoliuk et al., 2019). More advanced techniques might be needed to extract the relevant oscillatory frequency from the M/EEG signal (Schaworonkow et al., 2018). Once the relevant oscillatory frequency has been determined, there are two potential technical solutions that can

directly account for oscillatory brain state during TMS: simultaneous tACS-TMS, and M/EEG-based “closed-loop” TMS (Y. Huang et al., 2017).

As discussed previously, TMS can be applied at the (controlled) optimal tACS phase (Fehér et al., 2017; Raco et al., 2016; ten Oever et al., 2016). Crucially, individuals differ in terms of their oscillatory brain rhythms. For instance, peak alpha frequencies (IAFs) can range between 7 and 14 Hz across individuals (Haegens et al., 2014). To ensure optimal tACS efficacy, it is therefore important to individually calibrate the tACS frequency, for instance based on a resting state M/EEG measurement (Janssens et al., 2021) or through functional identification (Gundlach et al., 2017; Schilberg et al., 2018). Besides personalizing the tACS frequency, it might also be necessary to individually determine the optimal tACS phase to deliver TMS, given the recent finding that no consistent alpha phase was correlated to high TMS-MEP amplitudes (i.e., high TMS responsivity) across participants (Schilberg et al., 2021). Simultaneous tACS-TMS has already been used to link tACS beta phase to motor cortex TMS reactivity (Guerra et al., 2016; Schilberg et al., 2018). It has furthermore been shown that single TMS pulses applied to dorsolateral prefrontal cortex propagate differently through a cortical network depending on the phase of concurrent theta-tACS (Fehér et al., 2017). Thus, by applying single-pulse TMS at the optimal (controlled) tACS phase, TMS signal propagation may be modulated. Besides its relevance for immediate TMS effects, tACS can also be used to enhance and prolong TMS aftereffects, as described above (Goldsworthy, Hordacre, et al., 2016; Guerra, Ascii, et al., 2020; Guerra et al., 2018).

Simultaneous tACS-TMS is useful, but not perfect. Individual peak frequencies show good within-subject test-retest reliability (Grandy et al., 2013; Haegens et al., 2014; Janssens et al., 2021), but peak frequencies can still fluctuate, and the extent to which this happens differs across individuals. For example, IAF decreased over the course of one hour during visual task performance, with some participants showing reductions of up to 2 Hz (Benwell et al., 2019). If tACS were to be applied at the originally determined peak frequency, tACS efficacy may be compromised, since the matching between the endogenous dominant frequency and the driving (tACS) frequency would not always be optimal (Romei et al., 2016). The best approach might thus be to continuously track the instantaneous dominant frequency, and to adjust the tACS frequency accordingly. However, it is difficult to

recover EEG signals during tACS due to the sizeable tACS artifacts (Kasten and Herrmann, 2019). Another complication of the simultaneous tACS-TMS approach is that if the effect of tACS on oscillatory activity is not verified through means of concurrent M/EEG measurements, we cannot be certain that the applied tACS phase corresponds to the phase of ongoing neuronal oscillations. Finally, it could be the case that there is an “optimal” amount of oscillatory power, in the sense that if tACS enhances oscillatory power above a certain threshold, it might reduce the reactivity of a brain area to TMS.

In contrast to simultaneous tACS-TMS, the second technical solution to account for oscillatory brain state during TMS does measure ongoing neuronal oscillations. In this so-called “closed-loop” TMS approach, the M/EEG signal is continuously measured, and the timing of TMS pulses is adjusted to the optimal power and/or phase of the ongoing oscillations (Bergmann et al., 2016; Guerra, López-Alonso, et al., 2020; Thut et al., 2017; Zrenner et al., 2016). This method can only be successful if the instantaneous phase can be reliably estimated (that is, if the power of the ongoing oscillations is sufficiently high). This has two important implications if the aim is to target specific oscillatory phases. Firstly, it might be necessary to control participants’ cognitive state (i.e., task engagement versus rest) to ensure high oscillatory power. Secondly, the closed-loop TMS approach might fail in individuals that show naturally/pathologically low oscillatory power.

Irrespective of these technical challenges, EEG-based closed-loop TMS has already been applied successfully. It was shown that MEP amplitudes were higher during the rising phase of ongoing slow (<1 Hz) oscillations compared to the falling phase, when TMS was applied to primary motor cortex (Bergmann et al., 2012). Interestingly, these findings were consistent across two neurocognitive states (wakefulness and sleep). In another study, rTMS applied to primary motor cortex at the troughs of the ongoing alpha rhythm enhanced MEP amplitudes, while rTMS applied at alpha peaks did not (Zrenner et al., 2018). These findings clearly show that temporally targeting TMS pulses to the optimal oscillatory state improves its efficacy both in terms of signal propagation (*immediate effects*) and the induction of neuroplasticity (*aftereffects*).

### 3.9 Conclusion

TMS is widely used in both research and clinical settings. Still, its immediate and prolonged effects are not robust and reliable, as is evident from both intra- and inter-subject variability. One potential source of this variability may be the spontaneous fluctuations of neuronal oscillations. We showed this for both immediate TMS effects (TMS-MEP amplitudes, TMS phosphene induction, TMS-fMRI signal propagation), and for TMS aftereffects (of rTMS, TBS, or PAS). The oscillatory brain state can be accounted for during TMS by using either simultaneous tACS-TMS or closed-loop M/EEG-TMS. This may reduce both inter- and intra-individual variability in TMS effects. The described multimodal TMS approaches allow enhanced control over the individual outcome of TMS protocols aimed at modulating information flow and/or neuronal plasticity in the healthy and diseased brain. They therefore pave the way to stronger and more consistent TMS-induced improvements in cognition, mood, and behavior.

## 3.10 References

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# *Chapter 4*

## **Assessing brain-wide TMS-evoked responses depending on neurocognitive and oscillatory state: a simultaneous TMS-EEG-fMRI project**

**Based on:**

Janssens, S. E. W., de Graaf, T. A., Duecker, F., Schuhmann, T., & Sack, A. T. (2022). Assessing TMS-evoked cognitive network responses depending on neurocognitive and oscillatory brain state: A simultaneous TMS-EEG-fMRI project. *BioRxiv*. <https://doi.org/10.1101/2022.04.07.487517>.

## 4.1 Abstract

Complex cognition arises from information exchange within and between functionally connected brain networks. Alterations in such signal propagation across networks are linked to numerous disorders. Brain-wide signal propagation can be experimentally studied with simultaneous transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI), where TMS pulses introduce a signal at a certain network node and fMRI charts its propagation through the network. Yet, this approach ignores the fact that the (network) impact of a TMS pulse depends on brain state, where brain state fluctuates spontaneously from moment to moment (e.g. oscillatory state) as well as depending on what a participant does (neurocognitive state). Here, we assessed TMS-evoked fMRI activations as a function of neurocognitive state (eyes open versus eyes closed in complete darkness) and oscillatory state (low versus high pre-TMS alpha power, as measured with simultaneous electroencephalography (EEG)). We applied supra-versus sub-threshold triple-pulse TMS to the right posterior parietal cortex in eight participants, while simultaneously recording EEG and fMRI during two different ocular states. In this first application of the multimodal TMS-EEG-fMRI paradigm to a cognitive network hub, we unfortunately did not find evidence for a brain state modulation of TMS-induced signal propagation. Instead, we found state-independent TMS-evoked fMRI responses mostly in sensory areas such as the insula, superior temporal gyrus, anterior cingulate cortex, and thalamus, but also in the frontal eye fields. Interestingly, neurocognitive state did seem to modulate the fMRI response to non-specific (indirect) TMS effects such as sensory stimulation. These results lead to several important insights for future cognitive multimodal TMS experiments.

### *Key words*

Transcranial magnetic stimulation (TMS); functional magnetic resonance imaging (fMRI); electroencephalography (EEG); neurocognitive state; oscillatory state; brain-state-dependent TMS.

## 4.2 Introduction

A long-held assumption in the field of cognitive neuroscience is that specific cognitive functions can be mapped onto single brain areas, or “modules” (Fuster, 2000). However, accumulating evidence suggests that complex cognitive functions rely on communication between distributed and interconnected brain areas (Beaty et al., 2019; Braun et al., 2015; Bressler and Menon, 2010; Heinze et al., 1997; Mill et al., 2017; Schurz et al., 2020). Though the structural connections within the human brain are (relatively) stable over time, the brain nevertheless flexibly adapts to current environmental requirements through reconfiguration of dynamic functional connections (Bola and Sabel, 2015; Cohen and D’Esposito, 2016; McIntosh, 2000; Park and Friston, 2013). Several core functional brain networks have been identified (Deco et al., 2010), including the salience network (Seeley, 2019), the central-executive network (Chen et al., 2013), and the default mode network (Harrison et al., 2008; Raichle, 2015). Alterations in the functional connectivity of such networks are associated with a wide variety of disorders, including obesity (García-García et al., 2013), schizophrenia (Whitfield-Gabrieli and Ford, 2012), and depression (Mulders et al., 2015), and functional connectivity can predict treatment response (Cao et al., 2018; Moreno-Ortega et al., 2019; Reggente et al., 2018). Gaining an understanding of how signals propagate within- and between- such functionally connected brain networks is therefore essential, not only for fundamental research but also for clinical applications.

One way to investigate the propagation of signals through the brain is by using transcranial magnetic stimulation (TMS) in combination with functional magnetic resonance imaging (fMRI) (Bergmann et al., 2016; Bergmann et al., 2021; Bestmann et al., 2008; Driver et al., 2009; Polanía et al., 2018; Reithler et al., 2011; Ruff, Driver, et al., 2009). In this context, TMS serves as a non-invasive “system probe”, since it allows the direct stimulation of a cortical brain area (Hallett, 2000, 2007; O’Shea and Walsh, 2007; Pascual-Leone et al., 2000; Walsh and Cowey, 2000). It thus introduces a “signal” to a predetermined network node, while concurrent fMRI can then be used to visualize the propagation of such TMS-induced activation (signal) to functionally connected cortical (Hawco et al., 2018; Ruff et al., 2008; Ruff et al., 2006; Ruff, Blankenburg, Bjoertomt, Bestmann, Weiskopf, et al., 2009; Sack et al., 2007) and sub-cortical (Denslow et al., 2005; Oathes et al., 2021; Vink et al., 2018) areas. Crucially, the impact of TMS may depend on the current brain state, which can vary

for instance depending on what the participant is doing (*neurocognitive state*).

At any moment in time, individuals may be subjected to specific environmental demands, which may require them to switch to a different neurocognitive state. In an experimental setting, participants may be performing a cognitively demanding task, or may be asked to open their eyes, or to close their eyes. Such different neurocognitive states are associated with distinct underlying brain network signatures (Bianciardi et al., 2009; Wang et al., 2015; Yang et al., 2007; Yuan et al., 2014). For instance, eyes open versus eyes closed resting state is associated with differential functional connectivity patterns (Agcaoglu et al., 2019; Costumero et al., 2020; Hüfner et al., 2009; McAvoy et al., 2012; Weng et al., 2020; Yan et al., 2009; Zou et al., 2009), independent from light input (Jao et al., 2013; Marx et al., 2004; Marx et al., 2003). While eyes closed resting state engages an “interoceptive” brain network with activations in sensory brain areas, eyes open resting state engages an “exteroceptive” brain network with activations in oculo-motor and attention brain areas (Marx et al., 2003; Wei et al., 2018; Xu et al., 2014). Given these findings, it is conceivable that TMS-induced activity may spread differently throughout the brain during different neurocognitive states. Indeed, it has already been established that the neurocognitive state during TMS can influence TMS signal propagation (Blankenburg et al., 2010; Feredoes et al., 2011; Heinen et al., 2014; Heinen et al., 2011; Leitão et al., 2013a).

However, this approach is incomplete, because the impact of TMS not only depends on the neurocognitive state, but also on momentary fluctuations in neuronal oscillations (*oscillatory state*). Spontaneous oscillatory fluctuations even occur within the same neurocognitive state (e.g., Benwell et al., 2019; Nelli et al., 2017). Neuronal oscillations arise from rhythmic activations of neuronal ensembles, and can be measured with magneto-/encephalography (M/EEG) (Buzsáki and Draguhn, 2004). The peak frequency, power, and phase of neuronal oscillations in specific frequency bands vary over time within the same individuals (Benwell et al., 2019; Haegens et al., 2014; Janssens et al., 2021). Fluctuations in the 7 – 13 Hz oscillatory alpha band are related to the impact of TMS. For instance, there is an inverse relationship between EEG alpha power and the reactivity of the motor cortex (Schilberg et al., 2021) and visual cortex (Romei, Brodbeck, et al., 2008; Romei, Rihs, et al., 2008) to TMS. Using an innovative concurrent TMS-EEG-fMRI set-up, it was recently shown that the propagation of TMS-induced fMRI

activations throughout a cortico-subcortical motor network varies with pre-TMS alpha power (Peters et al., 2020). The standard practice of ignoring the oscillatory state during TMS may contribute to the substantial variability of TMS effects (Corp et al., 2021; Janssens and Sack, 2021; Pasley et al., 2009). Thus, there is a need to further assess how oscillatory state fluctuations may impact TMS signal propagation.

This study aims to combine these different lines of research, assessing whether TMS signal propagation depends on the neurocognitive and/or oscillatory brain state at the time of TMS, when TMS is applied to the right posterior parietal cortex (PPC). For the first time, the technically challenging simultaneous TMS-EEG-fMRI set-up was employed to target a known cognitive network hub (van den Heuvel and Sporns, 2013; Yan and He, 2011) rather than a motor network hub (Peters et al., 2020; Peters et al., 2013). In eight participants, we applied supra- versus sub-threshold 15 Hz triple-pulse TMS to right PPC during fMRI scanning acquisition gaps. The neurocognitive state was manipulated by including the simplest “tasks” imaginable in this first attempt, namely by instructing participants to open or close their eyes in complete darkness. The oscillatory brain state (i.e., low versus high alpha power) was measured from the EEG signal immediately preceding TMS. We first established that within-subject oscillatory brain state fluctuations were present in our experiment. We then validated that our manipulation of neurocognitive state was non-collinear with the spontaneous fluctuations in oscillatory state. Finally, we evaluated TMS-evoked fMRI activations as a function of neurocognitive state and oscillatory state. These TMS effects were evaluated in group analyses on three levels: across the whole brain, across the cortical surface, and in four regions of interest (left posterior parietal cortex, right posterior parietal cortex (TMS stimulation site), left thalamus, and right thalamus). Looking ahead, we did not obtain the key hypothesized finding of brain-state dependent TMS-induced signal propagation. Yet, our results do seem to indicate that fMRI responses to the side-effects of TMS were modulated by neurocognitive state.

## 4.3 Methods

### Participants

Eight healthy, right-handed volunteers participated in the current experiment (3 males, ages 23 – 38). Participants were screened for transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) contraindications and had prior experience with these two methods (Rossi et al., 2021; Rossi et al., 2009). Prior experience with electroencephalography (EEG) was not required. Participants provided written informed consent and were compensated with 10 euros in vouchers per hour. The experiment was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN).

### Procedures

The experiment involved one session of approximately 3.5 – 4 hours. Participants came into the lab 90 minutes prior to the start of the MRI scanning timeslot. They were first informed about the experiment and then signed the required screening and informed consent forms. Once the EEG preparation was nearly finished, all equipment was moved to the MRI console room. Preparation of the TMS-EEG equipment in the MRI scanner room, determination of the TMS stimulation intensities (see below) and positioning of the TMS coil took approximately 30 – 45 minutes. The scanning took maximally one hour, depending on participant comfort. Participants were then debriefed about the hypotheses of our study and received their compensation.

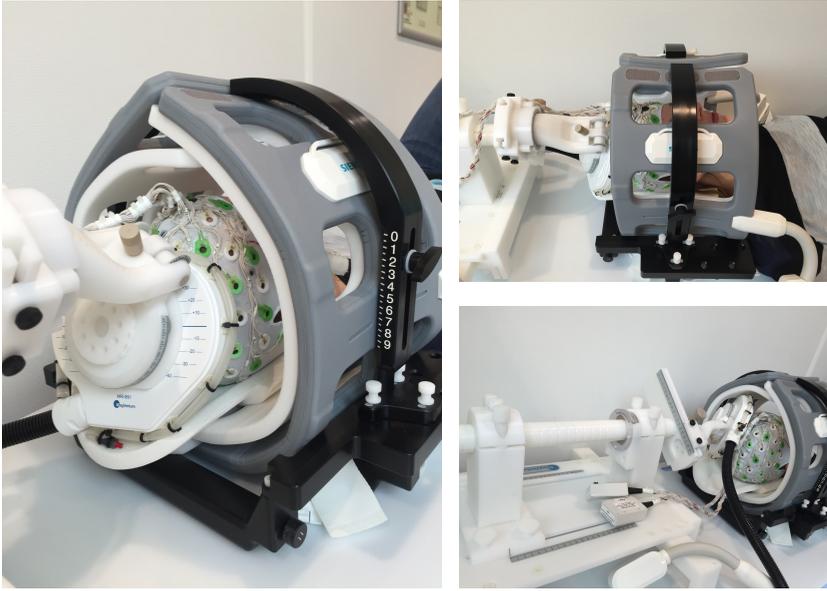
A complete description of the simultaneous TMS-EEG-fMRI setup, including safety and quality assurance measurements, can be found in a previous publication from our lab (Peters et al., 2013) (see Figure 4.1a). We applied sub- versus supra-threshold triple-pulse TMS to right posterior parietal cortex (PPC), a highly interconnected network hub and association area (van den Heuvel and Sporns, 2013; Yan and He, 2011), while acquiring simultaneous fMRI and EEG measurements. Ocular state was manipulated in complete darkness, thereby creating two neurocognitive states. A one-second tone was used to cue participants to open versus close their eyes (700 Hz vs 300 Hz, respectively) until instructed otherwise, while wearing a blindfold (Mindfold Inc., Tucson, Arizona, USA). All

participants indicated that they could easily distinguish between the high and low frequency tones and could comply with the instructions. The task was controlled with PsychoPy (v1.90.3) along with Python (version 2.7.15). Condition order was pseudo-randomized, with one level of each factor occurring maximally three times in a row. In this  $2 \times 2$  design (“eye closure”: open versus closed & “TMS intensity”: sub- versus supra-threshold), we analyzed blood-oxygenation level-dependent (BOLD) signal changes following TMS. We furthermore assessed whether TMS-evoked effects depended on the alpha power immediately preceding TMS.

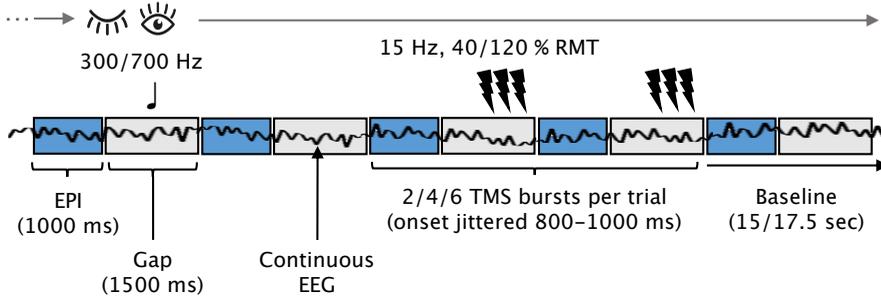
### **(F)MRI parameters**

Data were acquired on a 3 Tesla Magnetom Prisma scanner using two 4-channel MRI flex coils (Siemens, Erlangen, Germany) to create sufficient space for the TMS-EEG equipment (see Figure 4.1a). Pillows were added below the participants’ head and neck, and on both sides of the head, to increase comfort and to minimize head motion. We collected three ( $n=1$ ), five ( $n=1$ ), seven ( $n=1$ ) or eight ( $n=4$ ) functional runs of 6.25 minutes (150 volumes), or two ( $n=1$ ) functional runs of 12.5 minutes (300 volumes) (echo-planar imaging (EPI), 3 mm isotropic resolution, multiband 2 with interleaved slice excitation, 30 slices with R>L encoding direction, FoV =  $222 \times 168$  mm, TR = 2500 ms including a 1500 ms gap, TE = 30 ms, FA =  $62^\circ$ , bandwidth 1536 Hz/Px). While EEG was recorded throughout the functional runs, TMS was delivered only within EPI acquisition gaps (see Figure 4.1b). During the first TR of each trial, an instructive sound stimulus was presented during the EPI acquisition gap. We furthermore acquired a 3D T1-weighted high-resolution anatomical scan (magnetization-prepared rapid gradient echo (MPRAGE), 1 mm isotropic resolution, 192 sagittal slices, FoV  $256 \times 256$  mm, TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FA =  $9^\circ$ , GRAPPA acceleration factor 2). For each participant, we used (from existing data) or acquired (in a separate, 15-minute session) another high-resolution anatomical scan using a 64-channel head/neck coil (Siemens, Erlangen, Germany), using the same scanning parameters. This birdcage coil generates higher quality anatomical images compared to the flex coils, since it is closer to the brain and has more channels.

A



B



**Figure 4.1: Experimental setup and trial design. A) Simultaneous TMS-EEG-fMRI equipment.**

The MRI-compatible TMS coil was fixed within a custom-built plastic coil holder. The electrodes cables of the 64-channel EEG cap were wired together and contained two connectors that were attached to the two amplifiers (at the back of the MRI scanner). The two MRI flex coils (grey) were kept in place by a black plastic frame. **B) Single trial design.** EEG data were recorded throughout the entire scanning session. Each echo-planar image (EPI, 1000 ms) was followed by a 1500 ms scanning gap. In the first gap of each trial, a high (700 Hz) or low (300 Hz) frequency tone was presented for 1000 ms, instructing participants to open or close their eyes, respectively. Participants then kept their eyes open or closed until instructed otherwise (dark grey arrows). A trial contained either two, four, or six 15 Hz TMS triplets, each triplet being presented within a separate (consecutive) scanning gap. The figure shows an example trial with two TMS bursts. All TMS triplets within the same trial were either at sub- or supra-resting motor threshold (RMT) intensity (40% versus 120% RMT, respectively). Each trial ended with a baseline period of 15 or 17.5 sec.

### TMS parameters

Biphasic TMS pulses were delivered using an MRI-compatible figure-of-eight coil (“MRI-B91”). The 6-meter-long cable was relayed to the back of the MRI bore, and connected through an RF filter box to a MagPro X100 stimulator (MagVenture, Farum, Denmark) in the adjacent technical room. We determined the resting motor threshold (RMT) by finding the right hemispheric “motor hotspot” and subsequently adjusting the stimulation intensity until a visible movement was caused in the contralateral index finger in half of the cases (RMT:  $M = 68\%$  maximum stimulator output (MSO), range = 62% – 75% MSO) (Rossini et al., 2015). Participants were stimulated with 15-Hz TMS triplets at sub-threshold (40% RMT) intensity in half of the trials, and at supra-threshold (120% RMT) intensity in the other half. We could not reliably determine the RMT in one participant, after which we set the stimulation intensities to a tolerable level (i.e., 40% versus 70% MSO). We positioned the TMS coil over the right PPC (electrode position P4 of the international 10-20 system) using a custom-built MRI-compatible TMS coil holder (see Figure 4.1a). TMS triplets were triggered via a parallel port and were delivered 800 – 1000 ms (randomly jittered) after the offset of an EPI acquisition (i.e., during a scanning gap, see Figure 4.1b). Each trial started with a TR in which a sound was presented, followed by a TR without any stimulation. Subsequently, either two, four or six TMS triplets were delivered (one triplet per TR, with an inter-burst interval of at least 1170 ms). A resting period without pulses then followed for either 15 or 17.5 seconds. Table 4.1 presents an overview of the number TMS pulses/triplets delivered to each participant.

Subject	Nr. runs	Nr. pulses (triplets) per run	Nr. pulses (triplets) total
1	2	96 (32)	192 (64)
2	8	48 (16)	384 (128)
3	8	48 (16)	384 (128)
4	8	48 (16)	384 (128)
5	3	48 (16)	144 (48)
6	5	48 (16)	240 (80)
7	8	48 (16)	384 (128)
8	7	48 (16)	336 (112)

**Table 4.1:** Overview of the number of fMRI scanning runs, the number of TMS pulses (and triplets) per run, and the total number of TMS pulses (and triplets) for each participant.

## EEG parameters

EEG data were acquired using two MRI-compatible “BrainAmp MR plus” amplifiers (sampling rate: 5000 Hz, resolution: 0.5  $\mu$ V, operating range: 16.384 mV, without online filtering) and two rechargeable “PowerPacks” (Brain Products, GmbH, Gilching, Germany). A “SyncBox” was used to synchronize the clock of the amplifiers with the clock driving the gradient switching of the MRI scanner. We furthermore used a TMS- and MRI-compatible EEG cap that was equipped with 64 sintered Ag/AgCl scalp “Multitrodes” arranged according to the standard international 10/20 and 10/10 systems, and one drop-down ECG electrode (Brain Products, GmbH, Gilching, Germany). The cap included a ground (AFz) and online reference (Cz) electrode. The electrodes were ring-shaped with a central opening of 6 mm and their flat profile (<3.5 mm) was designed to increase participant comfort. Electrode cables were combined into bundles and fixed with sandbags, to prevent cable motion artifacts. Electrodes were filled with conductive gel (OneStep Cleargel) and all impedances were kept below 25 k $\Omega$ . The EEG electrode cables were connected to the amplifiers situated at the back of the MRI scanner. Measurements were conducted using BrainVision Recorder (Brain Products, GmbH, Gilching, Germany) on a PC in the console room, to which the amplified EEG signals were relayed via fiberoptic cables.

## Data analyses

Data were analyzed using BrainVoyager Version 22.0.2 (BrainVoyager, Maastricht, the Netherlands), ITK-SNAP Version 3.6.0 (Yushkevich et al., 2006), MATLAB Version 2017a (TheMathWorks, Inc. Natick, Massachusetts, United States) along with Fieldtrip toolbox version 2017-10-30 (Oostenveld et al., 2011), and Python 3.0.

### *EEG preprocessing.*

Epochs were created from 500 msec before until 5 msec before each TMS triplet. Noisy channels were excluded for the calculation of the average signal, manually for each participant, by visual inspection of the data quality (see Table 4.2 for an overview of excluded electrodes – note that the electrode of interest (i.e., P4) did not have to be excluded in any participant). Data were downsampled to 500 Hz and re-referenced to the average of all included channels. Data were furthermore

detrended and baseline corrected (450 to 50 msec before each TMS triplet). Data were filtered with a Notch (50 Hz) and Butterworth band-pass (0.5 – 40 Hz) filter. For each pre-TMS epoch, we calculated the FFT (Hanning tapers, zero-padding to 1 sec to obtain 1 Hz frequency resolution, frequencies 1 – 40 Hz) and log-transformed the power spectra (Smulders et al., 2018). We then obtained the pre-TMS alpha power by calculating the sum of the power at the frequencies 7 – 13 Hz. Each pre-TMS epoch was then labeled as a low or high alpha power epoch by a median split.

Subject	EEG channels excluded from average
1	C2
2	Cz, Pz, Oz, CP5, TP7, CPz
3	None
4	F1, F2, C1, C2, P1, P2, AF3, AF4, TP7, TP8, PO7, PO8, FT9, FT10, Fpz, Cpz
5	F1, F2, C1, C2, P1, P2, AF3, AF4, TP7, TP8, PO7, PO8, FT9, FT10, Fpz, Cpz
6	F1, F2, C1, C2, P1, P2, AF3, AF4, TP7, TP8, PO7, PO8, FT9, FT10, Fpz, Cpz
7	None
8	None

**Table 4.2:** Overview of EEG channels that were excluded from the calculation of the average signal (for the “re-referencing to the average” preprocessing step).

### *EEG analyses.*

To evaluate the extent spontaneous fluctuations in oscillatory alpha power, we plotted all pre-TMS alpha power values per subject using raincloud plots (Allen et al., 2019). We furthermore evaluated whether alpha power was higher during eyes closed versus eyes open resting state in our experiment (the so-called “Berger effect”) (Barry et al., 2007; Berger, 1929, 1933). We calculated the average pre-TMS alpha power for eyes open versus eyes closed epochs for each participant, and compared the two conditions with a paired t-test.

### *(f)MRI preprocessing.*

The anatomical MRI scans were inhomogeneity-corrected and manually transformed into ACPC and Talairach space. The higher-quality anatomical MRI scan (acquired in another session, with the MRI birdcage coil) was aligned to the lower-quality anatomical MRI scan (acquired in the simultaneous TMS-EEG-fMRI session, with the MRI flex coils). A group-averaged anatomical scan was created in

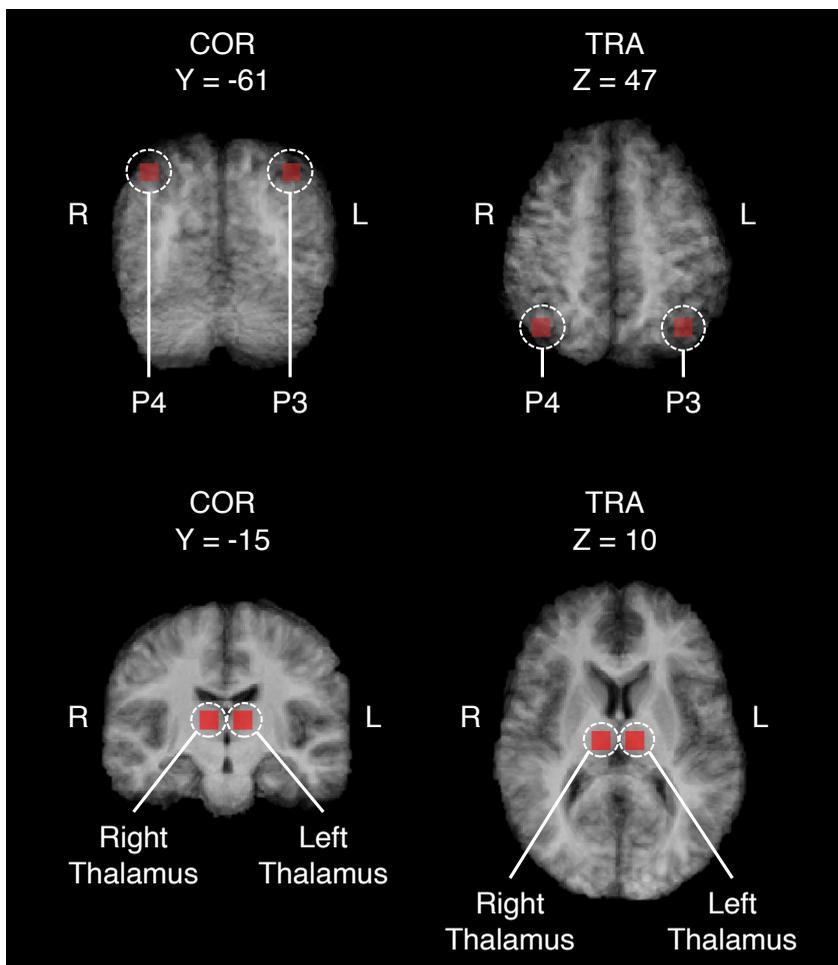
volume space. Each high-quality anatomical MRI scan was then segmented automatically in BrainVoyager. The segmentations were manually adjusted in ITK-SNAP (Yushkevich et al., 2006), and subsequently reconstructed into cortical meshes for each hemisphere. The reconstructed cortical hemispheres from all participants were aligned using a cortex-based alignment (CBA) procedure, and an average cortical mesh was created for each hemisphere (Fischl, Sereno, and Dale, 1999; Fischl, Sereno, Tootell, et al., 1999; Frost and Goebel, 2012).

Preprocessing of the fMRI data included slice scan time correction (with cubic spline interpolation), three-dimensional motion correction (with trilinear interpolation for motion detection and sinc interpolation for motion correction; each volume was aligned to the first volume of that run), and temporal high-pass filtering (using the FFT approach, removing frequencies  $<0.0080$  Hz). fMRI data were aligned with the anatomical scan acquired within the same session. The single-subject, single-run design matrices contained the following 2-gamma HRF-convolved predictors: eight predictors for TMS triplets delivered in the different conditions ( $2 \times 2 \times 2$  design, “TMS intensity”: supra-versus sub-threshold, “neurocognitive state”: eyes open versus eyes closed, and “oscillatory state”: low versus high pre-TMS alpha power), one predictor for the instructive sound stimulus, and one constant predictor to account for the baseline activation. These design matrices were all combined to create one multi-subject multi-run design matrix for the group analyses.

Whole-brain responses to TMS triplets were estimated by fitting a fixed-effects General Linear Model (GLM) to the voxel time courses (volume space). Cortical responses to TMS were estimated by fitting that same GLM to the mesh time courses (surface space). Finally, we assessed responses to TMS in four regions of interest (ROIs): the brain area underneath electrode position P4 (the TMS stimulation site), the corresponding contralateral brain area (underneath electrode position P3), the left thalamus, and the right thalamus (see Table 4.3 and Figure 4.2). The thalami were included as subcortical ROIs, since they showed oscillatory state-dependent TMS-evoked responses in a recent publication by our lab (Peters et al., 2020). The definition of these four ROIs was based on previously published Talairach coordinates (Herwig et al., 2003; Koessler et al., 2009) (see Table 4.3 and Figure 4.2). The data were %-transformed and corrected for serial correlations using a second-order autoregressive model (AR2).

Region of interest	X	Y	Z
P3 (contralateral to TMS site, left hemisphere)	-38	62	47
P4 (TMS site, right hemisphere)	38	62	47
Left thalamus	-8	-15	9
Right thalamus	8	-15	9

**Table 4.3:** Talairach center coordinates for the four regions of interest (ROIs). ROIs were created by creating a cube of 10 voxels around the Talairach center coordinates. We verified that all ROIs were located fully inside the brain.



**Figure 4.2: Regions of interest (ROIs).** The brain area under electrode positions P3 and P4, and the left and right thalamus are shown on the group-averaged anatomy (in volume space). COR = coronal slice; TRA = transversal slice; L = left hemisphere; R = right hemisphere.

***(f)MRI analyses.***

We first assessed whether supra-threshold TMS evoked any significant BOLD responses compared to sub-threshold TMS (main effect of “TMS intensity”, or “TMS effect”). We then assessed whether the effect of TMS (i.e., the difference between supra- and sub-threshold TMS) was different during eyes open compared to eyes closed blocks (interaction “TMS intensity”  $\times$  “neurocognitive state”). Furthermore, we assessed whether the effect of TMS differed as a function of pre-TMS alpha power (interaction “TMS intensity”  $\times$  “oscillatory state”). These two interaction effects were our key hypothesized findings, since they may highlight brain-state-dependent TMS-induced signal propagation. Besides this, we also evaluated the main effects of “neurocognitive state” and “oscillatory state”. These effects show fMRI activations in response to TMS for eyes open compared to eyes closed resting state, or for low pre-TMS alpha power compared to high pre-TMS alpha power, irrespective of “TMS intensity” (supra- versus sub-threshold). These contrasts may therefore be informative about brain state-dependent *non-specific* effects of TMS, such as auditory processing of the TMS “click” or the somatosensory experience of the pulse. Both of these are considerably stronger for MRI-TMS as compared to “conventional” TMS outside the scanner bore. Non-specific TMS effects could also include processing related to anticipation of the timed TMS pulses (within the fMRI acquisition gaps) and/or periods of relief at the offset of TMS trains. All main and interaction effects were evaluated on three different levels: 1) across the whole brain, 2) across the cortical surface, and 3) within four ROIs.

For the *whole-brain analysis* (in volume space), cluster-level statistical thresholding was performed to correct for multiple comparisons (threshold  $p = 0.001$ , number of iterations = 1000) (Forman et al., 1995). The resulting group activation maps were projected onto the group-averaged structural image in volume space. Activation clusters were automatically detected in BrainVoyager software. The center of gravity Talairach coordinates of each cluster were transformed into MNI coordinates and subsequently coupled with the name of the associated anatomical brain area using the BioImage Suite toolbox (Lacadie et al., 2008).

As a complementary, more focused analysis with higher statistical power but revealing only cortical activations, we also evaluated all main and interaction effects of interest specifically for the *group-aligned cortical surface* (in surface space) (Frost

and Goebel, 2012). The resulting activation maps were FDR-corrected (at  $p = 0.05$ ) and projected onto the averaged group cortical mesh for each hemisphere. The anatomical brain areas associated with the functional activation clusters in surface space were identified using an atlas of Brodmann areas (Goebel, 2012).

Finally, one ROI-GLM was performed for each of the *four defined ROIs* (see Table 4.3 and Figure 4.2).

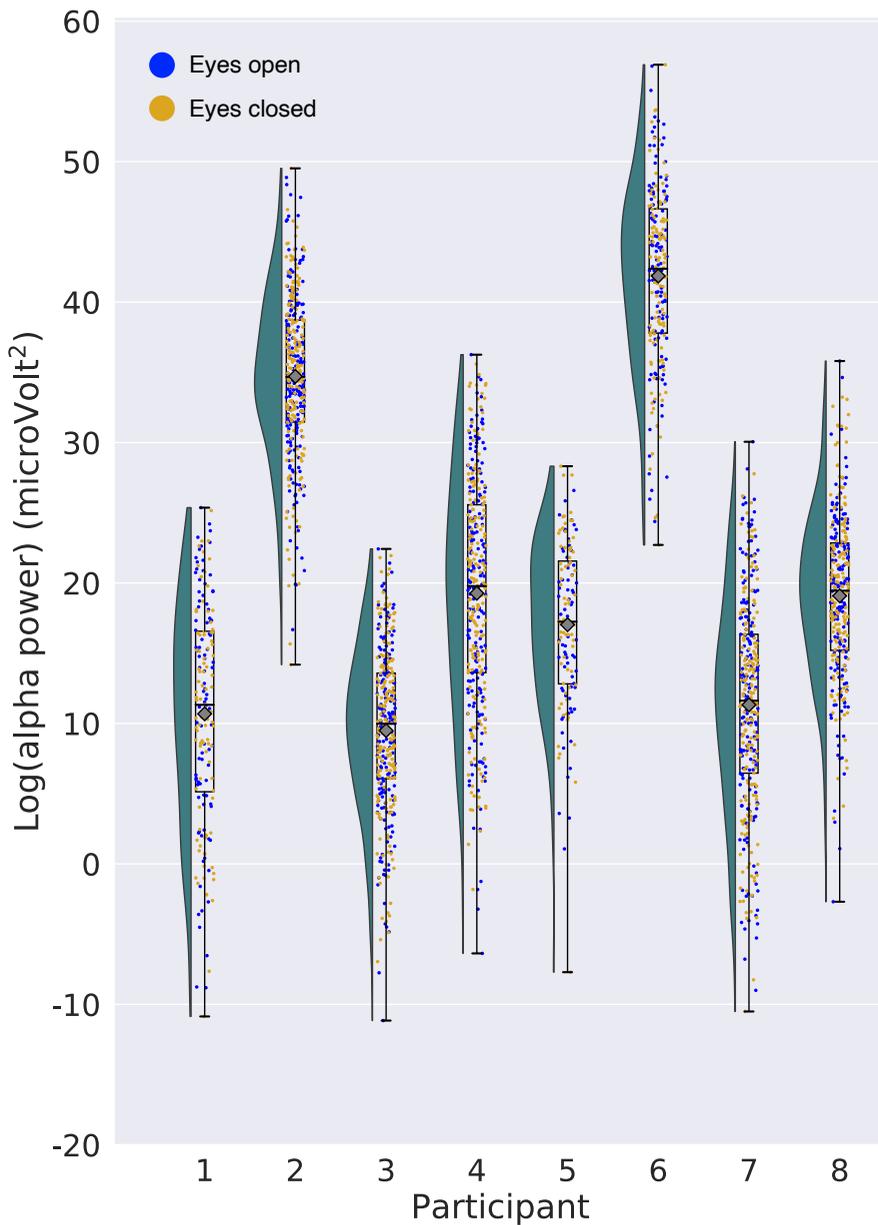
## 4.4 Results

Our main goal was to evaluate whether TMS-evoked fMRI responses depended on the neurocognitive and/or oscillatory brain state at the time of TMS. Below, we first report results regarding the fluctuations in oscillatory state. We then proceed to report the TMS-evoked fMRI activations irrespective of brain state. Finally, we evaluate TMS-evoked fMRI activations as a function of neurocognitive and oscillatory state.

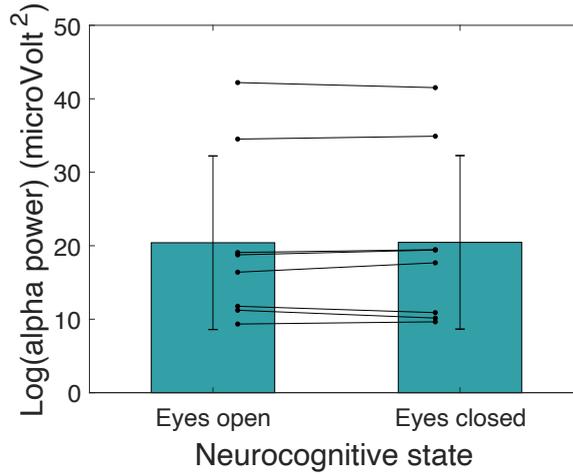
### Oscillatory state fluctuations

If the aim is to assess whether TMS-evoked fMRI responses depend on oscillatory state, then we must first establish that there are spontaneous fluctuations in oscillatory state in our experiment. We therefore visualized the extent of spontaneous pre-TMS oscillatory alpha power fluctuations over the course of the experiment for each participant (see Figure 4.3). As expected, alpha power fluctuates considerably over the course of a session within each participant (within-subject standard deviations were as follows:  $SD_1 = 7.92$ ,  $SD_2 = 5.87$ ,  $SD_3 = 5.87$ ,  $SD_4 = 8.29$ ,  $SD_5 = 5.96$ ,  $SD_6 = 6.47$ ,  $SD_7 = 7.62$ , and  $SD_8 = 5.92$ , compared to a between-subject  $SD$  of 11.04). Considering this, pre-TMS alpha power could therefore be included as a potentially predictive variable within our fMRI analyses.

We also assessed whether there was any significant difference in alpha power during eyes closed versus eyes open epochs, but did not find any evidence for such an effect ( $t(7) = .17$ ,  $p = .827$ ,  $M = 20.41$  and  $SD = 11.81$  for eyes open,  $M = 20.46$  and  $SD = 11.81$  for eyes closed, see Figure 4.4). This could be due to several reasons, which are outlined in the Discussion. For the purpose of our experiment, the absence of an EEG Berger effect in the pre-TMS epochs is not a problem. On the contrary, it shows that our blocked manipulation of neurocognitive state (i.e., eyes open versus eyes closed) was non-collinear with the spontaneous fluctuations in oscillatory state as measured with EEG (pre-TMS alpha power). This is also evident from Figure 4.3, which shows that pre-TMS alpha power fluctuated within each neurocognitive state. Both variables could therefore be added as non-collinear predictors in our subsequent fMRI analyses.



**Figure 4.3: Visualization of the spontaneous fluctuations in oscillatory brain state.** For each of the eight participants, pre-TMS alpha power values are shown for the entire experimental session. Each dot represents the alpha power value during one pre-TMS epoch. Alpha power fluctuated spontaneously across a session and within each neurocognitive state (eyes open versus eyes closed, color-coded). Boxplots and distributions are shown. Grey diamonds represent the mean alpha power across all pre-TMS epochs.



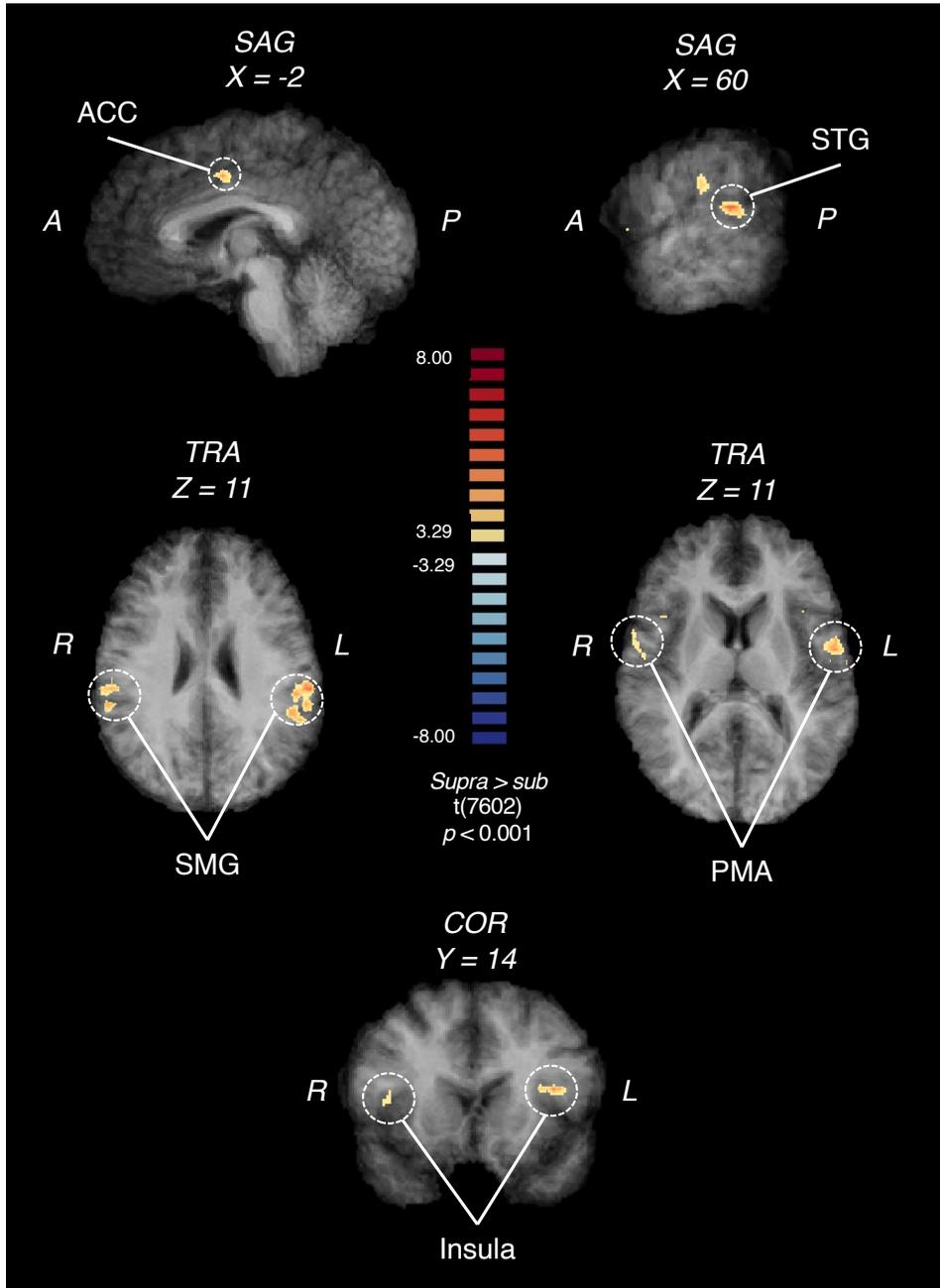
**Figure 4.4: Pre-TMS alpha power as a function of neurocognitive brain state.** Mean and individual pre-TMS alpha power is shown for eyes open and eyes closed epochs. Error bars show standard deviations.

### TMS-evoked fMRI responses irrespective of brain state

In the whole-brain analysis (performed in volume space), eight different clusters showed significantly enhanced TMS-evoked fMRI responses for supra-threshold compared to sub-threshold TMS (cluster threshold = 4; see Table 4.4 and Figure 4.5). These functional clusters were located in the bilateral premotor area (PMA), bilateral insula, bilateral supramarginal gyrus (SMG), left anterior cingulate cortex (ACC), and right superior temporal gyrus (STG).

Anatomical brain area	X	Y	Z	BA	Nr. voxels
Left premotor area	-49	-1	7	6	1775
Right premotor area	54	-1	10	6	218
Left insula	-35	15	16	13	175
Right insula	42	10	3	13	176
Left supramarginal gyrus	-54	-29	22	40	2785
Right supramarginal gyrus	55	-26	27	40	616
Left anterior cingulate cortex	-2	-2	40	24	287
Right superior temporal gyrus	59	-37	18	22	461

**Table 4.4: Center of gravity table for the TMS-evoked fMRI activation clusters detected in volume space (main effect of “TMS intensity”).** For each functional cluster, the name of the associated anatomical brain area is shown, along with the Talairach coordinates, the Brodmann area (BA), and the number of voxels. All clusters showed significantly increased activation for the contrast “supra-threshold TMS > sub-threshold TMS”.

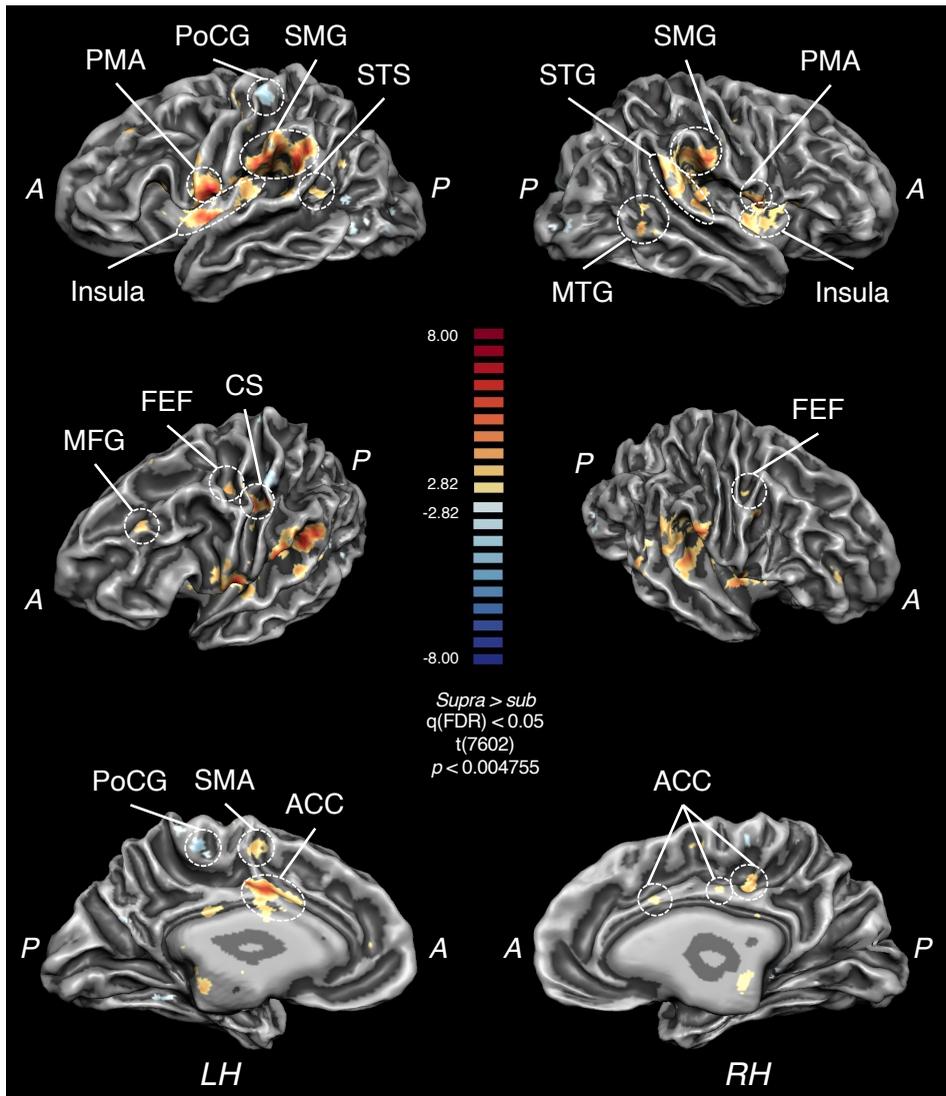


**Figure 4.5: TMS-evoked fMRI activations in volume space.** Eight activation clusters are shown for the fMRI contrast “supra- > sub-threshold TMS”. SAG = sagittal slice; TRA = transversal slice; COR = coronal slice; ACC = anterior cingulate cortex; STG = superior temporal gyrus; SMG = supramarginal gyrus; PMA = premotor area; A = anterior; P = posterior; L = left; R = right.

The analysis in surface space showed more extensive (de-)activations across the cortical surface when comparing supra- versus sub-threshold TMS (see Figure 4.6). Besides the brain areas reported above, activations were evident in the left middle temporal gyrus (MTG), the left middle frontal gyrus (MFG; or dorsolateral prefrontal cortex, DLPFC), the left supplementary motor area (SMA), and the central sulcus. Furthermore, a small significant cluster was visible in the bilateral frontal eye fields (FEF). A significant deactivation was found in the left medial and lateral post-central gyrus.

Most of these brain areas are part of the human sensory system (Avanzini et al., 2016). Activations in those areas can therefore be explained by the non-specific side effects of TMS, which includes auditory and somatosensory stimulation (Jung et al., 2016; Leitão et al., 2017; Leitão et al., 2013a; Ruff et al., 2006). One potential exception may be the bilateral FEF, which does not seem to be necessarily activated by non-specific TMS effects (Jung et al., 2016), and is functionally connected to the posterior parietal cortex (Heinen et al., 2017; Szczepanski et al., 2013; Vernet et al., 2014).

The ROI analysis showed a significant main effect of “TMS intensity” for the left thalamus ( $\beta = 0.22$ ,  $SE = 0.073$ ,  $p = 0.002$ ) and the right thalamus ( $\beta = 0.27$ ,  $SE = 0.068$ ,  $p < 0.001$ ), but not for the brain areas underneath electrode P3 ( $\beta = 0.10$ ,  $SE = 0.11$ ,  $p = 0.40$ ) or P4 ( $\beta = -0.03$ ,  $SE = 0.10$ ,  $p = 0.74$ ).



**Figure 4.6: TMS-evoked fMRI activations in surface space.** Cortical surface fMRI activation for the contrast “supra- > sub-threshold TMS” is shown. PMA = premotor area; PoCG = post-central gyrus; SMG = supramarginal gyrus; STS = superior temporal sulcus; STG = superior temporal gyrus; MTG = middle temporal gyrus; CS = central sulcus; FEF = frontal eye fields; MFG = middle frontal gyrus; SMA = supplementary motor area; ACC = anterior cingulate cortex; LH = left hemisphere; RH = right hemisphere; A = anterior; P = posterior.

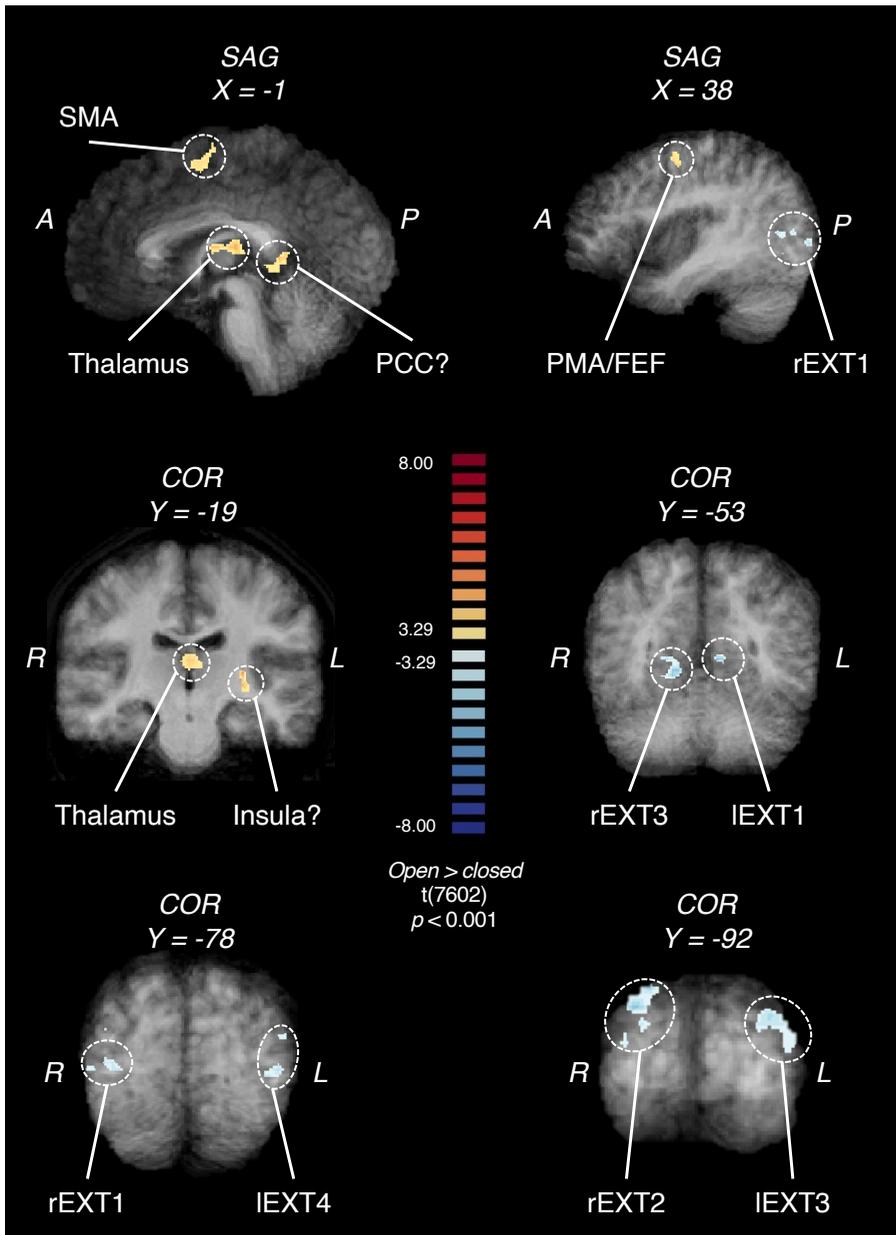
### TMS-evoked fMRI responses as a function of neurocognitive state

There were no significant activation clusters when testing for the interaction between “TMS intensity” and “neurocognitive state” (eyes open versus closed), neither in volume space nor in surface space. The ROI analysis also led to non-significant results for all ROIs (left thalamus:  $\beta = -0.08$ ,  $SE = 0.07$ ,  $p = 0.27$ ; right thalamus:  $\beta = 0.01$ ,  $SE = 0.07$ ,  $p = 0.86$ ; P3:  $\beta = 0.18$ ,  $SE = 0.11$ ,  $p = 0.12$ ; P4:  $\beta = -0.10$ ,  $SE = 0.07$ ,  $p = 0.17$ ).

We also evaluated the main effect of “neurocognitive state” (in response to TMS pulses of either intensity), which may be indicative of neurocognitive state-dependent non-specific TMS effects. The whole-brain analysis yielded 13 significant clusters (cluster threshold = 5; see Table 4.5 and Figure 4.7). For the contrast “eyes open > eyes closed”, significant activations were shown in the thalamus and supplementary motor area (SMA), and potentially in the posterior cingulate cortex and the left insula. Another activation cluster was located in the right premotor area or right frontal eye fields (FEF). Significant deactivations were shown in several visual cortex clusters in both hemispheres.

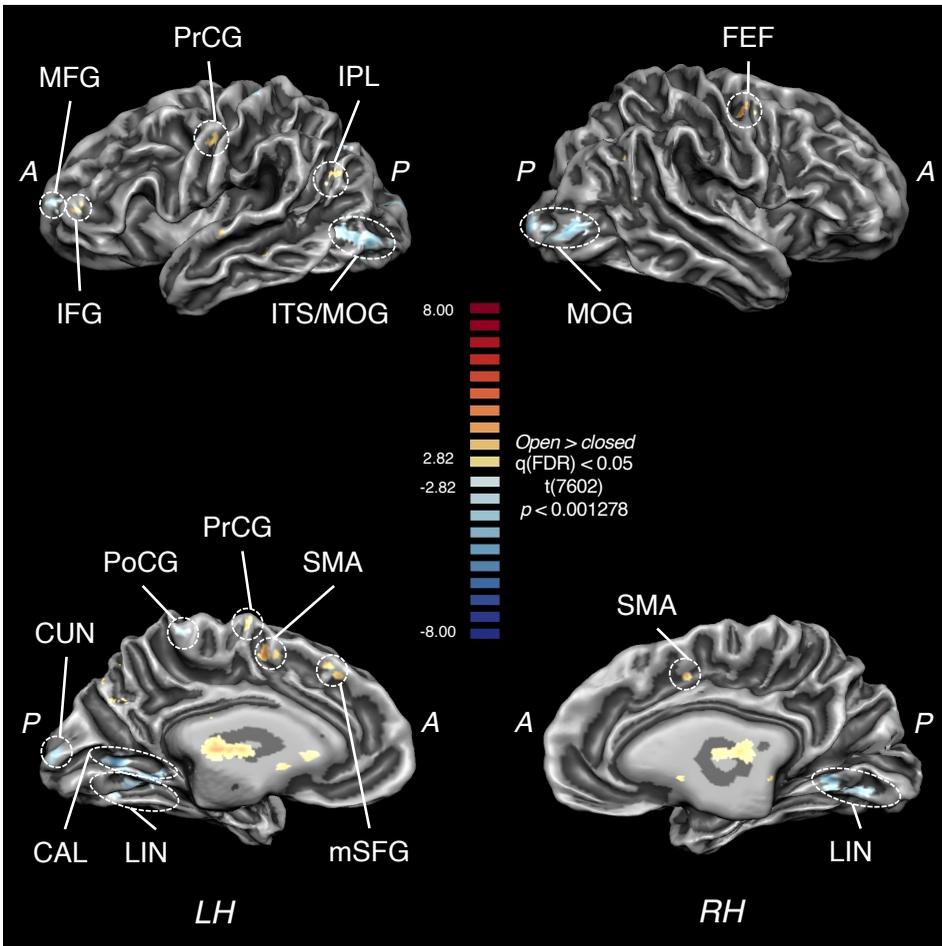
Anatomical brain area	+/-	X	Y	Z	BA	Nr. voxels
Supplementary motor area	+	-1	-2	55	6	359
Right premotor area/FEF	+	38	-6	49	6/8	236
Left extrastriate cortex (cluster 1)	-	-31	-89	15	18	747
Left extrastriate cortex (cluster 2)	-	-13	-53	3	19	621
Left extrastriate cortex (cluster 3)	-	-17	-56	-4	19	139
Left extrastriate cortex (cluster 4)	-	-40	-78	0	19	189
Right extrastriate cortex (cluster 1)	-	35	-79	5	18	1398
Right extrastriate cortex (cluster 2)	-	19	-91	21	18	579
Right extrastriate cortex (cluster 3)	-	13	-56	-1	19	1856
Right thalamus	+	7	-3	5	N/A	393
Left insula*	+	-28	-18	1	X	144
Left thalamus*	+	-1	-15	13	X	603
Posterior cingulate*	+	1	-38	5	X	364

**Table 4.5: Center of gravity table for the TMS-evoked fMRI activation clusters depending on “neurocognitive state”, irrespective of “TMS intensity” (main effect of “neurocognitive state”).** For each functional cluster, the name of the associated anatomical brain area is shown, along with the Talairach coordinates, the Brodmann area (BA), and the number of voxels. A “+” indicates increased activation and a “-” indicates decreased activation for the contrast “eyes open > eyes closed”. The center of gravity coordinates for the clusters marked with “\*” fell outside the range of identified BAs and should therefore be interpreted with caution. For these areas, names of anatomical brain areas were based on visual inspection of the group-averaged anatomical scan in volume space (and are therefore less precise).



**Figure 4.7:** TMS-evoked fMRI activations depending on "neurocognitive state", irrespective of "TMS intensity", in volume space. Activation clusters are shown for the main effect of "neurocognitive state" (contrast: eyes open > eyes closed). SAG = sagittal slice; COR = coronal slice; SMA = supplementary motor area; PCC = posterior cingulate cortex; PMA = premotor area; FEF = frontal eye field; rEXT1 – 3: right hemisphere extrastriate clusters 1 – 3; IEXT1 – 4: left hemispheric extrastriate clusters 1 – 4; R = right hemisphere; L = left hemisphere.

Similarly, the cortical surface analysis showed activations in SMA and right FEF, and deactivations in several visual cortical clusters in the bilateral lingual gyrus, bilateral middle occipital gyrus (or, potentially, inferior temporal sulcus), left cuneus, and left calcarine sulcus (see Figure 4.8). Additional activation clusters were found in the left precentral gyrus, the left inferior frontal gyrus, the left medial superior frontal gyrus, and the left inferior parietal lobe. Finally, additional deactivation clusters were found in the left middle frontal gyrus and left medial postcentral gyrus.



**Figure 4.8: TMS-evoked fMRI activations depending on “neurocognitive state”, irrespective of “TMS intensity”, in surface space.** Cortical surface fMRI activation for the contrast “eyes open > eyes closed” is shown. MFG = middle frontal gyrus; IFG = inferior frontal gyrus; PrCG = precentral gyrus; IPL = inferior parietal lobe; ITS/MOG = inferior temporal sulcus / middle occipital gyrus; FEF = frontal eye fields; PoCG = postcentral gyrus; SMA = supplementary motor area; CUN = cuneus; CAL = calcarine sulcus; LIN = lingual gyrus; mSFG = medial superior frontal gyrus; LH = left hemisphere; RH = right hemisphere.

The ROI analysis showed a significant main effect of “neurocognitive state” for both the left thalamus ( $\beta = 0.40$ ,  $SE = 0.07$ ,  $p < 0.001$ ) and the right thalamus ( $\beta = 0.34$ ,  $SE = 0.07$ ,  $p < 0.001$ ). The P3 ROI also showed a significant main effect of “neurocognitive state” ( $\beta = 0.34$ ,  $SE = 0.11$ ,  $p = 0.003$ ), which is in line with the activation shown in the left inferior parietal lobe (see Figure 4.8) (Herwig et al., 2003). The P4 ROI did not show a significant main effect of “neurocognitive state” ( $\beta = 0.13$ ,  $SE = 0.10$ ,  $p = 0.20$ ).

### TMS-evoked fMRI responses as a function of oscillatory state

There were no significant activation clusters when testing for the interaction between “TMS intensity” and “oscillatory state” (i.e., low versus high alpha power), neither in volume space nor in surface space. The ROI analysis also showed no significant interaction (left thalamus:  $\beta = -0.05$ ,  $SE = 0.12$ ,  $p = 0.71$ ; right thalamus:  $\beta = -0.04$ ,  $SE = 0.11$ ,  $p = 0.75$ ; P3:  $\beta = 0.20$ ,  $SE = 0.19$ ,  $p = 0.30$ ; P4:  $\beta = 0.11$ ,  $SE = 0.17$ ,  $p = 0.53$ ). Similarly, there were no significant activation clusters for the main effect of “oscillatory state”, neither in volume space nor in surface space. There was also no significant main effect in the ROI analysis (left thalamus:  $\beta = -0.08$ ,  $SE = 0.12$ ,  $p = 0.54$ ; right thalamus:  $\beta = 0.02$ ,  $SE = 0.11$ ,  $p = 0.87$ ; P3:  $\beta = -0.11$ ,  $SE = 0.19$ ,  $p = 0.55$ ; P4:  $\beta = 0.10$ ,  $SE = 0.17$ ,  $p = 0.58$ ).

## 4.5 Discussion

This study presents the first application of the innovative simultaneous TMS-EEG-fMRI set-up to a known cognitive network hub (i.e., the right posterior parietal cortex; van den Heuvel and Sporns, 2013; Yan and He, 2011) instead of a motor area (Peters et al., 2020; Peters et al., 2013). Our main aim was to investigate whether TMS-evoked fMRI activations depended on neurocognitive state (eyes open versus eyes closed resting state) and oscillatory state (low versus high alpha power) at the time of TMS. But before investigating this, we first confirmed that oscillatory state fluctuated considerably between TMS epochs over the course of our experiment. This is in line with previous studies showing that the oscillatory brain state fluctuates within the same individuals over time (Benwell et al., 2019; Haegens et al., 2014; Romei, Brodbeck, et al., 2008), and is a prerequisite for investigating oscillatory state-dependent TMS effects. We also confirmed that the oscillatory state (i.e., pre-TMS alpha power) was non-collinear with our manipulation of neurocognitive state (i.e., eyes open versus eyes closed resting state), which ensured that both predictors could be included in our fMRI analyses.

It may seem surprising that we did not find a difference in alpha power during eyes closed compared to eyes open pre-TMS epochs, since it is well-documented that eyes closed resting state shows enhanced alpha power compared to eyes open resting state (the so-called “Berger effect”) (Bazanov and Vernon, 2014; Berger, 1929, 1933; Kirschfeld, 2005; Quigley, 2021). However, our experimental set-up was different from such earlier reports in several ways. Our participants were lying down in a noisy and unaccustomed environment without any visual input, while expecting TMS pulses. In standard EEG studies, the situation is quite different: generally, participants are in a seated position without any strong sound stimuli, they are not wearing a blindfold, and they are in a “true” resting state (not expecting any stimuli). Any of these factors might have influenced the difference in alpha power during the eyes open versus the eyes closed neurocognitive state. For instance, prolonged blindfolding with repeated eye opening and eye closure has previously been reported to cause a disappearance of the EEG Berger effect (de Graaf et al., 2017). Furthermore, standard EEG studies typically measure the EEG signal for several uninterrupted minutes, while we here looked at < 1 second segments that were interleaved with TMS and fMRI. In any case, the absence of the Berger effect within our EEG data is not a concern for our main analyses of interest.

Regarding TMS-evoked fMRI activations, we found widespread activations for supra-threshold compared to sub-threshold TMS in a network of sensorimotor areas, including the bilateral premotor area, bilateral insula, bilateral supramarginal gyrus, and the frontal eye fields. The region of interest analysis also revealed significant activations in the bilateral thalamus, but not in the left or right posterior parietal cortex. TMS does not necessarily cause detectable fMRI activations in the brain area directly underneath the TMS coil (Bergmann et al., 2021; Bestmann et al., 2008). Activations in sensorimotor areas are likely due to the non-specific side effects of TMS (Jung et al., 2016; Leitão et al., 2017; Leitão et al., 2013a; Ruff et al., 2006), though the frontal eye fields might be an exception (Jung et al., 2016). In contrast to our expectations, we did not find any significant interaction between the effect of TMS (i.e., supra- compared to sub-threshold TMS) and the neurocognitive or oscillatory state. Unfortunately, we thus did not obtain the key hypothesized finding of brain state-dependent TMS-induced signal propagation. Perhaps, these signals were simply too subtle to be detected with our experimental set-up and/or design. It is furthermore possible that the detection of brain-state dependent TMS effects requires visual stimulation.

However, we did find differential fMRI activations for eyes open compared to eyes closed resting state in response to TMS pulses irrespective of their stimulation intensity. This analysis may highlight areas which respond to non-specific TMS effects (e.g., auditory and somatosensory stimulation, and/or expectancy effects) in a neurocognitive state-dependent manner. The contrast “eyes open > eyes closed” revealed activations in the SMA, thalamus, right FEF, and left inferior parietal lobe, and deactivations across multiple areas of the visual cortex in both hemispheres. This may relate to previous findings showing differential functional connectivity when the eyes are open versus closed (Agcaoglu et al., 2019; Costumero et al., 2020; Hübner et al., 2009; Jao et al., 2013; Marx et al., 2004; Marx et al., 2003; McAvoy et al., 2012; Weng et al., 2020; Yan et al., 2009; Zou et al., 2009). Our analyses revealed motor and attention brain areas in response to TMS when the eyes were open, and visual cortical areas when the eyes were closed, which is in line with prior studies showing an “exteroceptive” versus “interoceptive” brain network when the eyes were open versus closed, respectively (Marx et al., 2003; Wei et al., 2018; Xu et al., 2014). Our findings are also in line with prior studies showing that eye opening/closure can influence auditory and somatosensory processing (Brodoehl, Klingner, Stieglitz, et al., 2015; Brodoehl

et al., 2016; Brodoehl, Klingner, and Witte, 2015; Götz et al., 2017).

Based on this first application of the simultaneous TMS-EEG-fMRI set-up in a cognitive network hub, several factors need to be considered in future experiments investigating brain state-dependent TMS-evoked fMRI effects. Firstly, it is important to control for TMS side effects, such as the auditory and somatosensory stimulation, but also the potential expectancy effects that are associated with the predictability of upcoming TMS pulses (Duecker et al., 2013; Tran et al., 2021). Though we here varied the baseline period and jittered the time at which TMS triplets were delivered within fMRI acquisition gaps, participants still knew approximately when a TMS triplet would be delivered. Already for the first triplet in a series of TMS triplets, and of course even more so in the subsequent triplets in that series. Furthermore, our supra-threshold and sub-threshold TMS intensities both caused auditory and somatosensory stimulation, but not to the same extent. In future studies, the auditory side-effects of TMS can be prevented by noise masking the “TMS” clicks (ter Braack et al., 2015), and the somatosensory side effects of TMS can be prevented by creating space between the TMS coil and the scalp (Dowdle et al., 2018) or by rotating the TMS coil towards the non-stimulating side (Jung et al., 2016). An alternative approach is to include a “control” brain area, such as the vertex (Jung et al., 2016), or to compare TMS to “no TMS” and to verify that TMS effects are present in specific regions of interest and not in other brain areas (Peters et al., 2020).

The second factor to consider is the determination and visualization of the TMS target site. We positioned the TMS coil on the international 10-20 EEG electrode position P4, which is above the right posterior parietal cortex (Herwig et al., 2003; Koessler et al., 2009). Our experimental aims did not require precise targeting of the TMS coil, and regions of interest could be created based on published Talairach coordinates. Alternatively, the TMS coil could be visualized using vitamin capsules (e.g. Sack et al., 2007), a water tube (e.g. Leitão et al., 2013b), or other markers (Yau et al., 2013), though these approaches have not yet been systematically compared. When precise TMS targeting is required, neuronavigation can be used to navigate towards anatomically or functionally defined cortical brain areas (Ahdab et al., 2010; Rusjan et al., 2010; Sparing et al., 2008), or even to cortical areas that show strong structural and/or functional connectivity to an indirect (sub-cortical) target (Klooster et al., 2021).

Another factor to consider is that there is generally a tradeoff between statistical power within individual subjects and statistical power in group-based analyses. When resources are limited, it may be best to either acquire a lot of data for only a few participants, or to acquire less data for many participants. The former could be challenging, considering that participants cannot comfortably stay within the simultaneous TMS-EEG-fMRI environment for more than 1 hour. But even when collecting a large amount of data in a single participant, the fMRI correlates of a real (neural) TMS effect can be difficult to detect (de Graaf et al., 2018). State-dependent TMS-induced fMRI effects are likely small/weak as well, which calls for better ways of revealing them.

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# *Chapter 5*

## **Calibrating rhythmic stimulation parameters to individual EEG markers: the consistency of individual alpha frequency in practical lab settings**

### **Corresponding manuscript:**

Janssens, S. E. W., Sack, A. T., ten Oever, S., & de Graaf, T. A. (2021). Calibrating rhythmic stimulation parameters to individual EEG markers: the consistency of individual alpha frequency in practical lab settings. *European Journal of Neuroscience*. <https://doi.org/10.1111/ejn.15418>.

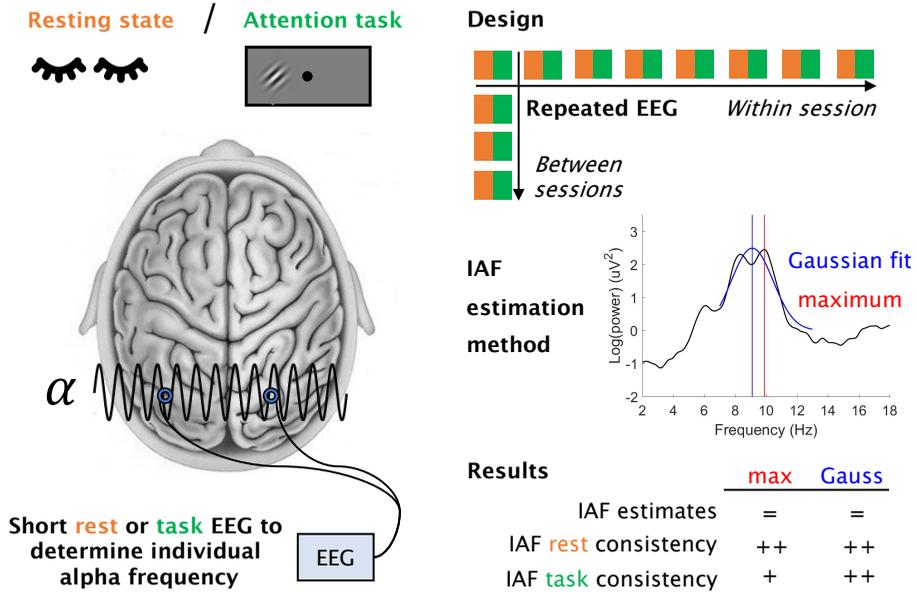
## 5.1 Abstract

Rhythmic stimulation can be applied to modulate neuronal oscillations. Such “entrainment” is optimized when stimulation frequency is individually calibrated based on magneto/encephalography (M/EEG) markers. It remains unknown how consistent such individual markers are across days/sessions, within a session, or across cognitive states, hemispheres, and estimation methods, especially in a realistic, practical, lab setting. We here estimated individual alpha frequency (IAF) repeatedly from short EEG measurements at rest or during an attention task (cognitive state), using single parieto-occipital electrodes in 24 participants on four days (between-sessions), with multiple measurements over an hour on one day (within-session). First, we introduce an algorithm to automatically reject power spectra without a sufficiently clear peak to ensure unbiased IAF estimations. Then we estimated IAF via the traditional “maximum” method and a “Gaussian fit” method. IAF was reliable within- and between-sessions for both cognitive states and hemispheres, though task-IAF estimates tended to be more variable. Overall, the “Gaussian fit” method was more reliable than the “maximum” method. Furthermore, we evaluated how far from an approximated “true” task-related IAF the selected “stimulation frequency” was, when calibrating this frequency based on a short rest-EEG, a short task-EEG, or simply selecting 10 Hertz for all participants. For the “maximum” method, rest-EEG calibration was best, followed by task-EEG, and then 10 Hertz. For the “Gaussian fit” method, rest-EEG and task-EEG-based calibration were similarly accurate, and better than 10 Hertz. These results lead to concrete recommendations about valid, and automated, estimation of individual oscillation markers in experimental and clinical settings.

### *Key words*

Consistency; electroencephalography (EEG); individual alpha frequency (IAF); intra-class correlation coefficient (ICC); neuronal oscillations; reliability.

## 5.2 Graphical Abstract



We repeatedly measured electroencephalography (EEG) between- & within-sessions, during resting state & attention task, from two posterior electrodes. The “maximum” method on average yielded the same individual alpha frequency (IAF) estimates as a “Gaussian fit” method, but the latter was more consistent, and rest-IAF was more consistent than task-IAF. When calibrating rhythmic stimulation protocols to individual EEG markers, we thus recommend rest-EEG along with a Gaussian fit method.

### 5.3 Introduction

The investigation of neuronal oscillations in the human brain has progressed beyond merely correlational magneto-/encephalography (M/EEG) research. Different approaches have been developed to explicitly modulate neuronal oscillations in specific frequency bands, in both research and clinical settings. For instance, rhythmic visual stimulation at alpha frequency has been used to enhance (or “entrain”) neuronal oscillations and thereby influence visual perception (Chota and VanRullen, 2019; de Graaf et al., 2013; Mathewson et al., 2010; Mathewson, Prudhomme, et al., 2012; Ronconi et al., 2018; Spaak et al., 2014; Wiesman and Wilson, 2019). More direct neuromodulation methods include magnetic and electric non-invasive brain stimulation (NIBS; Antal and Paulus, 2013; Hallett, 2000). Both repetitive transcranial magnetic stimulation (rTMS) and transcranial alternating current stimulation (tACS) have been employed to establish causal links between alpha oscillations and cognitive processing (Herrmann et al., 2013; Herrmann et al., 2016; Ruhnau et al., 2016; Thut et al., 2011). For instance, 10 Hertz tACS to parieto-occipital cortex could increase the power of neuronal alpha oscillations (Helfrich et al., 2014), and bias response times in an endogenous attention task (Schuhmann et al., 2019). Such findings support a causal role for parietal alpha oscillations in visuospatial attention.

The alpha band is generally considered to contain frequencies between 7 and 13 Hertz (Berger, 1929, 1933), and has been linked to a large number of cognitive functions (Clayton et al., 2018), including learning (Freyer et al., 2013; Mathewson, Basak, et al., 2012; Sigala et al., 2014), memory (Bonnefond and Jensen, 2012; Jensen et al., 2002; Klimesch, 1999), and visuospatial attention (Gallotto et al., 2020; Sauseng et al., 2005; Worden et al., 2000). Importantly, there are substantial differences in the peak alpha frequency across individuals (Klimesch, 1999). These inter-individual differences in individual alpha frequency (IAF) are related to general cognitive abilities (Dickinson et al., 2018; Grandy, Werkle-Bergner, Chicherio, Lövdén, et al., 2013), language processing (Bornkessel et al., 2004) and memory (Cross et al., 2020; Moran et al., 2010), and can in part be explained by genetic variations (Bodenmann et al., 2009; C. Smit et al., 2006; D. Smit et al., 2005; van Beijsterveldt and van Baal, 2002). Differences in IAF can furthermore drive aspects of visual perception, as exemplified by an association between IAF and the temporal resolution of the double flash illusion (Samaha and Postle, 2015).

These findings are especially relevant for rhythmic stimulation studies, since stimulation might most effectively induce modulatory effects if delivered at individually calibrated frequencies (Stecher and Herrmann, 2018). Indeed, it was recently shown that a leftward visuospatial attention bias resulted from tACS at IAF, but not tACS at IAF  $\pm$  2 Hertz (Kemmerer et al., 2020). Increasingly, neuromodulation studies make use of individually calibrated stimulation protocols, for instance by using IAF instead of a fixed (e.g. 10 Hertz) frequency (Fresnoza et al., 2018; Kasten et al., 2016; Kasten et al., 2020; Vossen et al., 2015; Zaehle et al., 2010). This approach also has clinical relevance, since it was recently shown that deviations between IAF and the stimulation frequency predict NIBS treatment outcome for depression patients (Corlier et al., 2019; Roelofs et al., 2020). Moreover, although we focus on IAF as an example, these considerations apply to other frequency bands as well, including individual gamma (Baltus et al., 2018), beta (Schilberg et al., 2018), and theta (Reinhart and Nguyen, 2019) frequency.

Thus, for both research and clinical applications, it is beneficial to tailor rhythmic stimulation protocols to individual participants or patients. Typically, stimulation protocols are based on quick frequency analysis of short EEG measurements, often recorded from only one or a few electrodes. Different approaches exist to determine individual peaks (e.g., IAF) from a power spectrum (Goljahani et al., 2012). Most widely reported is the “maximum” method, in which a peak is determined by simply selecting the frequency with the highest power within a pre-defined (e.g., alpha) frequency range (Kemmerer et al., 2020; Koch et al., 2008; Petersén and Eeg-Olofsson, 1971; Schuhmann et al., 2019; C. Smit et al., 2006). Another possibility might be called the “Gaussian fit” method, which involves fitting a Gaussian curve to the power spectrum within a restricted (e.g., alpha) frequency range. A peak frequency (e.g., IAF) is then estimated by finding the center parameter of the fitted Gaussian curve (Albada and Robinson, 2013; Dickinson et al., 2018; Haegens et al., 2014). Aside from peak frequency, this method also allows estimation of peak width.

It remains unknown to what extent IAF estimates can be used to reliably calibrate rhythmic stimulation protocols across days, or cognitive states. Simply stated, if one estimates IAF from a posterior electrode after 3 minutes of resting-state EEG, how likely is that IAF to be (in)correct in general? How likely is it to be (in)correct an hour later, or in the second session next week? How

representative is it for IAF during a cognitive task of interest? Though IAF is often assumed to be stationary, a recent study reported a decrease in peak alpha frequency during 1 hour of visual task performance (Benwell et al., 2019). The change was small on average, but individual effects reached as high as 2 Hertz. While previous studies established that alpha peak frequency at rest reflects, in principle, a stable trait (Gasser et al., 1985; Grandy, Werkle-Bergner, Chicherio, Schmiedek, et al., 2013; Kondacs and Szabó, 1999; Näpflin et al., 2008; Salinsky et al., 1991), we here systematically chart IAF based on realistic, practical (i.e., short and constrained) lab settings.

Before the consistency of IAF estimates can be investigated, another concern should be addressed. Specifically, sometimes the power spectrum does not show any clear peak, especially when based on M/EEG data measured during cognitive task performance. Researchers or clinicians are then forced to subjectively decide to either accept or reject the result that a peak estimation method delivers. Going forward, it would be helpful to develop tools that algorithmically accept or reject power spectra, for instance prompting lab technicians, clinicians, or experimenters, to perform a new M/EEG measurement. Or, in the current context, to prevent bias in the IAF estimation procedures and subsequent statistical analyses, by only including power spectra that show a sufficiently clear peak. To this end, we developed an algorithm to automatically reject EEG power spectra that do not contain a clear alpha peak. Based on accepted power spectra, we could then explicitly evaluate the consistency of repeated estimations of IAF (and IAF peak width) across estimation methods, days, and cognitive states.

We performed short, repeated EEG measurements in 24 participants on four separate days, in the left and right hemisphere, during eyes closed resting state and during an endogenous visuospatial attention task (Posner, 1980; Posner et al., 1980). In one session, we performed these measurements repeatedly across approximately 1 hour. IAF was estimated for each participant, time point, hemisphere, and cognitive state, using the “maximum” method and the “Gaussian fit” method. Our experimental aims were threefold. First, we investigated to what extent the “maximum” and “Gaussian fit” methods led to similar IAF estimations. Second, we assessed how consistent repeated IAF estimates were within and between sessions, for both hemispheres, cognitive states, and estimation methods. Third, we investigated whether there is an advantage of measuring EEG instead of

simply using a standard (i.e., 10 Hertz) frequency, and whether resting-state EEG calibration is sufficient, or even better, for estimating the relevant individual frequency during task performance than an estimation based on EEG collected during performance of that same task.

## 5.4 Materials and Methods

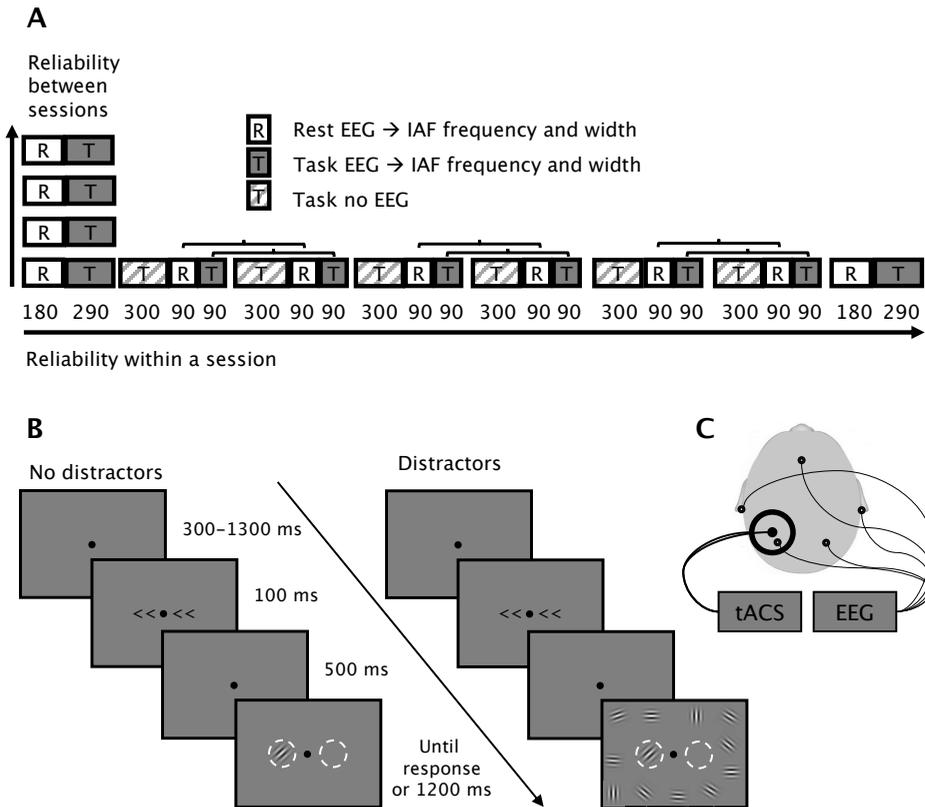
### Participants

Twenty-four healthy volunteers participated in this experiment (11 male, ages 19 – 34). All participants were right-handed and had (corrected-to-)normal vision. Compensation was provided in the form of participation credits or vouchers. The experiment was approved by the Ethical Review Committee Psychology and Neuroscience at Maastricht University.

### Project overview

The current data stem from a large project on brain stimulation. In that project, we stimulated participants' left parietal cortex with four different tACS protocols on separate days. Prior to any tACS, EEG baseline data were collected during eyes closed resting state and during visuospatial attention task performance from two parieto-occipital electrodes (see below for details). Since potential brain stimulation effects are outside the scope of the current paper, none of the data reported here were assessed after active tACS. Instead, the included data were measured pre-tACS in four different sessions, and at different time points during an extended (placebo tACS) session (see Figure 5.1a). This allowed the dedicated evaluation of the consistency of IAF and IAF width (in *Supplementary Materials III*) between sessions (prior to any brain stimulation) and within a session (repeated estimation at regular intervals within the extended session, across approximately one hour (see Figure 5.1a), relative to the consistency across participants.

In terms of the repeated EEG task/rest baseline measurements, all four sessions were identical, session order was fully counterbalanced across participants, and there was a minimum of two days between sessions. Upon entering the lab, participants were screened for tACS contraindications and provided written informed consent. We then prepared the tACS and electroencephalography (EEG) electrodes, as well as calibrating an eyetracker. These preparations took approximately 1 hour altogether.



**Figure 5.1: Experimental design.** **A) Experimental procedure and included EEG data.** Indicated times are in sec. EEG data were collected for 3 min rest and 5 min task in four sessions on separate days. In one more extended session (lowest section), after the initial measurement, EEG data were collected six times for 1.5 min rest and 1.5 min task, spaced 5 min apart. During these 5 min (striped segments), participants were under the (false) impression of receiving tACS; these data were excluded and never analyzed. Consecutive 1.5 min blocks were combined to yield again 3 min data (brackets), meaning that there were five repeated measurements for both rest and task. **B) Endogenous attention task.** After a randomly jittered fixation period, an endogenous cue was presented. Cues were valid (pointing towards the upcoming target), neutral (pointing to both sides), or invalid (pointing away from the upcoming target). A target grating was presented in the left or right hemifield 500 ms after the cue disappeared. White dashed circles indicate possible target locations and were not actually shown on the screen. Participants responded as quickly and as accurately as possible whether the target grating was rotated (counter-)clockwise. The target disappeared once a response was given or when 1200 ms had elapsed. In half of the trials, distractors with random orientation, frequency, and (drifting) phase were presented bilaterally from target onset until target offset. **C) tACS and EEG set-up.** A tACS ring electrode was centered on P3. EEG electrodes were placed on PO3 and PO4, with the ground electrode on Fz and reference electrodes over both mastoids. Note that no tACS was applied before or during any of the data collected and reported in this paper.

### Stimuli and task

In each session, participants performed an endogenous attention task (see 5.1B) (Posner, 1980; Posner et al., 1980). Stimuli were presented using MATLAB (The

MathWorks, Inc., Natick, Massachusetts, United States) and Psychophysics Toolbox (Brainard, 1997) on a gamma-corrected 24 inch monitor with a 60 Hertz refresh rate and a resolution of 1920 x 1080 pixels. Participants continuously fixated on a black dot of 0.2 degrees visual angle (DVA) presented in the center of a grey screen with a background luminance of 125 cd/m<sup>2</sup>. Their heads were stabilized using a chin rest that was positioned 60 cm away from the computer screen. Eyetracking was performed to assess fixation stability. After a randomly jittered fixation period (300 – 1300 ms), an endogenous cue was presented for 100 ms. The cue was either valid (two arrows pointing in the direction of the upcoming target), neutral (one arrow pointing to the left and the other to the right), or invalid (pointing away from the upcoming target) at a ratio of 3:1:1. After a cue-to-target interval of 600 ms, a target stimulus with a diameter of 3.5 DVA was presented at 7 DVA eccentricity on either the left or the right side of the screen. Target stimuli were sinusoidal gratings of 0.8 Michelson contrast (MC), rotated either 45 DVA clockwise or counter-clockwise, with random spatial frequency and phase. Participants performed a two-alternative forced choice (2AFC) task for each target grating. More specifically, they indicated as quickly and as accurately as possible the orientation of the target, pressing with their right hand either the left arrow button or the right arrow button for counter-clockwise and clockwise oriented gratings, respectively. The target grating disappeared once the participant responded or when 1200 ms had passed without a response. In half of the trials, only the target grating was presented. In the other half of the trials, distractors were displayed bilaterally at target onset until target offset. Distractors were displayed around the target locations and had a random orientation, phase and spatial frequency. Distractor contrast was 0.8 MC and a drift speed of 4 Hertz was used to make the distractors appear to move in space, thereby make them more salient. Average trial duration was 2100 ms. The pre- and post-measurement each contained 120 attention task trials, while the main measurement contained 960 trials divided equally over the six blocks.

### **Electroencephalography (EEG)**

EEG data were recorded with 5000 Hertz sampling frequency and a hardware band-pass filter of 0.1-1000 Hertz using BrainVision Recorder (BrainVision LLC, Morrisville, North Carolina, United States) and a BrainAmp DC amplifier (BrainProducts, GmbH, Gilching, Germany). Reference electrodes were placed

over A1 and A2 and the ground electrode was placed over Fz. The two electrodes of interest were placed over PO3 (within the tACS ring electrode) and PO4 (see Figure 5.1c). EEG electrodes were filled with conductive gel (OneStep Cleargel) and impedances were kept below 5 k $\Omega$  (ground and reference electrodes) or 10 k $\Omega$  (electrodes of interest). Note that the participants' skin could not be prepared as thoroughly as in conventional EEG studies due to the presence of the tACS electrode. In the current context this is a valuable aspect of our data, given that the goal was to assess individual EEG markers in realistic, practically constrained lab settings, representative of conditions in rhythmic stimulation experiments often relying on such EEG measurements and IAF estimation.

### Analysis

Data were analyzed using MATLAB version 2019a, FieldTrip Toolbox (Oostenveld et al., 2011), Python 3.0 and IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). As mentioned above, the current paper only includes EEG data that do not contain any tACS effects (see Figure 5.1).

**Preprocessing.** EEG files with data from electrodes PO3 and PO4 were loaded and cut into 5 sec epochs. The main blocks of the extended session included 90-sec data segments (see Figure 5.1). In order to have sufficiently long data segments, these 90-sec data segments were grouped together to yield 180 sec data segments for task and rest (thus, blocks 1 and 2, blocks 3 and 4, and blocks 5 and 6 were grouped together). Epochs were sorted into task and rest epochs for each of the five time points in the extended session, or single time point in the other sessions. Note that “task” data segments were either 290 sec long (initial measurement in all four sessions, and the final measurement in the extended session) or 180 sec long (the middle three measurements in the extended session), and “rest” data segments were always 180 sec long. Per electrode, we removed epochs with extreme signal variance relative to signal variance in other epochs, based on the inter-quartile range ( $> Q3 + 1.5 \times IQR$  criterion) (as in de Graaf et al., 2017). Power at frequencies 1 – 49 Hertz was determined by calculating FFTs using Hanning tapers, separately for every time point and each cognitive state (task versus rest). Epochs were zero-padded to 10 sec to reach a frequency resolution of 0.1 Hertz and power values were log-transformed (Smulders et al., 2018). We then estimated the 1/f component in each power spectrum by fitting a first-order polynomial to the log-transformed power and

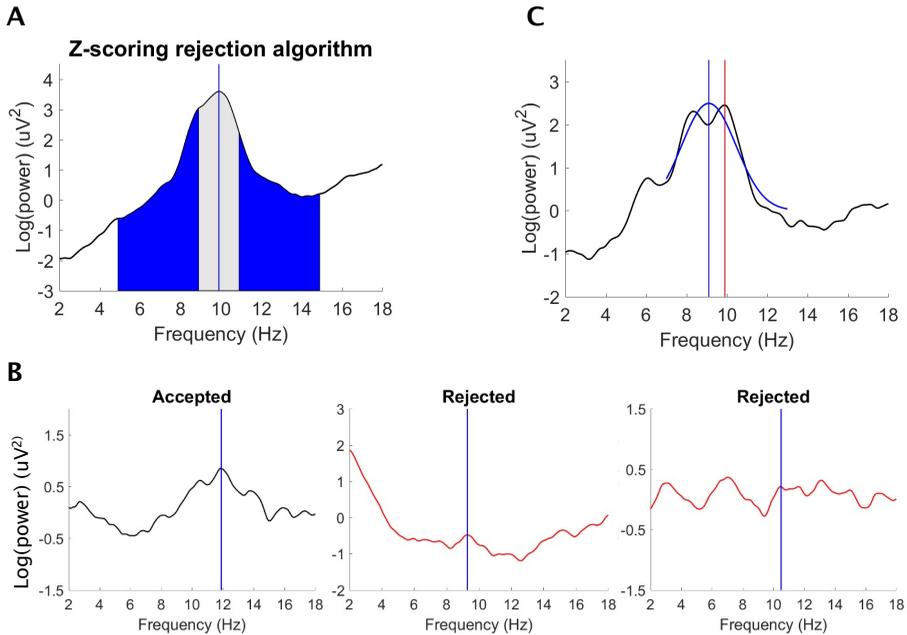
log-transformed frequency axis values (since the log-log-transformed EEG spectrum is approximately linear; Le Van Quyen et al., 2003; Nikulin and Brismar, 2004). We then subtracted this linear fit from each power spectrum. Lastly, we decreased the influence of noise in the power spectra by spectral smoothing them using a Savitzky-Golay filter (SGF frame width: 27, which corresponds to a frequency span of 2.7 Hertz, polynomial degree 5) based on parameters suggested by Corcoran et al. (2018).

*Power spectrum rejection algorithm.* To answer any research questions related to individual alpha peaks, it is important to exclude those power spectra that do not contain an obvious alpha peak. This could in principle be done by visually inspecting power spectra and manually rejecting those cases without a clear peak. From informal conversations, it seems that “subjective peak-picking” is indeed common practice. However, given the large amount of power spectra in our study (768 in total, from 24 participants in 2 cognitive states and 2 hemispheres at 8 time points), we instead tried to develop an algorithm for power spectrum rejection. In this algorithm, the MATLAB “findpeaks” function was used to detect the highest peak within the 7–13 Hertz alpha range (settings: sort peaks in descending order, number of peaks 1, with default settings: minimum peak height -Inf, minimum peak prominence 0, threshold 0). We selected the power spectrum surrounding that highest peak (+/- 5 Hertz), and then cut out the frequencies directly surrounding the peak (+/- 1 Hertz) while including the peak value itself (see Figure 5.2a). Then, we z-scored the selected portion (i.e., 83 values) of the power spectrum, and assessed the resulting z-score of the peak. If the z-score of the detected peak was small, this would indicate that the detected peak did not clearly stand out from surrounding values and might therefore not be regarded as a sufficiently convincing (“real”) peak.

In our case, if the z-scored power at the detected peak frequency was below 1.75, that power spectrum was rejected as not containing an alpha peak, and not included in further analyses. Figure 5.2b shows examples of accepted and rejected power spectra. Ultimately, our parameters for this “filtering algorithm” were subjective, i.e. the selected frequency windows and z-score cutoff were tweaked based on visual inspection of accepted versus rejected power spectra for different parameter sets. Likely, other datasets might be better served by other parameters or even other procedures. But since uncertainty about whether or not a power

spectrum contains a “convincing peak” are somewhat common, especially when it comes to IAF during task performance, or peaks in other frequency bands, it is interesting that we did find a fully automatic algorithm that worked satisfactorily. Such automatic “rejection” tools might help lab technicians or clinical practitioners decide to accept an individual EEG marker, or rather repeat a measurement to possibly obtain a better result. In our case, parameters were fixed such that the algorithm was relatively strict, in the sense that ambiguous power spectra (i.e., those in which it was not entirely clear whether a peak was present) were rejected. This was to avoid that spurious IAFs, based on unclear peaks, might contaminate our analyses. Still, only few power spectra were rejected (50 in total (~6.5%), task data: 41 (~10.5%), rest data: 9 (~2%). More details on our rejection algorithm, including more examples of accepted and rejected power spectra, can be found in *Supplementary Materials I*.

***Two methods for estimating IAF.*** Two different methods were used to determine the IAF (see Figure 5.2c). The “maximum” method involved finding the frequency with maximum power in the alpha band (7 – 13 Hertz) using the “findpeaks” MATLAB function (i.e., largest local maximum; Kemmerer et al., 2020; Klimesch et al., 2003; Zaehle et al., 2010). The “Gaussian fit” method involved fitting a Gaussian curve to the alpha band-limited power spectra (frequencies 7 – 13 Hertz; Albada and Robinson, 2013; Haegens et al., 2014) and extracting the center frequency of that fit. The “Gaussian fit” method allows an estimation of both the location and the width of the IAF peak by using the center and standard deviation parameters of the Gaussian fit, respectively (Gauch and Chase, 1974). We thus had three dependent variables: IAF as determined by the “maximum” method, IAF as determined by the “Gaussian fit” method, and IAF peak width based on the standard deviation parameter from the fitted Gaussian. Note that analyses on IAF peak width are reported in *Supplementary Materials III*; in the main text we focus on IAF. We specifically aimed to investigate the consistency of these different IAF estimates. From a methodological perspective, potential within-subject outlier values are thus of relevance and should not be excluded from the analyses. We therefore did not assess whether within-subject outlier values were present in our data. There were no outlier participants (as defined by a mean score more than 3 standard deviations away from the mean across participants) for any of the dependent variables.



**Figure 5.2: Power spectrum rejection and IAF estimation.** **A) Power spectrum rejection algorithm.** The  $1/f$ -removed and spectrally smoothed power spectrum is shown in black. The vertical blue line shows the largest peak as detected by the MATLAB “findpeaks” function. We selected the power spectrum in the range peak  $\pm 5$  Hertz (blue area), cut out the frequencies directly surrounding the peak ( $\pm 1$  Hertz, grey area), and z-scored the selected portion of the power spectrum. If the z-score of the detected peak was below 1.75, the power spectrum was rejected. **B) Representative examples of accepted and rejected power spectra.** Vertical blue lines indicate the largest peak as detected by the MATLAB “findpeaks” function. An accepted power spectrum is shown in black, while rejected power spectra are shown in red. **C) “Maximum” versus “Gaussian fit” method.** An example power spectrum is shown in black. The red vertical line is the IAF value as determined by the “maximum” method. The blue vertical line shows the IAF value as determined by the “Gaussian fit” method, and the blue curve shows the fitted Gaussian curve. This power spectrum with two peaks provides an example where the “maximum” and the “Gaussian fit” methods result in different IAF values.

*Directly comparing the “maximum” and “Gaussian fit” methods.* One of our experimental aims was to assess whether the IAF values obtained by the “maximum” method differed from those obtained by the “Gaussian fit” method. To this aim, we performed simple linear regression analyses and paired t-tests.

*Consistency of IAF estimates.* Another experimental aim was to investigate the reliability of IAF estimates within and between sessions, for both estimation methods, cognitive states, and hemispheres. To this aim, test-retest reliability was quantified by calculating intra-class correlation coefficients (ICC; Bravo and Potvin, 1991; Espenhahn et al., 2017; Koo and Li, 2016; McCusker et al., 2020). To assess

reliability on a shorter (within-session) timescale, we compared the IAF estimates of the five time points within the extended session. To assess reliability on a longer (between-session) timescale, we compared the IAF estimates from the initial measurements of the four sessions. F-tests were used to assess whether ICC's were significantly greater than 0.75 (indicating good reliability; Koo and Li, 2016). Note that the ICC calculation procedure inherently excludes participants with at least one missing value. Ten participants were excluded, leaving 14 participants for the ICC calculations (one participant had missing values due to a corrupted EEG file, the other nine participants had missing values since some power spectra did not contain a clear alpha peak and were thus rejected). Furthermore, we report within- and between-subject standard deviations to quantify the variability in IAF estimates. Single-subject data and mixed-model analyses are reported in *Supplementary Materials II*.

In standard practice, IAF is often based on one EEG measurement at the start of a session. It would be useful to see how far subsequent IAF estimations fall from this initial estimation. Per participant, we assessed such deviations of repeated IAF estimations from their initial estimate. We constructed distributions of these deviations to allow easy visual evaluation of the proportion of IAF estimates that fell within a certain distance (in Hertz) from the initial estimate, separately for both cognitive states (rest and task).

*Comparing three ways determining “stimulation frequency”.* In most experiments, the goal of frequency calibration is to determine a stimulation frequency to use during a clinical protocol or an experimental task. For the latter, if the goal is to “entrain” the task-relevant oscillations, presumably the target stimulation frequency should be the peak frequency during task. This might suggest that the logical approach is to determine IAF during a short task-EEG block. On the other hand, since alpha peaks are most visible at rest and with eyes closed, it makes sense to determine IAF at rest. A third option is just to stimulate everyone at 10 Hertz and forego calibration altogether.

Here, we were curious to see how closely the rest-EEG IAF, and simply 10 Hertz, would approximate the “true” individual frequency of interest, which was the IAF during our cognitive task. Would a a short task-EEG-based IAF better approach that “true” IAF than the commonly used rest-EEG-based IAF? We compared three ways of estimating the “true” IAF during our task: 1) using the

same 10 Hertz frequency for every participant (i.e., no individual calibration), 2) using the “standard practice IAF”, based on an eyes-closed resting state EEG measurement at the start of a session, 3) using the “standard practice IAF” based on a task EEG measurement at the start of a session.

For this analysis, we needed an approximation of the actual, “true”, task IAF for every participant. Any one short task-EEG might not yield this IAF sufficiently accurately, so we approximated the “true” task IAF by taking the median IAF from all repeated task measurements of both hemispheres. We then calculated deviations between the three frequency calibration approaches (10 Hertz, rest-IAF, task-IAF) and this “true” task-IAF, and constructed probability distributions showing, across participants, how close these approaches brought us to the approximated “true” IAF (i.e., the optimal target frequency for rhythmic stimulation). In order to prevent a bias (i.e., spuriously lower variability) in the comparison between standard practice task IAF and the “true” task IAF, for that particular probability distribution, the calculation of the “true” IAF excluded that standard practice task IAF measurement (although this did not appreciably change the resulting kernel density distributions or conclusions).

## 5.5 Results

Below, we report the results regarding our three experimental aims. First, we directly compare IAF values as obtained with the “maximum” versus “Gaussian fit” method. Second, we assess the consistency of IAF estimates. Finally, we investigate how much different approaches to determining a “stimulation frequency” deviate from the optimal target frequency for rhythmic stimulation (i.e., the “true” task-IAF for each participant).

### Do the “maximum” and “Gaussian fit” methods lead to similar IAF outcomes?

Linear regression analyses and paired samples t-tests showed that the “maximum” and “Gaussian fit” methods mostly led to highly similar IAF values. We assessed this for IAF values as determined during “standard practice” (based on a single, predefined EEG measurement at the start of a session, at rest [standard practice rest IAF] or during task [standard practice task IAF]). We also assessed this for approximated “true” rest- and task-IAF values (approximated by the median of all rest-EEG or task-EEG measurements) (see Figure 5.3). The standard practice rest IAF did not significantly differ between the “maximum” or “Gaussian fit” methods ( $t(23) = .20, p = .840$ ), nor did the “true” rest IAF ( $t(23) = .43, p = .670$ ). Also for the task-EEG, standard practice task IAF for the “maximum” method ( $M = 10.49, SD = 0.98$ ) was not significantly different compared to the “Gaussian fit” method ( $M = 10.41, SD = 1.01$ ) ( $t(23) = 1.87, p = .070$ , two-tailed, uncorrected), neither was “true” task IAF (“maximum” method:  $M = 10.51, SD = 1.00$ ; “Gaussian fit” method:  $M = 10.36, SD = 0.91$ ;  $t(23) = 1.96, p = .060$ , two-sided, uncorrected). Thus, even with uncorrected p-values there are no significant differences, and any descriptive differences in IAFs resulting from both methods are, for practical intents and purposes, negligibly small. We thus conclude that the “maximum” and “Gaussian fit” methods, on the whole, yield the same IAFs. The question then becomes how consistently they yield those IAFs across measurements, days, and cognitive states.

The mean IAF was approximately 10.4 Hertz across cognitive states and hemispheres, for both the “maximum” method (see Table 5.1) and the “Gaussian fit” method (see Table 5.2). This value is close to the standard 10 Hertz that is often used in rhythmic stimulation research (de Graaf et al., 2020; Helfrich et al., 2014; Hopfinger et al., 2017; Schuhmann et al., 2019). Interestingly, both methods

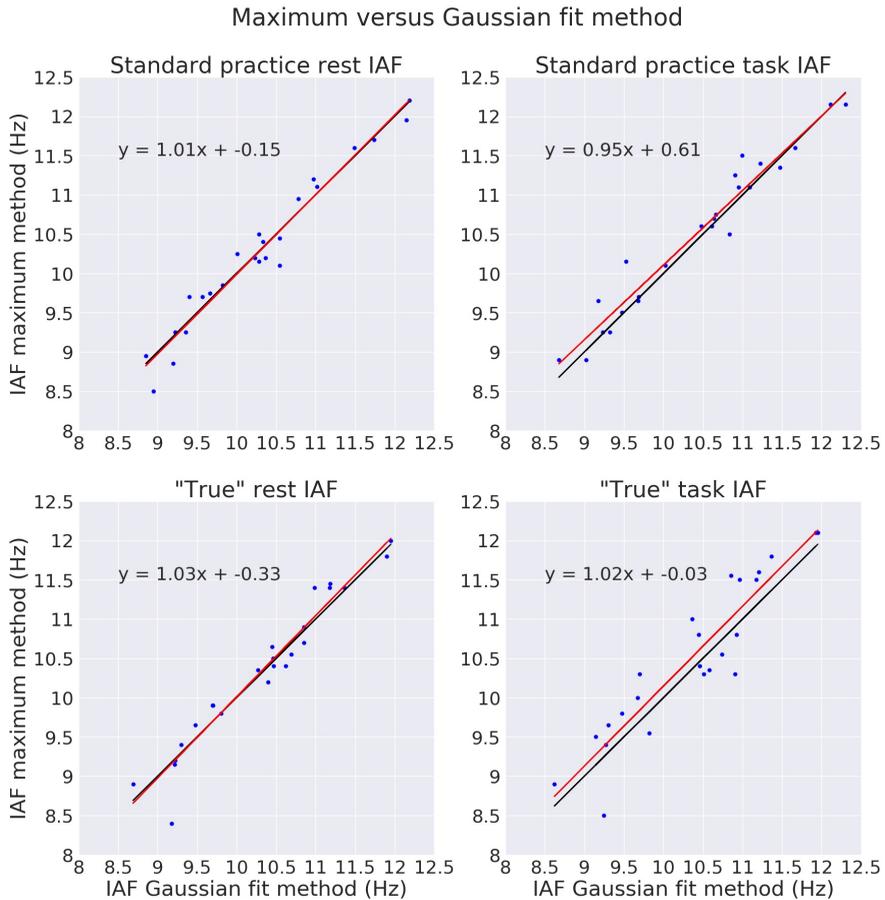
showed a significant effect of “cognitive state”, with IAF values during task being higher than those during rest (“maximum” method:  $M = 10.52$  versus  $M = 10.31$ ,  $SE = 0.047$ ,  $p < 0.001$ ; “Gaussian fit” method:  $M = 10.33$  versus  $M = 10.28$ ,  $SE = 0.021$ ,  $p = 0.014$ ; for a complete overview of mixed model analyses, see *Supplementary Materials II*). This finding is in line with previous studies showing that IAF values can increase with task demands (Angelakis et al., 2004; Babu Henry Samuel et al., 2018; Gray and Emmanouil, 2020; Haegens et al., 2014; Hülzdünker et al., 2016). The fact that task IAF can be significantly different from resting state IAF might suggest that it is best to always calibrate a stimulation frequency based on task-EEG. However, the difference in IAF between cognitive states is very small (i.e., 0.05 - 0.20 Hertz). In practical situations, one can reasonably ask whether a resting-state EEG IAF might still be the better choice for individual calibration, if it can be estimated more reliably than a task-EEG IAF. This is an empirical question we address below.

	Mean	Min	Max	SDwp_ws	SDwp_bs	SD_bp
Rest, Left	10.28	8.10	12.60	0.47	0.29	0.99
Rest, Right	10.35	8.00	12.40	0.33	0.25	0.98
Task, Left	10.42	7.10	12.90	0.38	0.55	1.04
Task, Right	10.49	8.30	12.90	0.42	0.44	0.92

**Table 5.1: Descriptive statistics for the IAF values as determined by the “maximum” method.** Mean, minimum, maximum, and standard deviations of IAF values are shown per cognitive state and hemisphere. “SDwp\_ws” refers to standard deviations within-participants, within-session. “SDwp\_bs” refers to standard deviations within-participants, between-sessions. “SD\_bp” refers to standard deviations between participants.

	Mean	Min	Max	SDwp_ws	SDwp_bs	SD_bp
Rest, Left	10.29	8.49	12.64	0.16	0.20	0.96
Rest, Right	10.31	8.49	12.26	0.15	0.18	0.94
Task, Left	10.30	8.49	12.42	0.15	0.24	0.90
Task, Right	10.32	8.49	12.19	0.14	0.25	0.88

**Table 5.2: Descriptive statistics for the IAF values as determined by the “Gaussian” fit method.** Mean, minimum, maximum, and standard deviations of IAF values are shown per cognitive state and hemisphere. “SDwp\_ws” refers to standard deviations within-participants, within-session. “SDwp\_bs” refers to standard deviations within-participants, between-sessions. “SD\_bp” refers to standard deviations between participants.



**Figure 5.3: Directly comparing results from the “maximum” and “Gaussian fit” methods.** The uppermost panels compare the standard practice rest IAF (left) and standard practice (task) IAF values resulting from the maximum method with those from the Gaussian method. The lowermost panels compare the “true” (median) rest IAF (left) and the “true” (median) task IAF (right) values between the two methods. Black lines indicate the diagonals (i.e., no difference between maximum and Gaussian method results), red lines indicate least-square regression results. Every dot represents one subject.

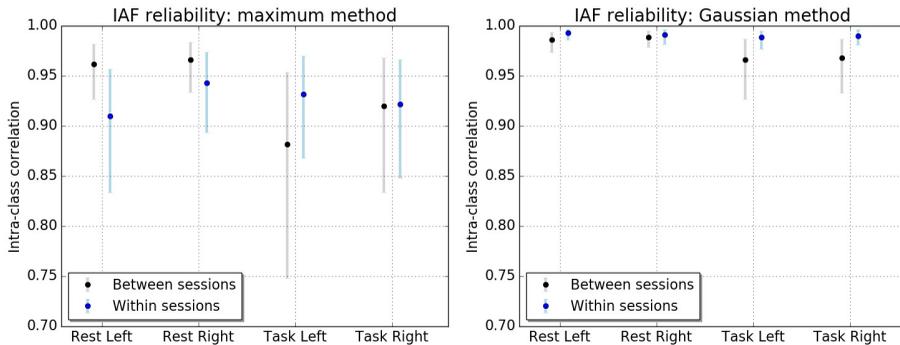
### How consistent are repeated IAF estimations?

Above, we concluded that the “maximum” and “Gaussian fit” approaches to IAF determination yielded, on the whole, the same results. Moreover, differences between IAFs from task and rest EEG, in the current “practical” context, were perhaps consistent but also very small. The question then is; how consistent are those IAFs obtained from short EEG measurements?

Overall, repeated IAF values seemed stable between sessions and within a session, for both estimation methods, cognitive states, and hemispheres (for single-subject data see Figures 5.11 and 5.12). There were some participants with inconsistent estimates, and occasional individual measurements with a seemingly incorrect result (showing as a single, strongly deviating point). As in previous studies, there was substantial variation across individuals, with a standard deviation of approximately 1 Hertz between participants (Haegens et al., 2014; Klimesch, 1997). Importantly, IAF values were more consistent (i.e., showed lower standard deviations) within individuals compared to between individuals, even more so for the “Gaussian fit” method (Table 5.2) compared to the “maximum” method (Table 5.1).

Intra-class correlation coefficients (ICCs) offer a quantification of such test-retest reliability (Koo and Li, 2016). Here, ICCs were significantly greater than 0.75 across cognitive states and hemispheres, indicating good reliability ( $p$ 's < 0.05) (see Figure 5.4). This was the case for both reliability within-session and between-sessions, and the ICC values we found are in line with previous results (Gudmundsson et al., 2007; Ip et al., 2018; Pöld et al., 2020).

Notably, test-retest reliability was higher for IAF values as obtained with the “Gaussian fit” method compared to the “maximum” method. Since alpha power gets suppressed with visual stimulation and task performance, it can become more difficult to detect an IAF in these conditions (Barry et al., 2007; Yamagishi et al., 2008). One might therefore expect that reliability decreases when IAF is measured during task as compared to rest. In our data, this might indeed have been the case for the reliability between sessions, as evidenced by the lower ICC's for task compared to rest data. As mentioned above, if the actual IAF from resting state and task state EEG differ only marginally, as well as between the “maximum” and “Gaussian fit” methods, a difference in reliability of the estimate itself might strongly impact the decision to base individual calibration on either a resting or task state EEG, using “maximum” or “Gaussian fit” approaches. From Figure 5.4, it seems that, for the current dataset, a “Gaussian fit” estimation approach on resting-state EEG is a good option for IAF calibration.



**Figure 5.4: Test-retest reliability of IAF estimates.** Left panel: Intra-class correlation coefficients (ICC) based on IAF values as estimated by the “maximum” method. ICC’s (dots) are plotted along with 95% confidence intervals (lines), separately per cognitive state (rest and task), hemisphere (left and right) and time interval (within- and between-sessions). **Right panel:** same, but based on IAF values as estimated by the “Gaussian fit” method.

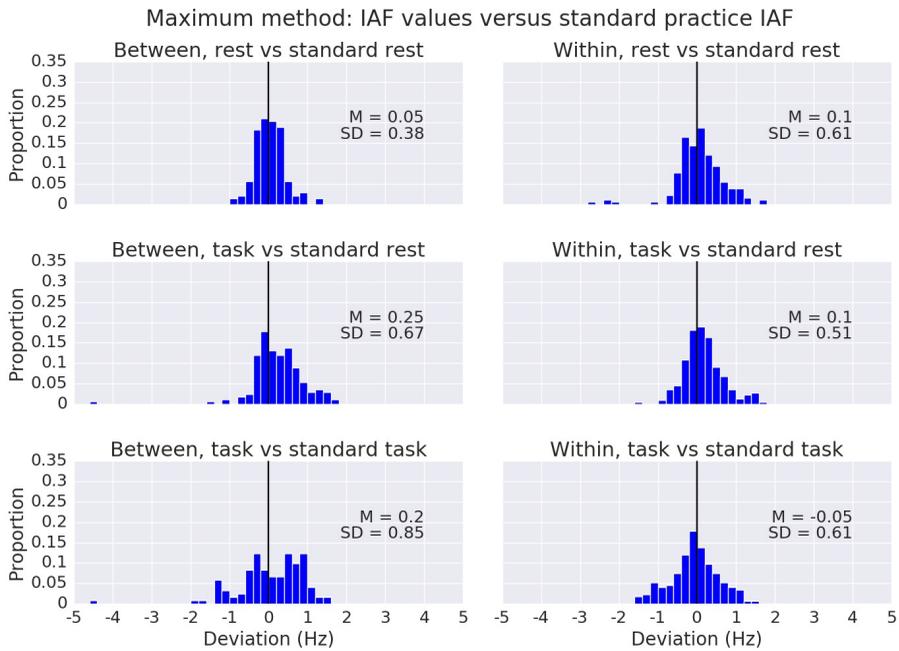
ICC provides a useful “summary measure” of the reliability of an estimate. For practical purposes, we might still want to evaluate how different a deviating measurement actually is. Typically, in rhythmic stimulation studies, IAF is measured once and used throughout the experiment (Cecere et al., 2015; Kemmerer et al., 2020; Mioni et al., 2020; Ronconi et al., 2018; Ronconi et al., 2020). We therefore compared all repeated IAF measurements with this “standard practice” IAF value, to assess its representativeness for subsequent sessions (between-session analysis, left column of plots in Figures 5.5 and 5.6), or subsequent time points within the same session (within-session analysis, right column of plots in Figures 5.5 and 5.6). We also quantified these same deviations of repeated IAF measurements during attention task, from the standard practice IAF obtained with resting-state EEG (second row of plots in Figures 5.5 and 5.6). And for comparison, even though this seems less common in practice, the deviations of these repeated task-EEG IAFs from an initial task-EEG IAF (third row of plots in Figures 5.5 and 5.6). This allows intuitive assessment of how acceptable the standard practice IAF estimation results are, to determine, on a case by case basis, whether the range of possible deviations would concern us.

Such “deviation distributions” may provide additional information. For instance, any systematic change in peak frequency across cognitive states would be reflected in a horizontal shift of these deviation distributions between the task-rest

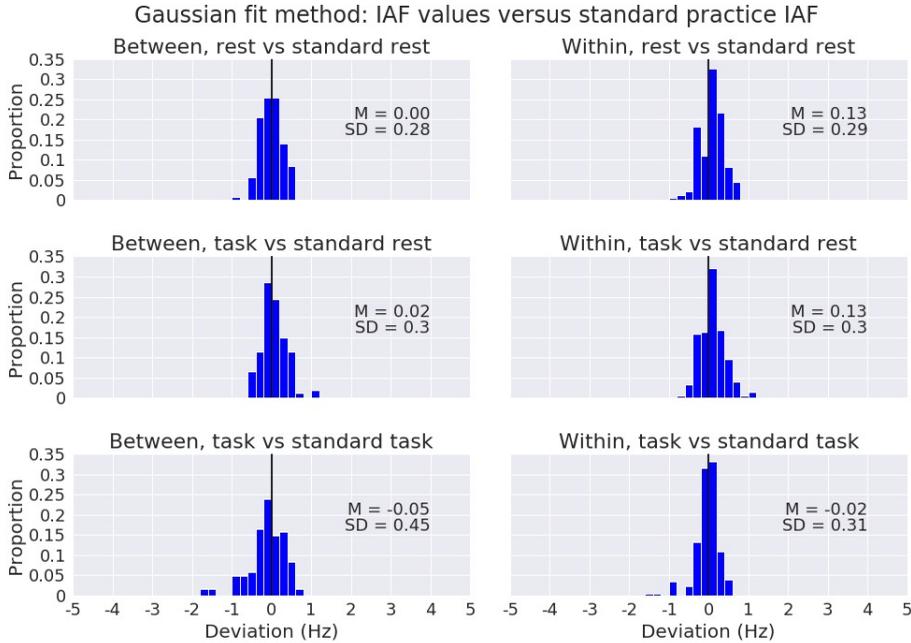
IAFs relative to the rest-rest IAFs. Or, if the deviation distributions for task-task IAFs are much narrower than the distributions for task-rest IAFs, this would suggest that task-EEG IAF estimations would be more reliable to calibrate rhythmic stimulation protocols to, than estimates of IAF based on resting state EEG as is often done. In these analyses, for every participant, their “standard practice” IAF value was calculated by averaging the IAF values from the left and right hemisphere from the initial measurement in the extended session, separately per cognitive state. Averaging across hemispheres was possible, since “hemisphere” did not affect IAF estimations (see linear mixed model results in *Supplementary Materials II*).

For the “maximum” method, repeated IAF rest measurements generally stayed within 1 Hertz from the standard practice rest IAF (see Figure 5.5, row 1). This shows good correspondence of repeated IAF rest measurements over time. There seems to be some bias and higher variability for repeated task measurements when comparing them to the standard practice rest IAF (Figure 5.5, row 2), but also when comparing them to the standard practice task IAF (Figure 5.5, row 3). Repeated task measurements thus seem to be less consistent in general, which was summarized by the lower ICC’s during task as compared to rest (see Figure 5.4, left panel).

Figure 5.6 presents the deviation histograms for IAF values as obtained with the “Gaussian fit” method. Conclusions were similar, but variability in general was lower than for the “maximum” method, as summarized by the higher ICC’s for the “Gaussian fit” as compared to the “maximum” method (Figure 5.4). In sum, repeated rest IAF measurements seem more consistent within participants than repeated task IAF measurements, and the “Gaussian fit” method generally showed more consistent results than the “maximum” method.



**Figure 5.5: Deviations between IAF values as estimated by the “maximum” method and standard practice IAF.** The upper row compares repeated IAF rest measurements for all subjects and both hemispheres to the standard practice rest IAF value. For each subject, the standard practice rest IAF was calculated by averaging the IAF values from the left and right hemisphere, of the initial measurement rest data of the extended session. The middle row compares repeated IAF task measurements for all subjects and both hemispheres to the standard practice rest IAF value. The lowest row compares repeated IAF task measurements for all subjects and both hemispheres to the standard practice task IAF value. For each subject, the standard practice task IAF was calculated by averaging the IAF values from the left and right hemisphere, of the initial measurement task data of the extended session. The left column includes repeated measurements taken during the initial measurements of the four different sessions (between-session comparison). The right column includes repeated measurements taken during the five time points of the extended session (within-session comparison). Black vertical lines indicate zero deviation. M = median, SD = standard deviation.



**Figure 5.6: Deviations between repeated IAF measurements as estimated by the “Gaussian fit” method and standard practice IAF.** The upper row compares repeated IAF rest measurements for all subjects and both hemispheres to the standard practice rest IAF value. For each subject, the standard practice rest IAF was calculated by averaging the IAF values from the left and right hemisphere, of the initial measurement rest data of the extended session. The middle row compares repeated IAF task measurements for all subjects and both hemispheres to the standard practice rest IAF value. The lowest row compares repeated IAF task measurements for all subjects and both hemispheres to the standard practice task IAF value. For each subject, the standard practice task IAF was calculated by averaging the IAF values from the left and right hemisphere, of the initial measurement task data of the extended session. The between-session comparisons (left column) include data from the initial measurements of the four sessions and the within-session comparisons (right column) include data from the five time points in the extended session. Black vertical lines indicate zero deviation. M = median, SD = standard deviation.

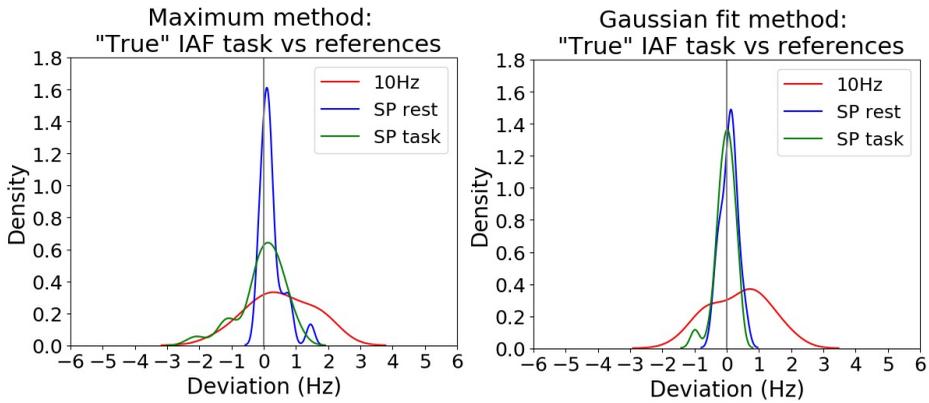
### How best to determine the rhythmic stimulation frequency?

Having quantified and visualized the consistency of repeated estimations of IAF at rest and during task, we can now ask explicitly: what should a researcher/clinician do? In the common scenario, one would prefer to rhythmically stimulate at the individual peak frequency relevant to a certain cognitive state/task. In our example dataset, that means that the goal would be to stimulate at the “true” task IAF. In practice, a researcher has three options for choosing the stimulation frequency: 1) a single frequency used for all participants without M/EEG calibration, 2) an individual frequency based on a short resting-state M/EEG measurement, or 3) an individual frequency based on an M/EEG measurement during task. In our example, these options translate to 1) 10 Hertz for every participant, 2) the standard practice rest IAF, 3) the standard practice task IAF. How closely does the result of each of these three options match the target frequency, namely, the “true” IAF during task? We evaluated this across participants and visualize the results in the form of probability curves, showing per procedure the proportion of participants falling within a certain distance (in Hertz) from the “true” task IAF (see Figure 5.7). This, ultimately, is the most relevant information when it comes to estimating the “success” of, for instance, an experiment relying on entrainment of that “true” IAF.

For every participant, we calculated the deviation of the three stimulation frequencies (10 Hertz, standard practice rest IAF, standard practice task IAF) to the approximated “true” task IAF for both the “maximum” and the “Gaussian fit” method (see “Analyses” section). For both methods, the standard practice rest IAF was more accurate (more often close to the target “true” IAF frequency) than simply using 10 Hertz (see Figure 5.7). This validates the common practice of basing stimulation frequency on a short resting state M/EEG.

Interestingly, in our dataset for our cognitive task, there was a difference between the “maximum” method and the “Gaussian fit” method in terms of how accurately a short task-EEG measurement could estimate the “true” task IAF. For the “maximum” method, though there was a small advantage of basing the stimulation frequency on task-IAF instead of using 10 Hertz, the IAF as estimated from rest-EEG was much more accurate (as evidenced by the greater/narrower peak in the probability curve). Instead, for the “Gaussian fit” method, the IAF as

estimated from rest-EEG and task-EEG were (nearly) equally accurate in estimating the true task IAF. This could be related to the fact that the “Gaussian fit” method can more consistently estimate IAF when power spectra are noisy due to alpha desynchronization (i.e., during task performance; Corcoran et al., 2018). In the Discussion, we outline the practical considerations and recommendations that follow from these results.



**Figure 5.7: Kernel density plots comparing three different methods for estimating the true task IAF.** **Left panel:** for every subject, we calculated the deviation between their true (median) task IAF and three different reference values: 10 Hertz (red), their standard practice (“SP”) rest IAF (blue), and their standard practice task IAF (green), estimated by the “maximum” method. For the comparison with 10 Hertz and SP rest, the true task IAF was calculated by taking the median of all repeated task measurements. For the comparison with SP task, the true task IAF was calculated by taking the median of all repeated task measurements except that SP measurement. Kernel density plots were constructed for each of these deviation distributions. **Right panel:** same as in the left panel, but for the IAF values as estimated by the “Gaussian fit” method.

## 5.6 Discussion

In this paper, we aimed to systematically assess the consistency of individual alpha EEG markers on a shorter (within-day) and longer (between-day) timescale, for two cognitive states (eyes closed resting state versus visuospatial attention task performance), estimation methods (“maximum” versus “Gaussian fit”), and hemispheres. We furthermore developed an algorithm to automatically reject power spectra without a clear peak. Results showed that both estimation methods yielded equivalent IAF estimates. Moreover, IAFs were significantly, but only very slightly, different (higher) during an attention task as compared to eyes-closed resting state. We found that IAF was overall reliable, but that the “Gaussian fit” method yielded more reliable estimates. We also concluded that, by and large, practical 3-minute EEG segments from single electrodes were sufficient to obtain these IAFs, and finally that – given these constraints and our particular attention task – a resting-state EEG more often yielded an adequate IAF than task-state EEG for the widely used “maximum” method of IAF determination.

We first investigated whether the “maximum” and “Gaussian fit” estimation methods led to similar IAF values. This is important, because if the methods overall yield the same result, the decision to use one or the other can be based wholly on how reliably each method yields that result. IAF values did not significantly differ between the two estimation methods for rest-EEG data, or for task-EEG data. Though the effect was minimal, both estimation methods led to slightly higher IAF values for task-EEG data compared to rest-EEG data, as in previous studies showing that IAF can increase with mental effort or task demands (Angelakis et al., 2004; Babu Henry Samuel et al., 2018; Gray and Emmanouil, 2020; Haegens et al., 2014; Hülzdünker et al., 2016) and even physical effort (Gutmann et al., 2015). Another study may or may not be in line with this, since they found decreased IAF over 1 hour of visual task performance, while mental effort might have either decreased (task learning or practice effects) or increased (fatigue) (Benwell et al., 2019). Taken together, we conclude that, for our data, the “maximum” and “Gaussian fit” methods provided equivalent IAF estimates.

After confirming this, we set out to quantify the consistency of repeated IAF estimates. Test-retest reliability of IAF was significant within- and between-sessions, for all cognitive states, hemispheres, and estimation methods. Repeated rest IAF

estimations mostly fell within 1 Hertz of the standard practice rest IAF for the “maximum” method, and within 0.5 Hertz for the “Gaussian fit” method. These results confirm that IAF values can differ across individuals, but are generally stable within an individual over time (Grandy, Werkle-Bergner, Chicherio, Lövdén, et al., 2013). Notably, the “Gaussian fit” method led to more reliable results than the “maximum” method, especially for data measured during task. This could be due to the fact that alpha power is suppressed during task performance, thereby making it more difficult to reliably detect an alpha peak (Yamagishi et al., 2008). It seems that the “Gaussian fit” method is less vulnerable to this (Corcoran et al., 2018; Haegens et al., 2014). Of note, the “Gaussian fit” method yields a different IAF than the “maximum” method if the power spectrum is strongly skewed, or if there are multiple alpha peaks in the power spectrum (Corcoran et al., 2018; Haegens et al., 2014). The “Gaussian fit” method can be used to separately estimate those peaks when alpha sub-bands are of interest (Doppelmayr et al., 1998; Klimesch et al., 1997). The latter is related to the idea of multiple coexisting alpha oscillators in the human brain (Benwell et al., 2019; Sokoliuk et al., 2019), possibly becoming more or less dominant depending on current task demands (Doppelmayr et al., 1998; Elshafei et al., 2018; Klimesch, 1997; Lobier et al., 2018; Shackman et al., 2010).

In rhythmic stimulation studies, IAF values are often measured during rest and applied during task (Kemmerer et al., 2020; Mioni et al., 2020; Ronconi et al., 2018; Ronconi et al., 2020). In many cases, it is desirable that the frequency of rhythmic stimulation is optimized to match the individual peak frequency relevant to the task of interest. We showed that using a standard 10 Hertz frequency for all participants to estimate this “true” task IAF was suboptimal, which is thus not recommended if close matching of stimulation frequency to individual task-relevant frequency is the goal. Variability decreased considerably when using a resting state EEG measurement, validating this common practice. Interestingly, only the “Gaussian fit” method led to similarly consistent results when using a task EEG measurement. For the “maximum” method, a task EEG measurement was better than using 10 Hertz, but not as consistent as a rest EEG measurement. In our data, a resting-state EEG measurement using the “Gaussian fit” method led to the most consistent results, and this approach is thus recommended. But future studies with other tasks and other frequencies of interest might aim to confirm this result. Similarly, based on our data, if only a task-EEG measurement is available, or

required, we would recommend to use the “Gaussian fit” method, but again future work should assess this for other tasks and frequencies.

There are several limitations to our current explorations. First of all, power spectra obtained from task-EEG data were more likely to be rejected for inclusion in our analyses due to alpha desynchronization (Yamagishi et al., 2008). For experiments that require an EEG measurement during task to obtain an individual peak frequency, this might make it more difficult to obtain a result. Note that this did not have a large influence in our experiment. Although more task data were rejected compared to rest data, only a small number of power spectra was rejected overall. Secondly, the current study was limited to 24 participants, included only one cognitive task, and focused on the alpha band. We should therefore be careful not to overgeneralize our results, and in the future aim to replicate them in a different and larger sample with a variety of cognitive tasks for different frequency bands. Moreover, IAF values during task were calculated by taking into account the EEG signal throughout visuospatial attention task performance, independently of specific task events such as the appearance of cues and targets. There are different ways of estimating the IAF during task performance, which might prove to be more reliable. For instance, perhaps IAF values based on the cue-target interval EEG signal constitute a better estimate of the task-relevant IAF. It would furthermore be worthwhile to assess how consistent IAF values are when based on an eyes open resting state measurement, here our resting state EEG was with eyes closed. It is also noteworthy to mention that our research questions are applicable to those rhythmic stimulation studies that aim to enhance the intrinsic peak frequency (i.e., when deviations between the stimulation frequency and the individual peak frequency should be avoided). There are also rhythmic stimulation studies with another aim, namely, to purposefully use a stimulation frequency that deviates from the dominant frequency, so as to speed up or slow down neuronal oscillations (Cecere et al., 2015). Another potential limitation is that the standard practice task measurement was longer (290 seconds) than the standard practice rest measurement (180 seconds). Lastly, of course we cannot actually know the “true” IAF values, but we can only approximate them by taking the median of the repeated measurements. In our view, these limitations are important to be aware of, but do not invalidate our core results.

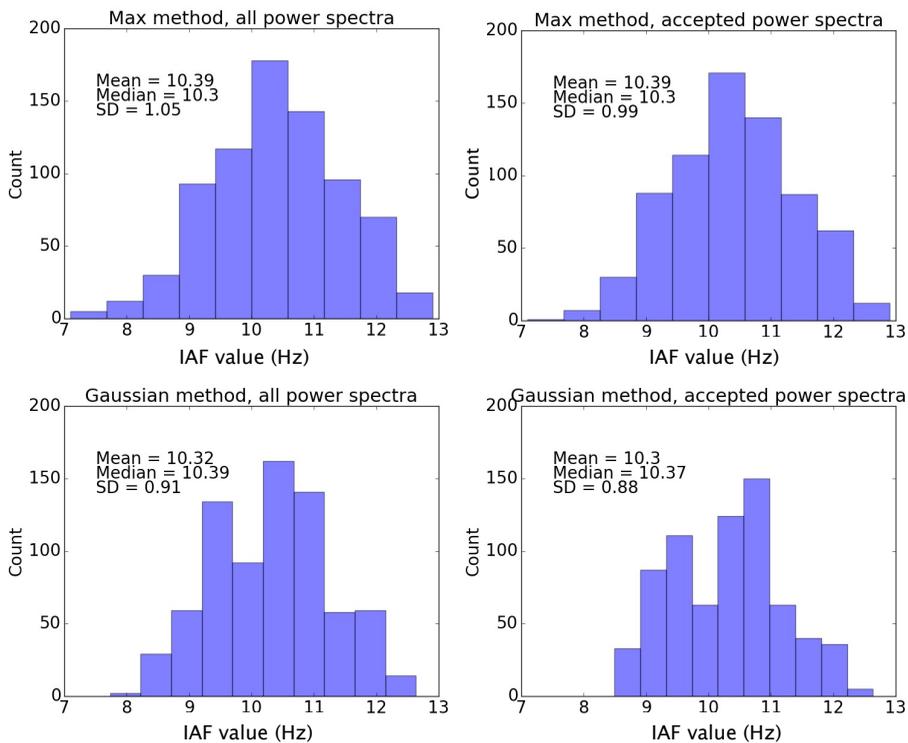
Our findings are of interest for personalizing rhythmic stimulation protocols using individual oscillation markers, or more generally for linking such markers to specific cognitive processes. Applications can cover a broad range of domains such as visual perception (Samaha and Postle, 2015), attention (Kemmerer et al., 2020), memory (Cross et al., 2020), language comprehension (Bornkessel et al., 2004), somatosensory processing (Craddock et al., 2019; Gundlach et al., 2016, 2017), and cross-modal perception (Cecere et al., 2015; Keil and Senkowski, 2017; Migliorati et al., 2019). Our results are furthermore relevant in clinical settings, for instance in neurofeedback training (Arns et al., 2012; Bazanova and Aftanas, 2010; Nan et al., 2012), but also for individualizing NIBS treatment for depression (Corlier et al., 2019; Garnaat et al., 2019; Leuchter et al., 2017; Roelofs et al., 2020), chronic pain (Ahn et al., 2019; Arendsen et al., 2018; Furman et al., 2018; Vries et al., 2013) and schizophrenia (Jin et al., 2012; Jin et al., 2005).

## 5.7 Conclusion

Rhythmic stimulation protocols can be optimized by calibrating the stimulation frequency based on individual M/EEG markers, such as IAF. When estimating such markers using peak detection methods, power spectra that do not contain a clear peak should first be rejected. IAF could be reliably estimated from short EEG measurements, and a “Gaussian fit” method was more reliable than the traditional “maximum” method. When selecting the optimal rhythmic stimulation target frequency, simply using a standard frequency for all participants does not seem to be a good approach if the goal is to closely match the task-relevant frequency. Instead, using a short resting-state EEG measurement led to more consistent results, validating a very common practice. A short EEG measurement during task performance led to similarly consistent results for the “Gaussian fit” method, but less so for the “maximum” method. Taken together, when calibrating rhythmic stimulation parameters to individual EEG markers, based on the current dataset we recommend a resting-state EEG measurement, along with the “Gaussian fit” approach. In future work, similar analyses might be applied to other tasks and frequency ranges.

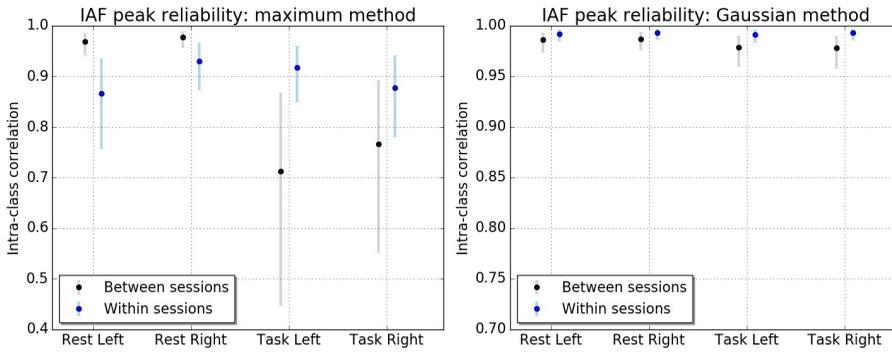
## 5.8 Supplementary Materials I: Power spectrum rejection algorithm

We developed an algorithm to automatically reject power spectra without a sufficiently clear peak. There were a few instances in which a to-be-included power spectrum was rejected. This is not a major problem for our analyses, since the total number of rejected power spectra was rather small (50 out of 768, or  $\sim 6.5\%$ , across 8 participants). There was no clear difference between the left (23) and right (27) hemispheres in terms of rejected power spectra. As expected, more power spectra were rejected for task data (41) as compared to rest data (9), since those data are generally noisier. Overall distributions of IAF values were similar before and after rejecting power spectra (see Figure 5.8).



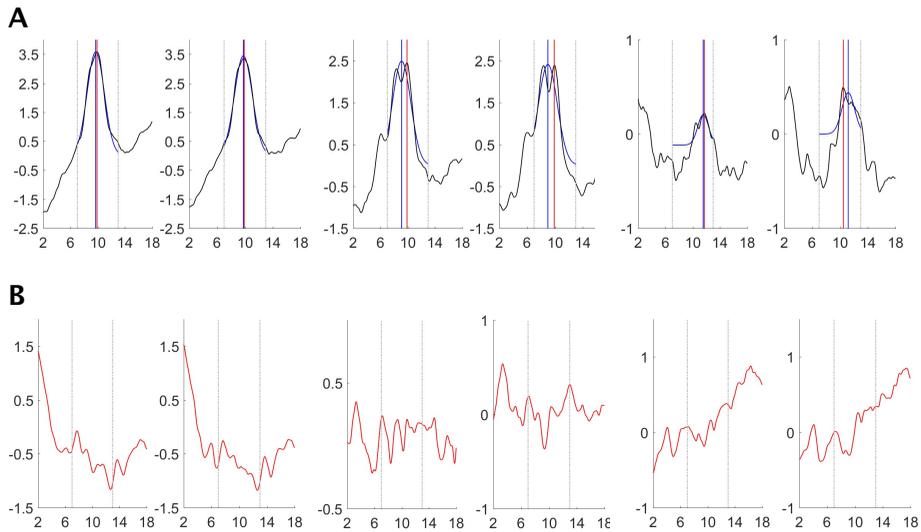
**Figure 5.8:** Distributions and descriptive statistics of IAF values as estimated by the “maximum” method (upper row) and “Gaussian fit” method (lower row), before (left column) and after (right column) exclusion of power spectra without a clear peak.

For the “Gaussian fit” method, test-retest reliability was similarly high before and after exclusion of power spectra without a clear peak (compare Figure 5.4 and Figure 5.9, right panels). For the “maximum” method, reliability increased after rejecting power spectra without a clear peak (compare Figure 5.4 and Figure 5.9, left panels).



**Figure 5.9: Test-retest reliability for IAF values as calculated with the maximum method (left panel) and the Gaussian method (right panel), before excluding power spectra.** Dots indicate intra-class correlation coefficients (ICC) and surrounding lines indicate 95% confidence intervals. Between-session reliability was calculated by comparing the initial measurement of the four separate sessions (in grey). Within-session reliability was calculated by comparing the five time points of the extended session (in blue). ICC values were calculated separately per cognitive state (rest versus task) and hemisphere (left versus right).

Figure 5.10 provides additional examples of accepted and rejected power spectra, along with IAF results obtained with the “maximum” and “Gaussian fit” methods (for accepted power spectra).



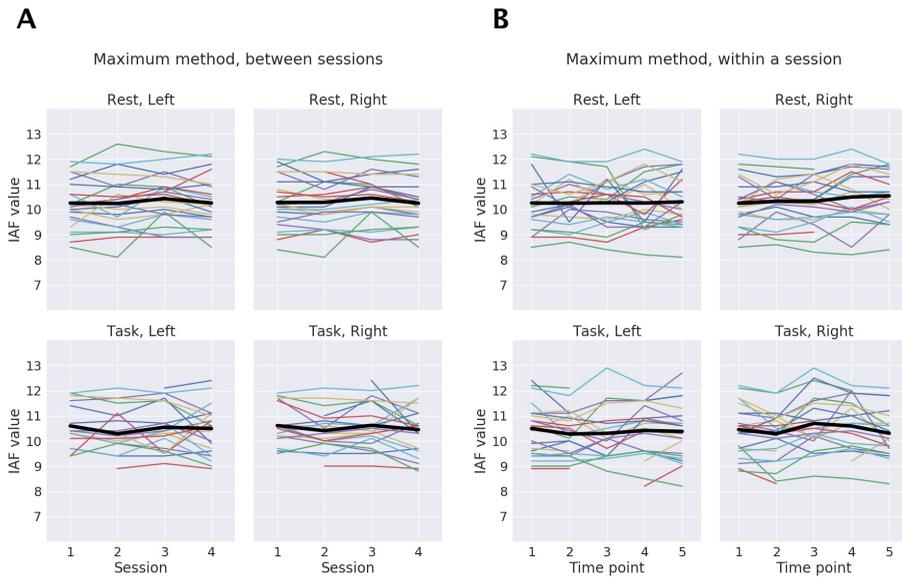
**Figure 5.10: Power spectrum rejection, “maximum” method, and “Gaussian fit” method examples. A) Representative examples of accepted power spectra.** Black lines indicate 1/f-removed and spectrally smoothed power spectra that were accepted by our power spectrum rejection algorithm. Grey vertical lines indicate the boundaries of the 7 – 13 Hertz alpha band. Red vertical lines show IAF values as obtained with the “maximum” method. Blue vertical lines show IAF values as obtained with the Gaussian method. Blue curves show the fitted Gaussian curve. **B) Representative examples of rejected power spectra.** X-axes show frequency in Hertz, y-axes show log-transformed alpha power ( $\mu V^2$ ).

## 5.9 Supplementary Materials II – Single-subject data and mixed model results

To quantitatively assess whether IAF estimates differed across time points, cognitive states and hemispheres, we performed two linear mixed-model analyses with a compound symmetry covariance structure, for each of the three dependent variables (IAF values as obtained by the “maximum” method, IAF values as obtained by the “Gaussian fit” method, and IAF width). IAF width results are reported in *Supplementary Materials III*. In one linear mixed model, the factor “time” included the four initial measurements of the different sessions (between-sessions comparison). In the other linear mixed model, the factor “time” included the five time points of the extended session (within-session comparison). Other included factors were “cognitive state” (rest versus task) and hemisphere (left versus right, or: electrode PO3 versus PO3). Follow-up simple effects analyses were performed where necessary.

### “Maximum” method

Single-subject IAF values as determined by the “maximum” method are shown in Figure 5.11. The between-sessions mixed model showed a significant main effect of “cognitive state” ( $F(1,311.31) = 20.42, p = .001$ ). IAF values were higher during task as compared to rest ( $M = 10.52$  versus  $M = 10.31, SE = 0.047$ ). Furthermore, there was a significant main effect of “session” ( $F(3,311.06) = 2.91, p = .035$ ). IAF values were higher in session 3 compared to session 2 ( $M = 10.52$  versus  $M = 10.33, SE = 0.067, p = 0.005$  two-sided uncorrected), and higher in session 3 compared to session 4 ( $M = 10.52$  versus  $M = 10.38, SE = 0.067, p = 0.038$  two-sided uncorrected). The within-session mixed model showed a significant main effect of “cognitive state” ( $F(1,406.33) = 8.29, p = .004$ ), with IAF values being higher during task as compared to rest ( $M = 10.48$  versus  $M = 10.35, SE = 0.043$ ). Note that, although statistically significant, these differences are so small (i.e.,  $< 0.20$  Hertz), that they are negligible for our purposes.

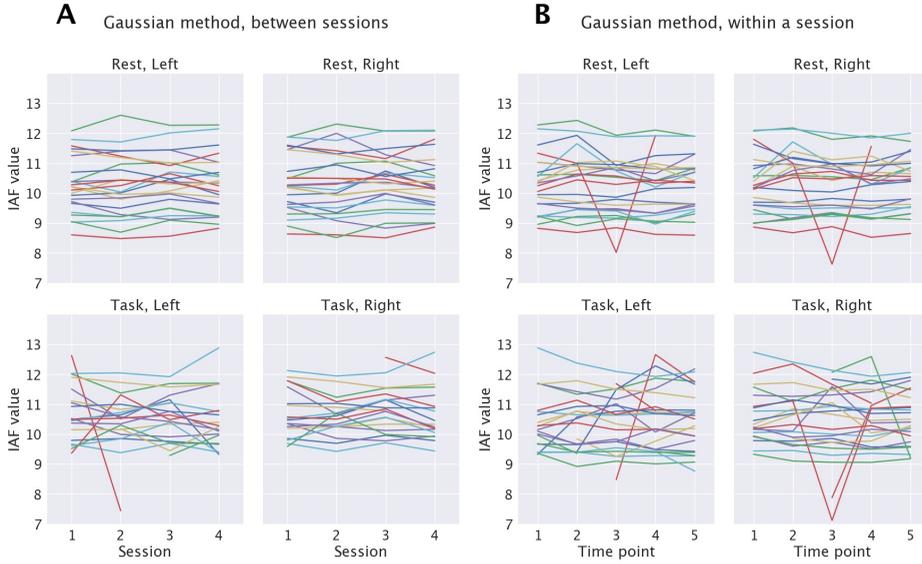


**Figure 5.11: IAF values as estimated by the “maximum” method. A) Repeated IAF measurements between sessions.** IAF values are visualized separately per cognitive state and hemisphere (four sub-plots), for every initial measurement of the four sessions (x-axes). Note that sessions were counterbalanced across individuals and thus session number does not represent session order. Each colored line represents data from a single subject. Black lines indicate between-subject averages. **B) Repeated IAF measurements within a session.** Single subject data as in A), but for the five time points within the extended session.

### “Gaussian fit” method

Single-subject IAF values as obtained by the “Gaussian fit” method are shown in Figure 5.12. The between-sessions linear mixed model analysis showed a significant effect of “cognitive state” ( $F(1,311.06) = 6.12, p = .014$ ). IAF values were higher during task as compared to rest ( $M = 10.33$  versus  $M = 10.28, SE = 0.021$ ). The main effect of “session” was significant as well ( $F(3,311) = 9.15, p = .001$ ). IAF values were significantly higher in session 3 ( $M = 10.36$ ) compared to session 1 ( $M = 10.28, SE = 0.19, p = 0.007$ , two-tailed uncorrected) and session 2 ( $M = 10.22, SE = 0.19, p < 0.001$ , two-tailed uncorrected). IAF values were also higher in session 4 ( $M = 10.36$ ) compared to session 1 ( $M = 10.28, p = 0.007$ , two-tailed uncorrected) and session 2 ( $M = 10.23, p < 0.001$ , two-tailed uncorrected). The within-session mixed model showed a significant main effect of “cognitive state” ( $F(1,406.06) = 19.81, p = .001$ ), a significant main effect of “time” ( $F(4,406) = 3.48, p = .008$ ), and a significant

“time”  $\times$  “cognitive state” interaction ( $F(4,406) = 3.15, p = .014$ ). However, follow-up simple effects analyses did not show any consistent pattern of IAF over time, and differences were again of negligible magnitude.



**Figure 5.12: IAF values as estimated by the “Gaussian fit” method. A) Repeated IAF measurements between sessions.** IAF values are visualized separately per cognitive state and hemisphere (four sub-plots), for every initial measurement of the four sessions (x-axes). Note that sessions were counterbalanced across individuals and thus session number does not represent session order. Each colored line represents data from a single subject. Black lines indicate between-subject averages. **B) Repeated IAF measurements within a session.** Single subject data as in A), but for the five time points within the extended session.

## 5.10 Supplementary Materials III: IAF peak width results

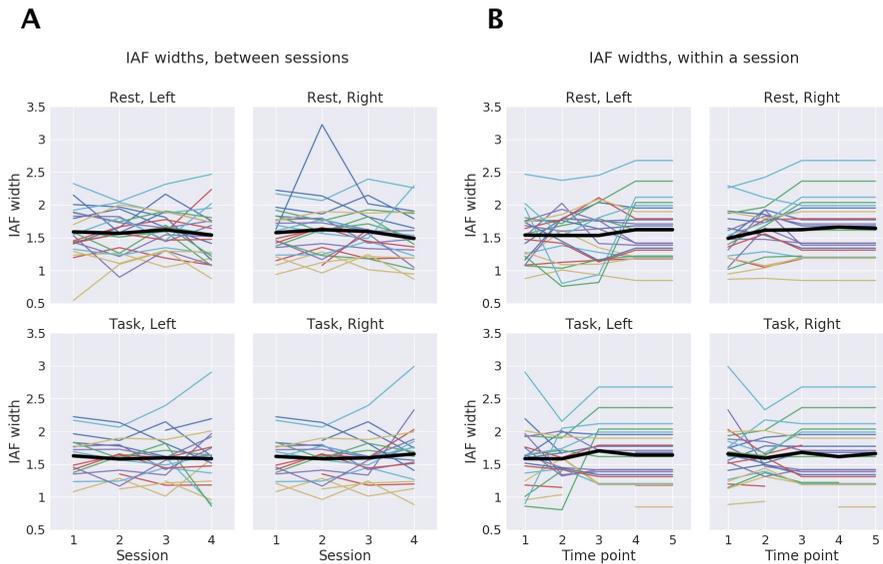
To the best of our knowledge, the IAF peak width has not yet been used for individualizing rhythmic stimulation protocols. This could potentially be an interesting direction for future research, if IAF peak width shows variability between participants, is a stable individual trait just like IAF peak center, and if it can be estimated with sufficient reliability. For instance, we have recently administered individually calibrated broadband electrical brain stimulation, directly based on the IAF peak frequency as well as peak width (Janssens et al., in preparation). And as brain stimulation advances, it seems plausible that stimulation protocols will be increasingly tailored to a multitude of relevant neuroimaging markers.

### How consistent are repeated IAF width estimations?

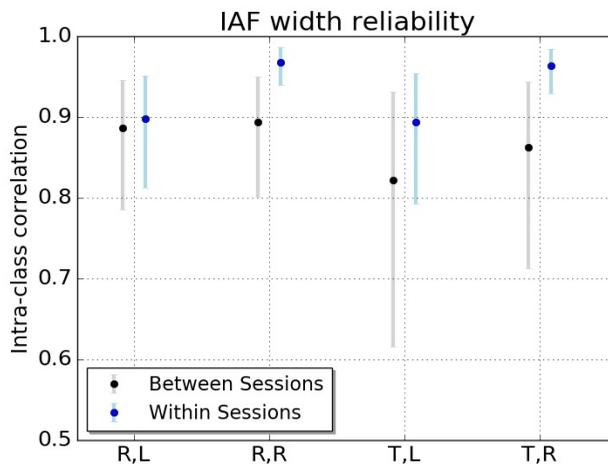
IAF peak widths were generally stable across sessions and within a session (see Figure 5.13), with occasional individual measurements with a seemingly incorrect result. Average IAF peak width was approximately 1.6 Hertz and did not significantly differ between cognitive states, hemispheres, or time points / sessions (all  $p$ 's > 0.10). As expected, within-subject standard deviations were lower than between-subject standard deviations (see Table 5.3). ICC values were significantly larger than 0.75 for both cognitive states and hemispheres ( $p$ 's < 0.05, see Figure 5.14), indicating that IAF width can be estimated with good test-retest reliability. Furthermore, deviation distributions generally showed low bias and low variability within- and between sessions (see Figure 5.15).

	Mean	Min	Max	SDwp_ws	SDwp_bs	SD_bp
Rest, Left	1.58	0.55	2.68	0.20	0.19	0.35
Rest, Right	1.59	0.85	3.22	0.13	0.18	0.38
Task, Left	1.61	0.81	2.90	0.19	0.20	0.35
Task, Right	1.63	0.85	2.99	0.12	0.18	0.35

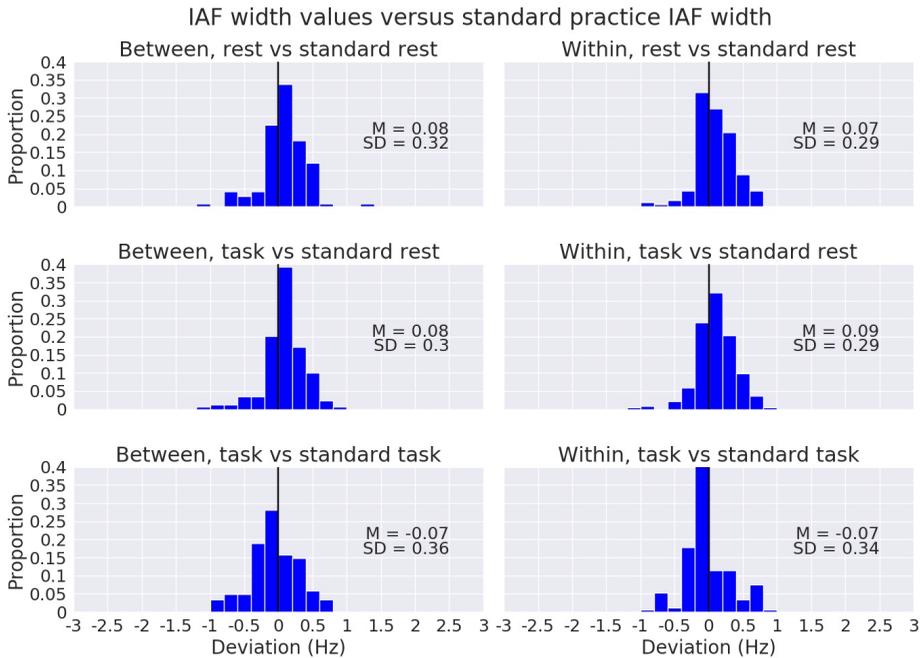
**Table 5.3: Descriptive statistics for the IAF widths.** Mean, minimum, maximum, and standard deviations of IAF widths are shown per cognitive state and hemisphere. “SDwp\_ws” refers to standard deviations within-participants, within-session. “SDwp\_bs” refers to standard deviations within-participants, between-sessions. “SD\_bp” refers to standard deviations between participants.



**Figure 5.13: IAF peak widths.** **A)** Repeated IAF width estimations between sessions. Peak widths are visualized for each cognitive state and hemisphere (four sub-plots), for every initial measurement of the four sessions (x-axes). Note that sessions were counterbalanced across participants and thus session number does not correspond to session order. Every colored line represents data from a single participant. Black lines show between-subject averages. **B)** Repeated IAF width estimations within a session. Same as in A), but for the five time points of the extended session.



**Figure 5.14: IAF peak width reliability.** Intra-class correlation coefficients (dots) are plotted with 95% confidence intervals (lines) per cognitive state (R = rest, T = task) & hemisphere (L = left, R = right).



**Figure 5.15: Deviations between repeated IAF width estimations and “standard practice” IAF width.** The upper row compares repeated rest IAF widths for all subjects and both hemispheres to the standard practice rest IAF width. For each subject, the standard practice rest IAF width was calculated by averaging the IAF widths from the left and right hemisphere, of the initial rest measurement of the extended session. The middle row compares repeated task IAF widths for all subjects and both hemispheres to the standard practice rest IAF width. The lowest row compares repeated task IAF widths for all subjects and both hemispheres to the standard practice task IAF width. Per subject, the standard practice task IAF width was calculated by averaging the IAF widths from the left and right hemisphere, of the initial measurement task data of the extended session. Between-session comparisons (left column) include data from the initial measurements of the four sessions; within-session comparisons (right column) include data from the five time points in the extended session. M = median, SD = standard deviation.

## Conclusion

In sum, it appears that IAF peak width, as IAF values, can be reliably assessed as individual markers capturing a different aspect of the frequency spectrum. Results and conclusions were largely in line with those presented for the IAF values.

## 5.11 References

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# Chapter 6

## **‘Broadband Alpha Transcranial Alternating Current Stimulation’: Exploring a new biologically calibrated brain stimulation protocol**

### **Corresponding manuscript:**

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## 6.1 Abstract

Transcranial alternating current stimulation (tACS) can be used to study causal contributions of oscillatory brain mechanisms to cognition and behavior. For instance, individual alpha frequency (IAF) tACS was reported to enhance alpha power and impact visuospatial attention performance. Unfortunately, such results have been inconsistent and difficult to replicate. In tACS, stimulation generally involves one frequency, sometimes individually calibrated to a peak value observed in an M/EEG power spectrum. Yet, the “peak” actually observed in such power spectra often contains a broader range of frequencies, raising the question whether a biologically calibrated tACS protocol containing this fuller range of alpha-band frequencies might be more effective. Here, we introduce “broadband-alpha tACS”, a complex individually calibrated electrical stimulation protocol. We band-pass filtered left posterior resting-state EEG data around the IAF, and converted that time series into an electrical waveform for tACS stimulation of that same left posterior parietal cortex location. In other words, we stimulated a brain region with a “replay” of its own spontaneous activity, focused on the alpha-range. Within-subjects (N=24), we compared to a sham tACS session the effects of broadband alpha tACS, power-matched spectral inverse (“alpha-removed”) control tACS, and individual alpha frequency tACS, on EEG alpha power and performance in an endogenous attention task previously reported to be affected by alpha tACS. broadband-alpha tACS significantly modulated attention task performance (i.e., reduced the rightward visuospatial attention bias in trials without distractors, and reduced attention benefits). Alpha-removed tACS also reduced the rightward visuospatial attention bias. IAF tACS did not significantly modulate attention task performance compared to sham tACS, but also did not statistically significantly differ from broadband-alpha tACS. This new broadband-alpha tACS approach seems promising, but should be further explored and validated in future studies.

### *Key words*

Transcranial alternating current stimulation (tACS); neuronal alpha oscillations; electroencephalography (EEG); visuospatial attention; individual alpha frequency (IAF).

## 6.2 Introduction

Non-invasive brain stimulation techniques such as transcranial alternating current stimulation (Antal and Paulus, 2013; Thut, Schyns, et al., 2011) have been used to enhance posterior alpha power (Helfrich et al., 2014; Kasten et al., 2016; Kasten and Herrmann, 2017; Neuling et al., 2013; Stecher et al., 2017; Vossen et al., 2015; Witkowski et al., 2016; Zaehle et al., 2010). Alpha tACS to left posterior parietal cortex (PPC), a brain area typically associated with visuospatial attention (Duecker et al., 2017), affected reaction times in an endogenous attention task (Kasten et al., 2020; Kemmerer et al., 2020; Schuhmann et al., 2019). Moreover, alpha activity seems to be causally involved in active distractor suppression, as evidenced by a reduced congruency effect in the Erikson flanker paradigm (Wiesman and Wilson, 2019) and improved performance in a visual conjunction search task (Müller et al., 2015) after alpha tACS. In line with this, inattentional blindness induced by alpha tACS has been explained by enhanced inhibition of irrelevant stimuli (Hutchinson et al., 2020). In sum, a number of studies successfully applied posterior alpha-frequency tACS to provide causal evidence for the involvement of alpha oscillations in visuospatial attention.

Nevertheless, not all results have been positive and consistent (Veniero et al., 2015). For instance, 10 Hz tACS does not always affect attention task performance and does not always lead to significant aftereffects on EEG alpha power (Battaglini, Mena, et al., 2020; Coldea et al., 2021). Such null findings may in part be explained by variations in individual alpha frequency (IAF) (Haegens et al., 2014; Stecher and Herrmann, 2018), which points to the importance of individualizing stimulation protocols (Hamidi et al., 2009; Janssens et al., 2021; Kemmerer et al., 2020; Lin et al., 2021). But even when tACS is delivered at IAF instead of at a standard (e.g., 10 Hz) frequency, sometimes there are no detectable effects on alpha power (Fekete et al., 2018). Such inconsistencies have not only been found at the neuronal level, but also at the behavioral level. For example, while alpha tACS to right PPC led to a visuospatial attention bias in a line bisection task in a first experiment, this finding could then not be replicated by the same experimenters in a second attempt (Veniero et al., 2017). Another study showed decreased detection performance, but not discrimination performance, after alpha tACS – but this effect was neither retinotopically- nor frequency-specific (Brignani et al., 2013). Furthermore, while some reports provided evidence for the involvement of alpha

oscillations in distractor processing (Schneider et al., 2021; Wöstmann et al., 2019), other studies did not find evidence for such a link (Noonan et al., 2016) or even directly contradicted the notion of a causal link (Antonov et al., 2020). Clearly, the role of alpha oscillations in distractor processing is not fully understood yet. Moreover, it is not entirely clear whether or under which constraints alpha tACS affects endogenous visuospatial attention. Even when effects are found, tACS effect sizes are generally small (Antal et al., 2008; Schutter and Wischniewski, 2016). It is therefore important to investigate whether previously found tACS effects can be enhanced by developing novel stimulation protocols. As tACS is increasingly being explored as a treatment strategy for a range of brain-based neurological and psychiatric disorders (Elyamany et al., 2020), any development in improving its efficacy is not only relevant for research, but also for clinical applications.

The standard tACS protocol, even when calibrated to an individual peak frequency, does not capture the complexity, or the idiosyncrasy, of the neuronal oscillatory response or intrinsic activity. For instance, IAF tACS stimulates at only one frequency, while the M/EEG power spectrum often shows enhanced power over a range of frequencies in the alpha-band (a “broad peak”). Moreover, M/EEG power spectra show substantial variability between participants with sometimes multiple peaks (Chiang et al., 2011; Haegens et al., 2014; Janssens et al., 2021). Parts of those more broadband signals might be attributable to the nature of the measurement, but others could reflect meaningful neuronal processes. There could be functionally relevant oscillators in posterior brain regions that operate at slightly slower or faster frequencies than the individual peak frequency (Benwell et al., 2019; Klimesch et al., 1997; Klimesch, 1999). While the precise mechanistic basis of tACS effects on behavior, as well as M/EEG measured oscillations, remains unknown, it might include processes of entrainment (Thut, Veniero, et al., 2011) and spike-timing dependent plasticity (Vossen et al., 2015). Spike-timing dependent plasticity mechanisms could be engaged by tACS in circuits operating with time-constraints closely matching the tACS frequency (Zaehle et al., 2010). If different circuits (oscillators) in posterior brain regions respond optimally to slightly different frequencies, tACS targeting a band of frequencies, as opposed to just a single frequency, might impact a larger range of functionally relevant circuits, and thereby yield a stronger effect on behavior and/or oscillatory activity as measured with M/EEG.

Here, we therefore developed individually tailored “broadband-alpha” tACS protocols directly based on resting-state EEG data from posterior parietal electrodes, essentially filtering out frequencies outside the alpha band and “feeding back” the native alpha-filtered time course content through electrical stimulation during attention task performance. This approach also naturally allowed us to develop an “alpha-removed” control protocol, which was the spectral inverse of the broadband-alpha tACS protocol. To create this protocol, we took the exact same individual EEG time series, but instead filtered out the alpha-band signals, keeping the content of all other frequencies between 1 and 49 Hz. This alpha-removed tACS protocol was matched to the broadband-alpha protocol in terms of overall power in the electrical waveform. We speculatively hypothesized that this alpha-removed protocol might effectively decrease, as opposed to increase, alpha-band activity in the brain. Thus, while the IAF and “broadband-alpha” tACS protocols may result in alpha synchronization, the “alpha-removed” tACS protocol could perhaps lead to alpha desynchronization (albeit in an indirect way, by promoting other frequencies). To our knowledge, this study is among the first to explicitly target enhancement of oscillatory power in a broader frequency band along these lines with cognitive effects. Encouragingly, a recent proof-of-principle study did already show that a replay of individual “neurodynamics” based on EEG measurements of motor cortex activity could more successfully enhance motor excitability than conventional tACS protocols (Cottone et al., 2018).

The aims of the current experiment were threefold. First of all, to develop and test the methodology for broadband-alpha tACS and power-matched spectral control stimulation protocols. Secondly, to assess whether broadband-alpha tACS can enhance posterior EEG alpha power and/or modulate visuospatial attention, not (or in opposite direction) shown for the alpha-removed protocol. Thirdly, to assess whether we could here replicate previous IAF tACS effects on alpha power and/or attention task performance, or whether broadband-alpha tACS might have more reliable effects in light of the inconsistency of IAF tACS reports.

We stimulated left PPC (10-20 electrode position P3) with a high-density (“ring electrode”) tACS montage, using four different tACS protocols (IAF tACS, broadband-alpha tACS, alpha-removed tACS, sham tACS) on separate days in 24 participants, in a counterbalanced fully within-subjects paradigm. The left hemisphere was chosen to replicate previous designs with positive results

(Kemmerer et al., 2020; Schuhmann et al., 2019, though see Coldea et al., 2021), and because effects have typically been stronger for or even restricted to the left hemisphere (Bagherzadeh et al., 2020; Kasten et al., 2020; Okazaki et al., 2014). In all four experimental sessions, participants performed a modified endogenous visuospatial attention task (Posner, 1980; Posner et al., 1980). Half of the attention task trials were traditional Posner trials with a central valid, neutral or invalid cue, followed by target gratings requiring an orientation judgment. The other half of the trials included bilateral, whole-field distractors during target presentation. Given the unclear role of neuronal alpha oscillations in distractor processing (as outlined above), alpha-tACS effects might differ between trials with and without distractors (because of alpha power increases following rhythmic stimulation, as hypothesized in de Graaf and Duecker, 2021). To investigate the effects of tACS on neuronal alpha power, EEG data were recorded during eyes closed resting state and during task performance, immediately after each 5-minute tACS/task block.

## 6.3 Materials and Methods

### Participants

Twenty-four healthy individuals participated in this experiment (11 males, age range 19 – 34). Participants were right-handed, had (corrected-to-normal) vision, and did not have any transcranial alternating current stimulation (tACS) contraindications (Antal et al., 2017). Participants were compensated with either research participation credits or vouchers. Ethical approval was obtained from the Ethical Review Committee Psychology and Neuroscience at Maastricht University.

### Procedures

The experiment consisted of four sessions of 2.5 – 3 hours each, taking place on separate days. Sessions were identical except for the brain stimulation protocol being administered. Session order was counterbalanced across participants, and brain stimulation was delivered single-blinded (the experimenter was aware of the conditions). Participants were informed about the (order of the) stimulation conditions only after study completion. Sessions were separated by at least two days. When entering the lab, participants were first screened for tACS contraindications and provided written informed consent. TACS and electroencephalography (EEG) electrodes were then prepared (for details see below). The eyetracker was set-up using a 5-dot calibration pattern and 1000 Hz sampling frequency (EyeLink1000, SR Research, Ottawa, Ontario, Canada). Preparations took approximately 1 hour altogether.

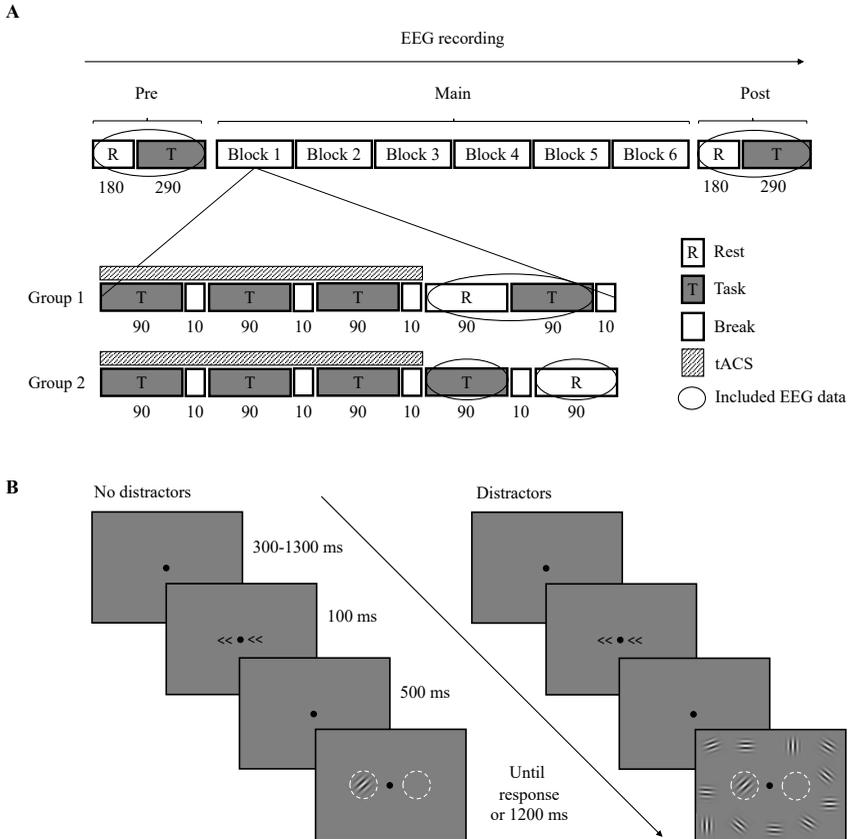
The experimental procedure consisted of three parts (see Figure 6.1a). The “*pre-measurement*” served to measure baseline EEG activity and task performance. It consisted of a 3-min eyes closed resting state EEG measurement, followed by a ~5-min EEG measurement during which participants performed an endogenous attention task (see below for task specifics). The “*main-measurement*” consisted of six identical blocks in which tACS was delivered and EEG was measured continuously. Each of the main blocks consisted of three components: 1) a 5-min attention task with concurrent tACS, 2) 90 sec of attention task without tACS and thus a tACS-artifact-free EEG signal, and 3) a 90-sec eyes closed resting state EEG measurement without tACS. The order of the last two components was

counterbalanced across two participant groups to prevent order effects. Four breaks of 10 sec were included during the attention task. Every main block took 520 sec and the entire main measurement lasted 52 min. The "*post-measurement*" was identical to the pre-measurement and was included to assess potential after-effects of tACS on EEG signal and/or task performance.

### Stimuli and Task

Participants performed an endogenous Posner task in all four sessions (see Figure 6.1b) (Posner, 1980; Posner et al., 1980). Stimuli were presented using MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) and Psychophysics Toolbox (Brainard, 1997) on a gamma-corrected 24 inch monitor with a 60 Hz refresh rate and a resolution of 1920 x 1080 pixels. Participants continuously fixated on a black dot of 0.2 degrees visual angle (DVA) presented in the center of a grey screen with a background luminance of 125  $\text{cd/m}^2$ . Their heads were stabilized using a chin rest that was positioned 60 cm away from the computer screen. Eyetracking was performed to assess fixation stability. After a randomly jittered fixation period (300 – 1300 msec), an endogenous cue was presented for 100 msec. The cue was either valid (arrows pointing in the direction of the upcoming target), neutral (one arrow pointing to the left and the other to the right), or invalid (pointing away from the upcoming target) at a ratio of 3:1:1. After a cue-to-target interval of 600 msec a target stimulus with a diameter of 3.5 DVA was presented at 7 DVA eccentricity on either the left or the right side of the screen. Target stimuli were sinusoidal gratings of 0.8 Michelson contrast (MC), rotated either 45 degrees clockwise or counter-clockwise, with random spatial frequency and phase. Participants performed a two-alternative forced choice (2AFC) task for each target grating. More specifically, they indicated as quickly and as accurately as possible the orientation of the target, pressing with their right hand either the left arrow button or the right arrow button for counter-clockwise and clockwise oriented gratings, respectively. The target grating disappeared once the participant responded or when 1200 msec had passed without a response. In half of the trials, only the target grating was presented. In the other half of the trials, distractors were displayed bilaterally at target onset until target offset. Distractors were displayed around the target locations and had a random orientation, phase and spatial frequency. Distractor contrast was 0.8 MC and a drift speed of 4 Hz was used to make the distractors appear to move in space, thereby make them more salient.

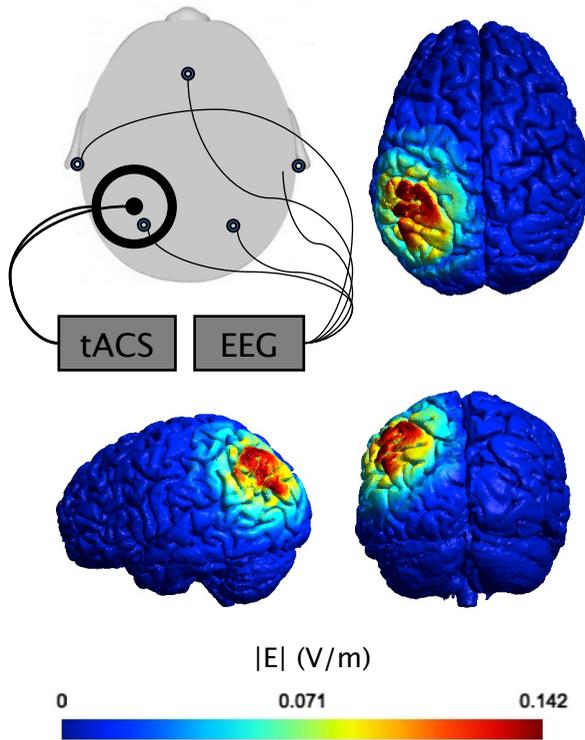
Average trial duration was 2100 msec (with pseudo-randomized jitter 1900 – 2300 msec), which was fixed such that the end of tACS always coincided with the end of the task. The pre- and post-measurement each contained 120 attention task trials, while the main measurement contained 960 trials divided equally over the six blocks.



**Figure 6.1: Experimental design.** **A) Procedures during a single experimental session.** In the “pre-measurement”, baseline EEG activity was measured during 3-min eyes closed resting state and ~5-min attention task performance. The “main-measurement” consisted of six identical blocks during which EEG was continuously recorded. Each block started with 5 min of attention task performance during which tACS was delivered (striped segments). Note that the same tACS protocol was delivered in all six blocks of an experimental session (and four tACS protocols were tested on different days). In the “post-measurement”, EEG data were recorded during 90 sec of eyes closed resting state and 90 sec of attention task performance without tACS, the order being counterbalanced across two participant groups. Only tACS-artifact-free EEG data could be included (circled segments). **B) Attention task example trials.** After a randomly jittered fixation interval, a symbolic cue was presented for 100 msec. This cue either pointed towards the upcoming target (valid), towards the opposite hemifield (invalid), or towards both hemifields (neutral). A target grating was presented in the left or right hemifield after a cue-target interval of 500 msec. Participants reported as quickly and as accurately as possible the orientation of the target (clockwise or counterclockwise). In half of the trials, distractors with random orientation, phase and spatial frequency were presented bilaterally from target onset until target offset.

### Electroencephalography (EEG)

EEG data were recorded with 5000 Hz sampling frequency and a hardware band-pass filter of 0.1-1000 Hz using BrainVision Recorder (BrainVision LLC, Morrisville, North Carolina, United States) and a BrainAmp DC amplifier (BrainProducts, GmbH, Gilching, Germany). Electrodes were placed over PO3, PO4, Fz (ground), A1 and A2 (references, computed offline) (see Figure 6.2). EEG electrodes were filled with conductive gel (OneStep Cleargel) and impedances were kept below 5 k $\Omega$  (ground and reference electrodes) or 10 k $\Omega$  (electrodes of interest).



**Figure 6.2: EEG and tACS electrode montages and tACS current simulation results.** A tACS ring electrode was centered position P3 of the international 10-20 system. EEG electrodes were positioned on P03, P04, Fz (ground) and both mastoids (references). tACS current simulations as created in SimNIBS show the norm of the electric field in V/m on an example brain, from three different viewpoints.

### Transcranial alternating current stimulation (tACS)

We used a tACS ring electrode montage (Datta et al., 2008; NeuroConn, Ilmenau, Germany) (inner/outer diameter 2.1/11 cm) to stimulate the left posterior parietal cortex (PPC) (Kemmerer et al., 2020; Schuhmann et al., 2019). The inner ring was placed over position P3 of the international 10-20 system and the outer ring was centered on the inner ring. TACS current flow was simulated in the software program SimNIBS (see Figure 6.2) (Heise et al., 2019; Saturnino et al., 2018; Saturnino et al., 2019). Conductive gel (Ten20, Weaver and Company, Aurora, CO, USA) was applied below both ring electrodes and the impedance was kept below 10 k $\Omega$ . Stimulation was controlled externally by using DataStreamer software, a digital-to-analog converter (National Instruments Corp., Austin, Texas, United States), and a Remote DC-Stimulator Plus (NeuroConn GmbH, Ilmenau, Germany). For an in-depth description of the experimental set-up, see ten Oever et al., 2016.

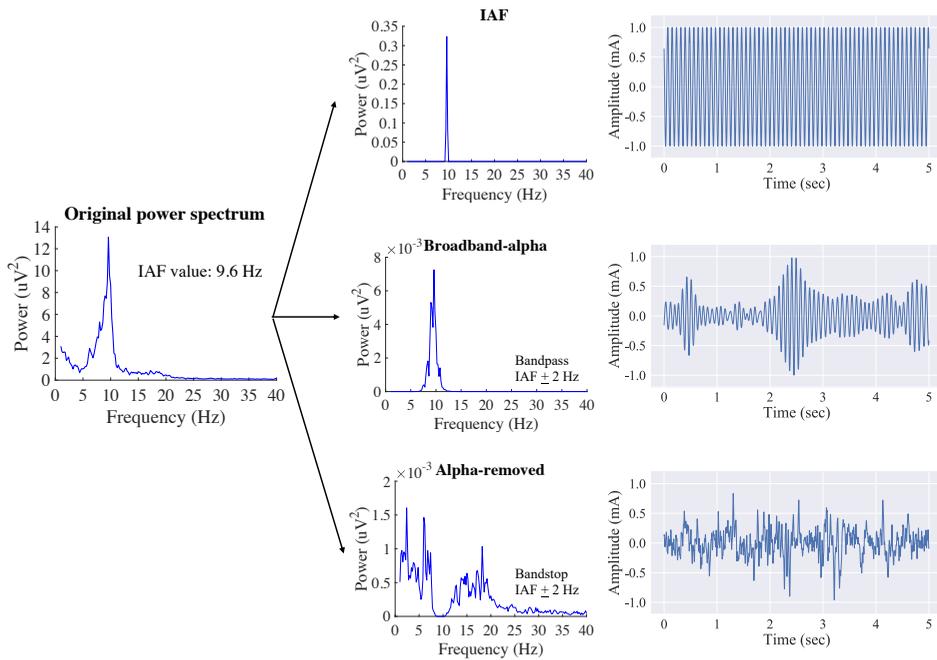
Four tACS protocols were created in MATLAB using FieldTrip Toolbox (Oostenveld et al., 2011). For each participant, tACS protocols were individualized based on the 3-minute eyes closed resting state EEG data recorded at the beginning of their first session, from electrode PO3 (left hemisphere) (see Figures 6.2 and 6.3). The “individual alpha frequency” (IAF) protocol was created by cutting 5 sec epochs, performing a fast Fourier transform with Hanning tapers, and creating a continuous sinusoid at the frequency with the highest power between 7 and 13 Hz (using a frequency resolution of 0.1 Hz). The “broadband-alpha” protocol contained a wider range of alpha frequencies, since it was created by band-pass filtering the EEG data using second-order Butterworth filters, first at 1 – 49 Hz and then at  $IAF \pm 2$  Hz. The “alpha-removed” protocol included frequencies outside of the alpha range and was created by first band-pass filtering the data using a second-order Butterworth filter at 1 – 49 Hz and then band-stop filtering the data at  $IAF \pm 2$  Hz.

The alpha-removed protocol was the spectral inverse of the broadband-alpha protocol. As a consequence, the alpha-removed tACS protocol contained more frequencies than the broadband-alpha tACS protocol. If left unchanged, any differences in the effects of broadband-alpha tACS and alpha-removed tACS might be explained by differences in the overall power present in these two tACS

protocols. To eliminate this confound, we matched power between the broadband and alpha-removed protocols as follows. First, we ensured that both protocols had a maximum absolute value of 1 in the time domain (corresponding to 1 mA) by convoluting the power spectra by  $1/\text{maximum value}$  across both conditions. As convoluting in the frequency domain is the same as multiplication in the time domain, this ensured that the maximum value in the time domain value was 1. Then, we equalized the sum of the powers across both protocols as follows: we took the protocol (power spectrum) with the minimum (i.e., smallest) summed (i.e., total) power, and scaled the *other* protocol to this one by dividing each power value by the relative summed power across both protocols. Then we put back the original phase estimates and inverted the FFT to get the normalized time courses. As recorded (pre-measurement resting state) EEG data were only 3 minutes long (see Figure 6.1a), we appended the data so that each protocol would cover the full intended stimulation duration (5 minutes). Though the power matching between the broadband and alpha-removed protocols was performed on the 3-minute data, this should only lead to negligible differences in the 5-minute protocols. Supplementary Table 1, we report the minimum amplitude, maximum amplitude, and the standard deviation of the amplitude for the created broadband-alpha and alpha-removed tACS protocols for each participant, to provide some insight in the parameters of tACS protocols in the time domain after these processing steps.

The “sham” protocol included a 15 sec ramp up and a 15 sec ramp down at IAF. All stimulation protocols included a 15 sec ramp up at the start of each stimulation block, but only the sham protocol included a ramp down. All protocols had a (maximum) intensity of 2 mA peak-to-peak (as in Kasten et al., 2020). Note that for the broadband-alpha and alpha-removed protocols, the stimulation did not constantly reach this intensity due to the nature of signals with multiple frequencies (see Figure 6.3). There were six stimulation blocks of 5 min each (see Figure 6.1a), leading to a total stimulation duration of 30 min.

Though we did not formally record tACS side-effects, participants generally perceived all tACS protocols as tolerable. Most of our participants were tACS novices, and therefore did not know in advance what “real” tACS feels like. Based on informal conversations, it seems that our participants did not know in which session they received sham (ineffective) tACS, and IAF tACS was typically perceived to be the most uncomfortable stimulation protocol.



**Figure 6.3: Creation of individualized tACS protocols.** Data are shown for one representative participant. The leftmost panel shows the original power spectrum resulting from the 3-min eyes closed resting state measurement at the beginning of the first session. Different brain stimulation protocols (middle panels) were created by filtering the original power spectrum (left panel) and calculating the inverse Fourier transform to go back to a time-domain signal (rightmost panels). The individual alpha frequency (IAF) protocol was created by selecting the frequency between 7 and 13 Hz with maximum power. The broadband-alpha protocol was created by band-pass filtering the power spectrum at  $\text{IAF} \pm 2$  Hz. The alpha-removed protocol was created by band-stop filtering the power spectrum at  $\text{IAF} \pm 2$  Hz. An additional processing step (see previous page) ensured that the broadband-alpha and alpha-removed protocols were matched in power. Rightmost panels show 5-sec example segments of the tACS protocols.

## Analyses

Data were analyzed using MATLAB version 2019a, FieldTrip Toolbox (Oostenveld et al., 2011), Python 3 and JASP version 0.12.2.

*Behavioral analyses.* The dependent variable for the two-alternative forced-choice (2AFC) task was reaction time (RT) in msec. Trials in which participants responded incorrectly or too fast ( $< 200$  msec) were excluded. Trials with blinks and/or saccades (defined as eye movements  $> 2$  DVA) during the cue-to-target interval were removed. On average 109 out of 1200 trials were excluded per session (63 due to blinks/saccades, 45 due to incorrect responses, and 1 due to a fast

response). Median RTs were calculated for all participants for each condition cell and values more than 3 standard deviations away from the mean across participants were removed. One participant was excluded due to technical problems in the lab (i.e., tACS equipment failure). Two planned analyses were performed on the RT data from the main measurement. The first analysis involved two separate three-way repeated-measures ANOVAs, one for trials with distractors and one for trials without distractors, including the factors “brain stimulation” (IAF, broadband-alpha, alpha-removed, sham), “hemifield” (left versus right), and “cue validity” (valid, neutral, and invalid). In the second analysis, we first calculated RT benefits (by subtracting scores in valid cue trials from those in neutral cue trials) and costs (by subtracting scores in neutral cue trials from those in invalid cue trials) (Duecker and Sack, 2015; Mangun and Buck, 1998). We then performed a three-way repeated-measures ANOVA on these attention benefits and costs, including the factors “brain stimulation”, “hemifield”, and “distractors” (present versus absent). As a post-hoc exploratory analysis, we then also performed the same three-way repeated-measures ANOVA for the dependent variable “cueing effect” (which was calculated by subtracting RTs in invalid cue trials from RTs in valid cue trials). Significant interaction effects were followed by simple effects analyses. To assess the consistency of tACS effects, single subject effects were visualized using “raincloud plots” (Allen et al., 2019).

*EEG preprocessing.* EEG files were cut into 5 sec epochs. Signal variance was calculated for each epoch and the six tACS offsets were pinpointed by detecting sudden drops in EEG variance between epochs. The insufficient dynamic range of our EEG system and the limited number of electrodes prevented the analysis of EEG data during tACS (Kasten and Herrmann, 2019). We therefore selected artifact-free EEG data (see Figure 6.1a), after which epochs were sorted into task and rest epochs. Epochs with a high signal variance were excluded based on the inter-quartile range ( $> [Q3 + 1.5 \times IQR]$  criterion) (as in de Graaf et al., 2017). Power at frequencies 1 – 49 Hz was determined by calculating FFTs using Hanning tapers, separately for each cognitive state (task versus rest) and hemisphere (left versus right). Epochs were zero-padded to 10 sec to reach a frequency resolution of 0.1 Hz and power values were log-transformed (Smulders et al., 2018). Alpha power was calculated by taking the sum of the power values from the frequencies within the range  $IAF \pm 2$  Hz. Next, we removed the  $1/f$  trend from the power

spectrum and fitted a Gaussian curve to the power spectrum. Alpha peak width was determined as the standard deviation of the fitted Gaussian (Albada and Robinson, 2013; Dickinson et al., 2018; Haegens et al., 2014). Alpha peak width was calculated to allow assessment of tACS effects on the shape/width of the alpha-range power spectrum in EEG, given the different ‘alpha-widths’ in the current experiment between the broadband-alpha tACS, IAF tACS, and alpha-removed tACS protocols. We previously reported that alpha peak width can be reliably estimated using this method (Janssens et al., 2021). For each of the four sessions, alpha power and alpha peak width values in the main-measurement and post-measurement were normalized to the pre-measurement. This was done by calculating the average alpha power/width in the pre-measurement, across cognitive states and hemispheres, and subtracting that value from the main- and post-measurement values.

*EEG analyses.* Our predefined analysis plan was to first investigate whether any brain stimulation effects were present in the main measurement (immediate tACS aftereffects). If this were to be the case, we would then proceed to analyze the post-measurement to investigate whether the brain stimulation effects persisted after the tACS had stopped entirely (longer tACS after-effects). Two participants were excluded from the analyses due to technical problems in the lab (one due to a corrupted EEG file, the other due to tACS equipment failure). Two more participants were excluded due to the presence of multiple outlier values (defined as values  $> 3$  SD away from the mean across participants). We then performed two repeated-measures ANOVAs with the factors “brain stimulation” (IAF, broadband, alpha-removed, and sham), “cognitive state” (task versus rest) and “hemisphere” (left/electrode PO3 versus right/electrode PO4), one for each dependent variable (alpha power and alpha peak width). Including the factor “hemisphere” allowed us to assess whether tACS affected alpha power and/or alpha peak width specifically in the left (stimulated) hemisphere, or perhaps also influenced the contralateral hemisphere.

We originally hypothesized that the alpha-removed tACS protocol would either have no effects on alpha power, or, if anything, might decrease alpha power (‘de-entrainment’) through a process of alpha desynchronization for instance by the enhancement of neighboring frequencies. From this perspective, in an explicitly exploratory analysis, we also assessed whether alpha-removed tACS increased

theta (3 – 6 Hz), beta (15 – 25 Hz), or gamma (30 – 40 Hz) power compared to sham tACS. Note that these frequency bands were non-overlapping with the individually created alpha bands (IAF  $\pm$  2 Hz), since the minimum IAF was 8.2 Hz and the maximum IAF was 12.2 Hz in our subject sample. We performed three repeated-measures ANOVAs with the factors “brain stimulation” (alpha-removed versus sham), “cognitive state” (task versus rest”), and “hemisphere” (left/electrode PO3 versus right/electrode PO4), one for each dependent variable (theta, beta, and gamma power).

It is possible that tACS effects were limited to particular experimental blocks in our cumulative tACS session, since early versus late tACS effects may be driven by different mechanisms (e.g., entrainment versus neuroplasticity) (Antal and Herrmann, 2016; Herrmann et al., 2013). We performed post-hoc analyses to explore this idea. More specifically, we repeated the above mentioned EEG analyses while including the factor “experimental block” (with three levels: blocks 1 & 2, blocks 3 & 4, and blocks 5 & 6). We furthermore performed the same EEG analyses specifically for block 1 and for block 6.

## 6.4 Results

In a counterbalanced within-subject design, we stimulated left PPC in 24 participants using individually calibrated broadband-alpha tACS, power-matched alpha-removed-tACS, IAF tACS, and sham-tACS. All tACS conditions were well-tolerated by participants. Below, we evaluate the effects of tACS on attention task performance with and without distractors. We then assess whether tACS led to aftereffects in EEG alpha activity.

### Behavioral results

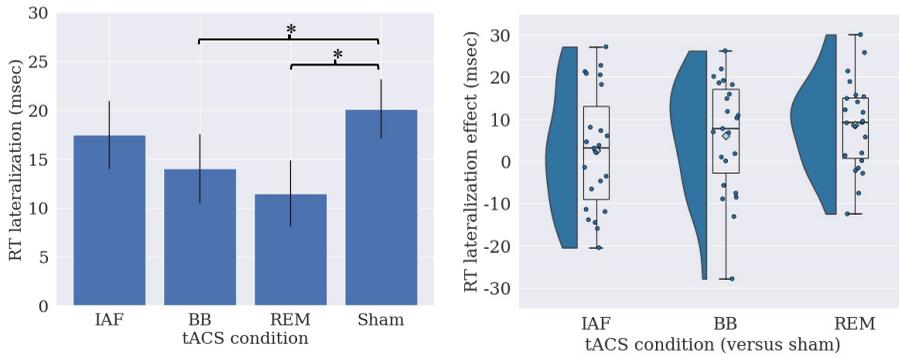
*Analysis 1.* The first planned analysis included two repeated-measures ANOVAs with the factors “brain stimulation” (IAF, broadband-alpha, alpha-removed, sham), “hemifield” (left, right) and “cue validity” (valid, neutral, invalid) on median RTs in msec – one for trials with distractors, the other for trials without distractors.

In trials with distractors, there was a significant main effect of “hemifield” ( $F(1,22) = 24.05, p < .001$ ). RTs were slower in the left hemifield as compared to the right hemifield (respectively  $M = 522.49$  and  $M = 496.29, SE = 10.60$ ). As expected, there was a significant main effect of “cue validity” ( $F(2,44) = 32.47, p < .001$ ) (Chica et al., 2014; Duecker and Sack, 2015; Mangun and Buck, 1998). There were significant attention benefits, as evidenced by significantly faster RTs for valid cue trials as compared to neutral cue trials ( $t(23) = 1.78, p = .040$ , one-tailed uncorrected, mean difference =  $-3.16, SE = 1.77$ ). Attention costs also turned out significant, since RTs were slower in invalid cue trials as compared to neutral cue trials ( $t(23) = 5.91, p < .001$ , mean difference =  $10.48, SE = 1.77$ ). The fact that we replicated these well-documented effects validates our modified Posner task with distractors, indicating that it can be used to study endogenous visuospatial attention. Interestingly, tACS did not seem to modulate attention task performance in trials with distractors, since the factor “brain stimulation” did not show any significant effects ( $p$ 's  $> 0.10$ ).

In trials without distractors, the main effects of “hemifield” and “cue validity” were significant as well ( $F(1,22) = 29.18, p < .001$  and  $F(2,44) = 37.39, p < .001$ , respectively). Again, RTs were slower in the left as compared to the right hemifield (mean difference =  $15.77, SE = 2.92$ ). Both attention benefits and costs turned out

significant (mean difference = 6.99 versus -6.84, respectively,  $SE = 1.60$ ,  $p$ 's < 0.001). There was a significant “brain stimulation”  $\times$  “hemifield” interaction ( $F(3,66) = 3.83$ ,  $p = .014$ ). Raw RT data in trials without distractors are shown in Supplementary Figure 1. The significant interaction was difficult to interpret, since follow-up simple effects analyses yielded no significant effect of “brain stimulation” for either hemifield in isolation ( $p$ 's > 0.10), and the effect of “hemifield” was significant for all brain stimulation sessions (IAF:  $F(1,22) = 25.04$ ,  $p < .001$ ; broadband-alpha:  $F(1,22) = 15.64$ ,  $p < .001$ ; alpha-removed:  $F(1,22) = 11.54$ ,  $p < .001$ ; sham:  $F(1,22) = 44.12$ ,  $p < .001$ ).

Therefore, to further explore the pattern of results underlying the brain stimulation  $\times$  hemifield interaction, and to replicate the analyses from two previous studies with positive results (Kemmerer et al., 2020; Schuhmann et al., 2019), we calculated RT lateralization scores (RTs to left hemifield targets minus RTs to right hemifield targets). Positive values indicate a rightward bias and negative values indicate a leftward bias. We conducted three planned follow-up paired t-tests, to compare the three “active” tACS conditions with the sham condition (see Figure 6.4). In contrast to previous reports (Kemmerer et al., 2020; Schuhmann et al., 2019), we did not find a significant difference in RT lateralization scores between IAF and sham stimulation ( $t(23) = 0.97$ ,  $p = 1.000$ , Bonferroni-corrected). We did find a significant difference between broadband-alpha and sham stimulation in the expected direction ( $t(23) = 2.23$ ,  $p = .040$  one-tailed, Bonferroni-corrected), with a smaller rightward bias for the broadband-alpha condition ( $M = 14.02$  versus  $M = 20.12$ ,  $SE = 2.74$ ). The direction of this effect is in line with the positive results from previous studies using 10 Hz tACS (Schuhmann et al., 2019) and tACS at IAF (Kemmerer et al., 2020). Though a direct comparison between the effects of broadband-alpha and IAF tACS was not statistically significant ( $F(1,22) = 1.31$ ,  $p = .260$ ), in this experiment, broadband-alpha tACS was able to reveal a hypothesized result that single-frequency (IAF) tACS could not successfully replicate. On the other hand, we also found a significant difference between alpha-removed and sham stimulation ( $t(23) = 3.15$ ,  $p = .010$  two-sided, Bonferroni-corrected), in the same direction as for broadband-alpha tACS, which was contrary to our expectations ( $M = 11.49$  versus  $M = 20.12$ ,  $SE = 2.74$ ). Note that the seemingly deviating observation in Figure 6.4 (broadband-alpha versus sham tACS, lowermost dot) was not an outlier statistically, and conclusions did not change after excluding that observation/participant.

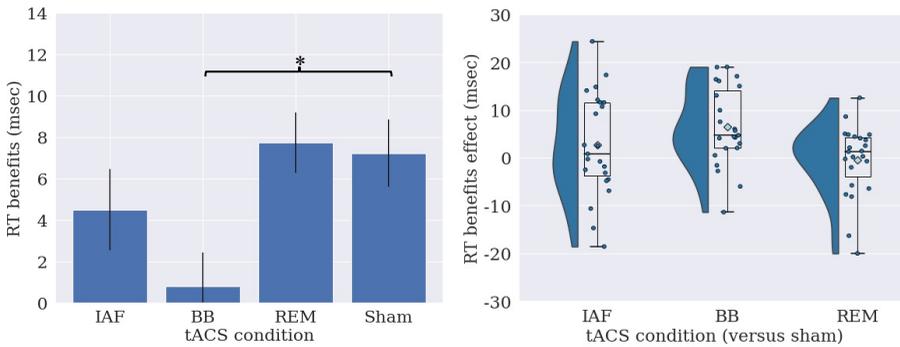


**Figure 6.4: The effects of brain stimulation on attention bias.** **Left panel:** average reaction time (RT) lateralization scores are shown for all tACS conditions (IAF = individual alpha frequency, BB = broadband-alpha, REM = alpha-removed). Error bars indicate standard error of the mean (SEM). Asterisks indicate statistically significant differences ( $p < 0.05$ ). **Right panel:** single subject RT lateralization effects for each of the three planned comparisons (x-axis). RT lateralization effect (y-axis) was calculated by subtracting RT lateralization scores for “active” (IAF, BB, or REM) tACS from sham tACS (i.e., RT lateralization sham-tACS minus RT lateralization active-tACS). A larger effect thus indicates a larger reduction in RT lateralization after “active” tACS compared to sham-tACS. Dots indicate single subject effects, diamonds indicate mean effects, and data distributions are visualized using boxplots and probability distributions. Note that 17 out of 23 (~74%) subjects showed an effect in the expected direction (i.e., a reduction in the rightward attention bias, compared to sham tACS, as shown by dots  $> 0$ ) in the broadband-alpha condition, but only 13 out of 23 (~57%) in the IAF condition.

*Analysis 2.* In the second planned analysis, we performed two repeated-measures ANOVAs to investigate whether attention benefits (decrease in RT after valid cues, from neutral cues) and costs (increase in RT after invalid cues, from neutral cues) were influenced by our experimental factors “brain stimulation” (IAF, broadband-alpha, alpha-removed, sham), “hemifield” (left, right), and “distractors” (present, absent). For the analysis on attention costs, the only significant effect was a main effect of “distractors” ( $F(1,22) = 7.08$ ,  $p = .014$ ), where attention costs were higher in trials with distractors compared to trials without distractors ( $M = 10.48$  versus  $M = 6.84$ , respectively,  $SE = 1.37$ ).

There was also a significant main effect of “distractors” on attention benefits ( $F(1,22) = 5.39$ ,  $p = .030$ ), with lower benefits in trials with distractors compared to trials without distractors ( $M = 3.16$  versus  $M = 6.99$ , respectively,  $SE = 1.65$ ). Importantly, there was also a strongly significant main effect of “brain stimulation” on attention benefits ( $F(3,66) = 4.77$ ,  $p = .005$ ). Three planned follow-up tests, comparing the three “active” brain stimulation conditions with the sham condition,

showed that only the broadband-alpha condition differed significantly from the sham condition ( $t(23) = 3.76$ ,  $p = .003$  two-tailed, Bonferroni-corrected; see Figure 6.5). Attention benefits were smaller (in fact, nearly absent) in the broadband-alpha condition ( $M = 0.82$  versus  $M = 7.24$  in the sham condition,  $SE = 1.71$ ), very consistently across participants (see Figure 6.5, right panel). As in *Analysis 1*, broadband-alpha tACS could reveal a significant effect (compared to sham tACS), while IAF tACS could not, though the direct comparison between the effect of broadband-alpha (versus sham) tACS compared to IAF (versus sham) tACS was not significant ( $F(1,22) = 1.88$ ,  $p = .180$ ). Even though tACS was left-lateralized, we did not find a significant “brain stimulation”  $\times$  “hemifield” interaction ( $F(3,66) = 0.81$ ,  $p = .490$ ). Raw RT data are shown in Supplementary Figure 1.



**Figure 6.5: The effects of brain stimulation on attention benefits.** **Left panel:** average reaction time (RT) benefits are shown for all tACS conditions (IAF = individual alpha frequency, BB = broadband-alpha, REM = alpha-removed). Error bars indicate standard error of the mean (SEM). Asterisks indicate statistically significant differences ( $p < 0.05$ ). **Right panel:** single subject effect for each of the three planned comparisons (x-axis). RT benefits effect (y-axis) was calculated by subtracting RT benefits for “active” (IAF, BB, or REM) tACS from sham tACS (i.e., RT benefits sham-tACS minus RT benefits active-tACS). A larger effect thus indicates a larger reduction in RT benefits after “active” tACS compared to sham-tACS. Dots indicate single subject effects, diamonds indicate mean effects, and data distributions are visualized using boxplots and probability distributions. Note that in the broadband-alpha condition, 19 out of 23 (~83%) participants showed an effect in the expected direction (i.e., a reduction in attention benefits compared to sham tACS, as shown by dots  $> 0$ ), but only 11 out of 23 (~48%) in the IAF condition.

In a post-hoc exploratory analysis, we did not find any statistically significant main or interaction effects of “brain stimulation”, “hemifield”, or “distractors” on the attentional cueing effect (RT valid – RT invalid cue trials; all  $p$ 's  $> 0.10$ ).

## EEG results

We performed a repeated-measures ANOVA with the factors “brain stimulation” (IAF, broadband-alpha, alpha-removed, sham), “cognitive state” (rest, task) and “hemisphere” (left/electrode PO3, right/electrode PO4) on the dependent variable “alpha power”. There was a significant main effect of “cognitive state” ( $F(1,19) = 45.09, p < .001$ ). In line with previous results, alpha power was higher during eyes closed resting state as compared to during task performance (mean difference = 31.05,  $SE = 4.63$ ) (Barry et al., 2007; Barry and De Blasio, 2017; Başar et al., 1999; Osaka, 1984; Yamagishi et al., 2008). Moreover, there was a significant main effect of “hemisphere” ( $F(1,19) = 12.75, p = .002$ ), with alpha power being higher in the left hemisphere as compared to the right hemisphere (mean difference = 8.97,  $SE = 2.51$ ). This finding is the opposite of two previous reports (Çiçek et al., 2003; Gallotto et al., 2020), but note that (Gallotto et al., 2020) looked at alpha power at a specific, short time window during an attention task. There were no significant main or interaction effects including the factor “brain stimulation” ( $p$ 's  $> 0.10$ ). When specifically comparing the IAF and sham conditions, these conclusions did not change.

We then performed a repeated-measures ANOVA with the same factors on the dependent variable “alpha peak width”. There was a significant main effect of “hemisphere” ( $F(1,18) = 9.31, p = .007$ ), with alpha peak width being larger in the left hemisphere as compared to the right hemisphere (mean difference 0.23,  $SE = 0.076$ ). There were no significant main or interaction effects including the factor “brain stimulation” (all  $p$ 's  $> 0.10$ ).

Since the alpha-removed protocol essentially stimulated frequencies outside the alpha-range, we performed exploratory repeated-measures ANOVAs on power in the theta, beta, and gamma bands (see “Methods”) focusing on factors “brain stimulation” (alpha-removed versus sham), “cognitive state” (rest, task) and “hemisphere” (left/electrode PO3 versus right/electrode PO4). There were no statistically significant effects for any of these ANOVAs/frequency bands (all  $p$ 's  $> 0.10$ ), also not when including the two statistical “outlier participants”.

Note that post-hoc analyses did not provide any statistical evidence to support the idea that tACS effects differed between experimental blocks (all  $p$ 's  $> 0.10$ ).

## 6.5 Discussion

We here introduced a new “broadband-alpha” tACS protocol, as well as its spectral inverse (“alpha-removed”) protocol, stimulating participants with electrical waveforms directly based on their own (filtered and scaled) EEG activity recorded from the same left posterior target site. We asked whether broadband-alpha tACS, including frequencies  $\pm 2$  Hz around individual alpha frequency (IAF), could amplify alpha power and/or modulate attention, perhaps more consistently or strongly than single-frequency IAF tACS. After all, while IAF tACS is tailored to individual M/EEG power spectra, it only marginally represents the complexity and distribution of alpha-band activity actually observed in neuronal oscillations. More complex, biologically informed tACS protocols targeting multiple frequencies could be superior, for instance if they impact a larger range of functionally relevant circuits with slightly different preferred frequencies.

A recent proof-of-principle study provided encouraging evidence that biologically inspired (EEG-based) electrical stimulation affords new, powerful neuromodulation approaches. Those authors extracted hand motor activity from primary motor cortex EEG based on functional source separation informed by coherence with electromyography (EMG) activity measured in the relevant contralateral hand muscles (Cottone et al., 2018). “Individual neurodynamics stimulation”, meaning electrical stimulation with a waveform based on such EEG/EMG-based endogenous hand motor activity, affected cortical excitability while conventional 20 Hz tACS did not. The current study took a similar approach, “replaying” individual cortical activity measured with EEG, but with the different goal of enhancing oscillatory power across a functionally relevant (alpha) frequency band, as opposed to general cortical excitability, to affect corresponding cognitive function. Our aims were to 1) develop this approach, 2) assess the effects of broadband-alpha tACS and a spectral inverse (“alpha-removed”) control tACS protocol on attention task performance and/or post-stimulation alpha power, 3) assess whether the effects of broadband-alpha tACS are more consistent compared to conventional (single-frequency) tACS.

We first investigated whether broadband-alpha tACS had any effects on EEG alpha activity and/or attention task performance. Broadband-alpha tACS did not cause any significant aftereffects on EEG alpha power (in fact, none of the tACS

protocols did, see below). Broadband-alpha tACS reduced the rightward attention bias in attention task trials without distractors. This effect was statistically significant and observable in the majority of participants. The direction of this effect is consistent with previous studies, since it has been shown that the rightward spatial attention bias that is typically present in healthy volunteers (i.e., “pseudoneglect”; Jewell and McCourt, 2000) can be reduced by alpha tACS to left PPC (Kemmerer et al., 2020; Schuhmann et al., 2019). However, we found an unexpected similar result for alpha-removed tACS. The purpose of this protocol was more explorative, serving as an interesting control condition but without clear expectations based on prior research. If anything, we a priori speculated that by enhancing frequencies outside of the alpha band, we might get a (relative) reduction of alpha power (alpha desynchronization, by “de-entrainment”) and consequently opposite behavioral effects compared to the broadband-alpha and IAF tACS protocols. One possibility to consider is whether our unexpected behavioral finding in the alpha-removed tACS condition was directly caused by increased beta power (Battaglini, Ghiani, et al., 2020; Samaha et al., 2017), or perhaps even theta or gamma power. Exploratory analyses did not reveal enhanced beta (or theta/gamma) power in post-tACS EEG activity. Unfortunately, we cannot determine what exactly alpha-removed stimulation did to oscillatory power online, since we could not reliably analyze the EEG data recorded during tACS. These results thus do not offer an explanation regarding the underlying neuronal effects of tACS. It is therefore difficult to explain why we found equivalent behavioral results for the broadband-alpha and alpha-removed tACS protocols in this particular analysis.

An effect that was specific to the broadband-alpha tACS condition was a reduction in attention benefits after broadband-alpha compared to sham tACS. There were no statistically significant effects of tACS on attention costs or on the “cueing effect”. Attention allocation involves alpha desynchronization (Gould et al., 2011), and broadband-alpha tACS was hypothesized to synchronize alpha oscillators across the individual alpha band (IAF  $\pm$  2 Hz). That synchronization might counteract the desynchronization that is required for attention benefits (e.g., de Graaf and Duecker, 2021; de Graaf et al., 2013). Since we stimulated the left hemisphere, we might have expected any effects of brain stimulation to differ between hemifields based on hemispheric lateralization (Duecker et al., 2013). However, in our data, the effect of broadband-alpha stimulation on attention

benefits did not significantly interact with the factor “hemifield”. We thus found a generic, hemifield-independent improvement in cued attentional orienting. Is tACS perhaps not focal enough, does it relate to interhemispheric interactions, are there more complicated mechanisms at play, or does broadband-alpha tACS not work the way we hypothesized? At this time, we cannot disentangle this further. In any case, the effects of broadband-alpha tACS cannot be explained by indirect tACS effects such as somatosensory stimulation (Asamoah et al., 2019; Matsumoto and Ugawa, 2017; Raco et al., 2014; Vieira et al., 2020). This is because the effects did not occur in the IAF tACS condition, which was typically perceived as involving stronger somatosensory stimulation (informal observation). Taken together, these statistically strong and consistent effects of broadband-alpha tACS are promising, and exciting to pursue in future studies. At the same time, for the reasons outlined above, not all results are easily interpretable, and the full pattern of findings across our complex experimental design does warrant caution.

After establishing that broadband-alpha tACS modulated attention task performance, we could assess whether it might do so more consistently than IAF tACS. As also recently reported by Coldea et al., 2021, we could not replicate previous reports of IAF tACS effects on attention task performance in similar paradigms (Kasten et al., 2020; Kemmerer et al., 2020; Schuhmann et al., 2019). This underlines that IAF tACS effects can be unreliable, or sensitive to precise conditions/parameters, and actually highlights the importance of developing more robust stimulation protocols. Perhaps, lower amplitude (e.g., 1 or 1.5 mA peak-to-peak) IAF tACS might have led to detectable changes in attention task performance because of the tACS strength-focality tradeoff (Tan et al., 2020), as in previous studies that used the same tACS electrode montage (Kemmerer et al., 2020; Schuhmann et al., 2019). It should also be mentioned that it is not possible to model the exact electric field induced by a tACS ring electrode montage, because the impedance can only be measured for the ring electrode as a whole (rather than for different subsections of the large ring). Future studies could opt for a tACS montage with a small center electrode surrounded with four (or more) small electrodes. In any case, IAF tACS did not induce any behavioral effects in the current study, while it seems broadband-alpha tACS did alter the endogenous attention bias, in the same participants with the same montage. After broadband-alpha tACS, the majority of participants showed behavioral effects in the expected direction. Though the direct comparison between broadband-alpha

tACS and IAF tACS was not statistically significant, these first findings are promising. Future studies are needed to establish whether these broadband-alpha tACS effects are reliable, and whether broadband-alpha tACS is superior to IAF tACS, for instance by also comparing it to lower amplitude IAF tACS in a double-blind design.

None of our tACS protocols caused changes in posterior alpha power following tACS. Our intermittent tACS blocks (5-minute blocks always separated by 3 minutes) might have been too short to cause measurable aftereffects (Strüber et al., 2015). Previous studies reporting tACS aftereffects mostly stimulated continuously for longer durations (20–35 minutes), but with a lower intensity (Kasten et al., 2016; Kasten and Herrmann, 2017; Kemmerer et al., 2020; Neuling et al., 2013; Schuhmann et al., 2019). At the same time, tACS aftereffects have been found after only 10 minutes of continuous stimulation (Stecher et al., 2017; Zaehle et al., 2010) and after intermittent stimulation of 8 seconds for 11-15 minutes (Vossen et al., 2015). At this point, it is thus unclear under what circumstances tACS to PPC can induce EEG aftereffects. In any case, online tACS effects might rely on different mechanisms than tACS aftereffects. Our lack of tACS aftereffects on EEG signals is perhaps interesting in light of some previous reports, but does not invalidate any potential online tACS effects on behavior. In order to more directly investigate the effects of tACS, analysis of M/EEG data during stimulation will be required, and artifact removal techniques will have to be improved (Helfrich et al., 2014; Holzmann et al., 2021; Neuling et al., 2015; Vosskuhl et al., 2020; Witkowski et al., 2016).

It is important to mention that our broadband-alpha tACS and alpha-removed tACS protocols were based on the individual EEG time series as measured during eyes closed resting state. We recently established that the IAF during cognitive (attention) task performance could be most accurately estimated using resting-state EEG data (rather than task EEG data) (Janssens et al., 2021). However, it is currently unknown to what extent the oscillatory power dynamics present within the entire EEG alpha band are consistent across cognitive states. Future studies should compare the effects of “replaying” the individual oscillatory alpha power dynamics as measured during rest (as done in our study) with the effects of “replaying” the individual oscillatory alpha power dynamics as measured during task. Furthermore, we currently cannot distinguish whether the “replay” of the

individual time series may be the crucial factor, or whether merely the distribution of alpha activity is relevant for inducing broadband-alpha tACS effects.

The broadband-alpha and alpha-removed tACS protocols that we introduced here both include a (small) range of frequencies rather than a single frequency (as in the traditional IAF tACS protocol). This brings to mind an existing form of transcranial electric stimulation (TES) that also includes multiple frequencies, namely, transcranial random noise stimulation (tRNS). Especially when it comes to the apparently similar effects of broadband-alpha and alpha-removed tACS on attention bias, one might wonder whether mechanisms underlying tRNS effects could explain some of our findings. Compared to our protocols, the frequency range in tRNS is much higher and broader (i.e., from  $\pm 0.1$  to  $\pm 100$  Hz for “low-frequency” tRNS and, more conventionally, 100 to 700 Hz for “high-frequency” tRNS; Antal and Herrmann, 2016; Moret et al., 2019; Paulus, 2011). Our broadband-alpha protocol contained frequencies between the range  $\text{IAF} \pm 2$  Hz, and the alpha-removed protocol contained frequencies between 1 and 49 Hz. Besides this, tRNS amplitude/frequency varies randomly, while for our protocols the amplitude/frequency was based on individual EEG data. High-frequency tRNS can increase cortical excitability (Terney et al., 2008), even after only 5 minutes of stimulation (Chaieb et al., 2011). A broad range of high frequencies (i.e., much higher/broader than used here) seems to be necessary to achieve this (Moret et al., 2019). Interestingly, tRNS to parietal cortex has recently been shown to affect attention task performance (Contò et al., 2021). This could possibly result from “stochastic resonance”, where tRNS introduces noise that can modulate the neuronal signal-to-noise ratio in a beneficial way – if delivered at the appropriate intensity (Pavan et al., 2019; van der Groen and Wenderoth, 2016). While we cannot control or account for tRNS-related mechanisms affecting our current results, our protocols seem quite different from conventional tRNS. Besides, such an explanation could only be part of the story, since we found similar effects of broadband-alpha and alpha-removed tACS on attention bias, but effects specific to broadband-alpha tACS on attention benefits. Nevertheless, future studies should explore this connection further, for instance by directly comparing the effects of broadband-alpha and alpha-removed tACS to the effects of established tRNS protocols.

From a clinical perspective, it could be worth pursuing these broadband tACS protocols in the future. TACS is increasingly being explored as a potential treatment strategy for several brain-based disorders (Elyamany et al., 2020). For instance, alpha tACS has successfully been applied to patients with depression (Alexander et al., 2019; Riddle et al., 2020) and substance use disorder (Daughters et al., 2020). For such clinical applications, a more robust or powerful tACS protocol would be highly meaningful. Even if broadband-alpha tACS were non-inferior (rather than superior) to IAF tACS in terms of its neural/behavioral effects, it could still be the preferred protocol if its somatosensory side-effects were less uncomfortable. It seems that the IAF tACS protocol was perceived to be the most “painful” stimulation type, though this needs to be systematically addressed in the future. Furthermore, any tACS protocol that could successfully *reduce* rather than enhance oscillations within a specific frequency band in a specific brain region, would enable interesting new applications. For instance, the strong rightward attention bias in hemineglect is associated with enhanced alpha power in the damaged right hemisphere (Lasaponara et al., 2019; Pirondini et al., 2020), and depression has been associated with increased gamma activity in frontal and temporal areas (Strelets et al., 2007). As a future outlook, oscillatory power *reducing* tACS protocols seem worthy of pursuit for the potential clinical applications alone. Unfortunately we could not produce convincing evidence that alpha-removed tACS had any suppressive effects on local alpha oscillations.

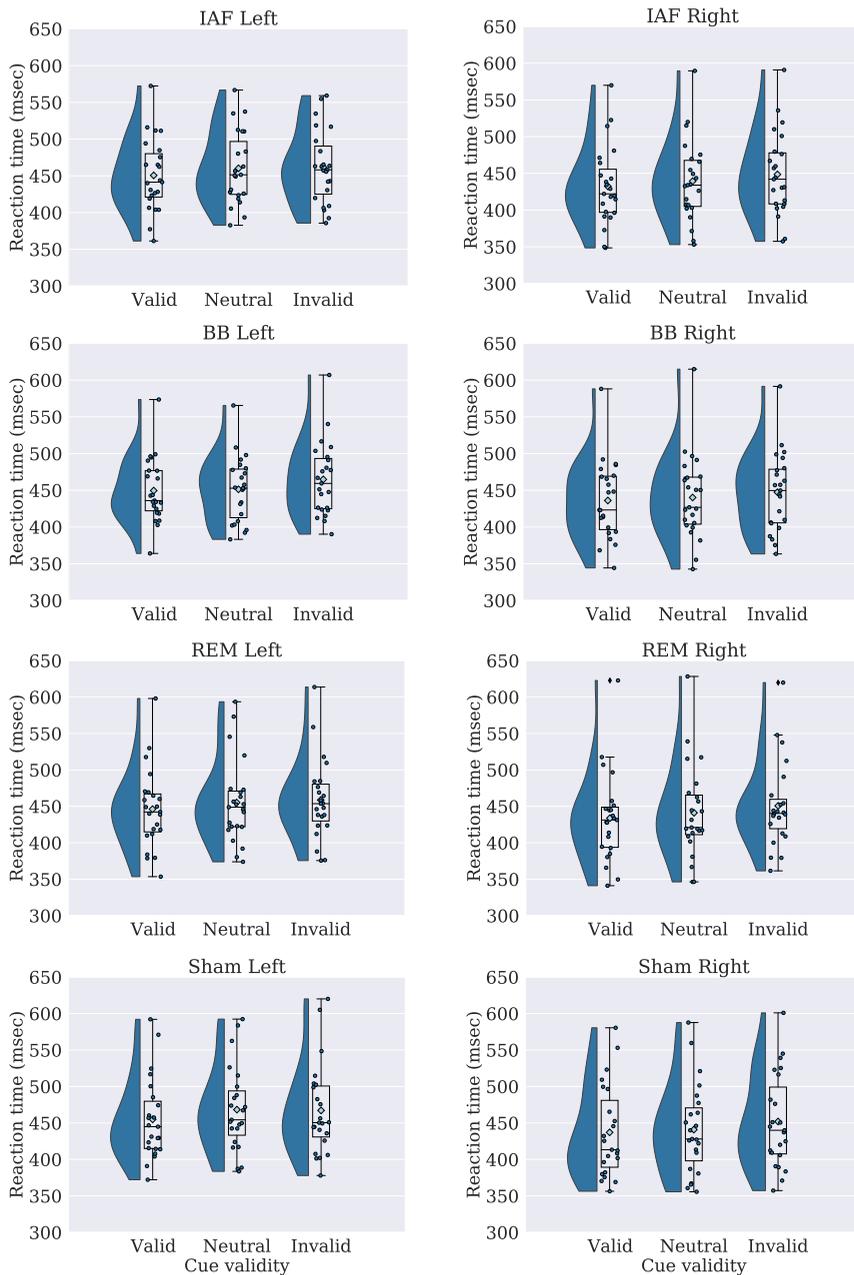
## 6.6 Conclusion

Our new, biologically informed broadband-alpha tACS protocol was well-tolerated, reduced the rightward attention bias in trials without distractors, and reduced attention benefits. These effects were statistically strong, consistent across individuals, and could not be explained by somatosensory side-effects. IAF tACS did not modulate attention, further highlighting that its effects are inconsistent, and that more robust tACS protocols are needed. Still, not all findings were as expected: alpha-removed tACS also reduced the rightward attention bias, the reduction in attention benefits after broadband-alpha tACS was not specific to one hemifield, and attention task performance did not significantly differ in a direct comparison between IAF & broadband-alpha tACS. These novel developments and findings are promising, but in need of further exploration and validation.

## 6.7 Supplementary Materials

<b>Subject</b>	<b>Min(BB)</b>	<b>Max(BB)</b>	<b>SD(BB)</b>	<b>Min(REM)</b>	<b>Max(REM)</b>	<b>SD(REM)</b>
<b>1</b>	-0.63	0.63	0.1539	-0.83	1.00	0.1543
<b>2</b>	-0.61	0.62	0.2154	-0.91	1.00	0.2152
<b>3</b>	-0.65	0.65	0.1621	-0.74	1.00	0.1624
<b>4</b>	-0.79	0.78	0.2572	-0.87	1.00	0.2585
<b>5</b>	-1.00	0.98	0.1718	-0.84	0.98	0.1781
<b>6</b>	-0.92	0.94	0.2540	-0.95	1.00	0.2546
<b>7</b>	-0.60	0.59	0.1694	-1.00	0.76	0.1695
<b>8</b>	-1.00	1.00	0.2247	-0.73	0.97	0.2253
<b>9</b>	-0.83	0.87	0.1652	-0.67	1.00	0.1648
<b>10</b>	-1.00	0.98	0.2153	-0.77	0.92	0.2154
<b>11</b>	-0.99	1.00	0.1866	-0.74	0.82	0.1873
<b>12</b>	-0.58	0.59	0.1523	-1.00	0.70	0.1526
<b>13</b>	-0.47	0.48	0.0949	-1.00	0.78	0.0953
<b>14</b>	-0.71	0.73	0.1922	-1.00	0.97	0.1922
<b>15</b>	-1.00	1.00	0.2233	-0.89	0.87	0.2228
<b>16</b>	-0.75	0.78	0.2449	-1.00	0.98	0.2449
<b>17</b>	-0.70	0.69	0.1495	-0.91	1.00	0.1492
<b>18</b>	-0.41	0.42	0.1539	-0.70	1.00	0.1535
<b>19</b>	-0.60	0.62	0.0376	-0.58	1.00	0.0377
<b>20</b>	-0.57	0.57	0.1573	-1.00	0.66	0.1576
<b>21</b>	-0.82	0.80	0.2052	-1.00	0.93	0.2051
<b>22</b>	-1.00	0.98	0.2175	-0.96	0.87	0.2177
<b>BS-SD</b>	0.19	0.19	0.05	0.13	0.11	0.05

**Supplementary Table 1. Descriptive statistics for the broadband-alpha and alpha-removed tACS protocols.** For each (included) participant, the minimum amplitude (Min), maximum amplitude (Max), and standard deviation of the amplitude (SD) are shown for the broadband-alpha tACS protocol (BB) and the alpha-removed protocol (REM). Four decimals are shown for the SD(BB) and SD(REM) to highlight the minor differences between the two columns. The lowermost row shows the between-subject standard deviations (BS-SD) for each of the columns.



**Supplementary Figure 1.** Raw reaction time data in trials without distractors for the individual alpha frequency ('IAF'), broadband-alpha ('BB'), alpha-removed ('REM'), and sham tACS conditions (subplot rows), for each hemifield (subplot columns) and cue validity (x-axes). Each dot represents data from a single subject. Mean reaction times are indicated with diamonds. Data distributions are visualized using boxplots and probability distributions. The seemingly deviating data points in the broadband-alpha and alpha-removed tACS conditions (second and third row of subplots) were no outliers statistically, and none of our conclusions changed when excluding those data points.

## 6.8 References

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# Chapter 7

## Can processing of face trustworthiness bypass early visual cortex? A transcranial magnetic stimulation masking study

### Corresponding manuscript:

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## 7.1 Abstract

As a highly social species, we constantly evaluate human faces to decide whether we can trust someone. Previous studies suggest that face trustworthiness can be processed unconsciously, but the underlying neural pathways remain unclear. Specifically, the question remains whether processing of face trustworthiness relies on early visual cortex (EVC), required for conscious perception. If processing of trustworthiness can bypass EVC, then disrupting EVC should impair subjective (conscious) trustworthiness perception while leaving objective (forced choice) trustworthiness judgment intact. We applied double-pulse transcranial magnetic stimulation (TMS) to right EVC, at different stimulus onset asynchronies (SOAs) from presentation of a face in either the left or right hemifield. Faces were slightly rotated clockwise or counterclockwise and were either trustworthy or untrustworthy. On each trial, participants discriminated 1) trustworthiness, 2) stimulus rotation, and 3) reported subjective visibility of trustworthiness. At early SOAs and specifically in the left hemifield, performance on the rotation task was impaired by TMS. Crucially, though TMS also impaired subjective visibility of trustworthiness, no effects on trustworthiness discrimination were obtained. Thus, conscious perception of face trustworthiness (captured by subjective visibility ratings) relies on intact EVC, while objective forced-choice trustworthiness judgments may not. These results are consistent with the hypothesis that objective trustworthiness processing can bypass EVC. For basic visual features, extrastriate pathways are well-established; but face trustworthiness depends on a complex configuration of features. Its potential processing without EVC is therefore of particular interest, further highlighting its ecological relevance.

### *Key words*

Trustworthiness; early visual cortex; TMS masking; objective versus subjective processing.

## 7.2 Introduction

When meeting someone for the first time, we immediately form an impression about whether that person is friend or foe. Solely based on facial features, a person is judged to be more or less trustworthy (Todorov et al., 2015; Todorov et al., 2008). An exposure of less than 100 ms is sufficient to make a trustworthiness judgment that is highly replicable and consistent across observers (Todorov et al., 2009; Willis and Todorov, 2006). This suggests that trustworthiness judgments rely on rapid and automatic processing streams, but does not establish this processing to be unconscious. On the other hand, for a range of basic visual features, as well as more complex inputs that are ecologically relevant, behaviorally relevant processing can occur outside of awareness (de Gelder et al., 2001).

Although there are different theories on the neural basis of visual awareness, they seem to agree that awareness involves recurrent activity within and between stages of the visual hierarchy (Dehaene and Naccache, 2001; Lamme and Roelfsema, 2000; Tononi, 2008). As a result, a conscious percept takes time to establish. For inputs that seem particularly relevant, additional processing time should not delay our initial behavioral or emotional responses. Such relevant information can guide our behavior before, or even fully without, the onset of awareness. Given the speed and ecological relevance of trustworthiness processing, can it, too, occur outside of awareness?

Recent studies addressed this question using continuous flash suppression (CFS). In CFS, a visual stimulus is presented to one eye and rendered unconscious by simultaneously presenting dynamic stimulation to the other eye (Tsuchiya and Koch, 2004). (Un)trustworthy faces took longer to “break through” CFS (i.e., become visible) compared to neutral faces (Getov et al., 2015; Stewart et al., 2012). Further evidence for unconscious processing of face trustworthiness comes from subliminal priming: subliminally presented (un)trustworthy faces biased the judgment of subsequent supraliminal neutral faces (Todorov et al., 2009). On a neural level, the amygdala shows response selectivity to both conscious (Santos et al., 2016) and unconscious (Freeman et al., 2014) face trustworthiness. In sum, both behavioral and neural studies suggest that face trustworthiness can be processed unconsciously.

The early visual cortex (EVC) is traditionally implicated in visual awareness (Ro et al., 2003). It has already been shown that emotion processing can occur without the involvement of EVC (Gainotti, 2012). Analogously, if processing of face trustworthiness can occur unconsciously, then it might not rely on EVC. One way to address this issue is to use transcranial magnetic stimulation (TMS) to disrupt EVC and thereby impair performance on visual tasks (for reviews see de Graaf et al., 2014; Kammer, 2007a, 2007b). That approach has successfully been used to investigate many visual functions, including letter identification (Amassian et al., 1989; Masur et al., 1993; Potts et al., 1998), number identification (Miller et al., 1996) and orientation discrimination (Beckers and Hömberg, 1991; Boyer et al., 2005; Kammer et al., 2005). In such TMS masking studies, TMS is delivered at several stimulus-onset asynchronies (SOAs). Visual task performance is most consistently impaired when TMS is delivered to EVC at around 70–130 ms SOA (de Graaf et al., 2014; Kammer, 2007a, 2007b).

Previous TMS masking studies have investigated the relevance of EVC for objective versus subjective processing. Subjective measures such as visibility ratings capture conscious visual perception, while objective measures such as forced-choice stimulus discrimination tasks might also capture unconscious visual processing (de Graaf et al., 2014). Several studies found TMS suppression of both objective and subjective processing of symbols and orientation stimuli (Jacobs et al., 2014; Jacobs et al., 2012; Koivisto, Railo, and Salminen-Vaparanta, 2011). Others reported that, when looking only at trials without conscious perception, visual task performance can remain above chance (Boyer et al., 2005; Koenig and Ro, 2018; Ro et al., 2004). One study reported that discrimination of schematic emotional expressions remained above chance after occipital TMS, even though participants were impaired in localizing the emotional expressions and reported not being aware of the stimuli (Jolij and Lamme, 2005). In other words, there was a dissociation between different objective visual tasks performed on the same schematic face stimuli, with emotion processing not being abolished by occipital TMS. Following similar logic, since trustworthiness judgments are highly ecologically relevant as well, we hypothesized that objective but not subjective processing of face trustworthiness may occur without the involvement of EVC.

To test this, we used double-pulse TMS at different SOAs to disrupt processing in right EVC. Participants performed three tasks in response to face stimuli. First, they performed a two-alternative forced-choice (2AFC) trustworthiness discrimination task, to capture “objective trustworthiness processing”. Then, they performed a 2AFC rotation discrimination (control) task, included to capture orientation processing and validate the neural efficacy of our TMS protocol (de Graaf and Sack, 2011, 2018). We furthermore implemented a subjective trustworthiness visibility rating task, to capture conscious trustworthiness perception, and to directly compare TMS effects on objective versus “subjective trustworthiness processing”. According to our hypothesis, TMS to right EVC should reduce subjective visibility of trustworthiness specifically in the left hemifield; but if objective trustworthiness processing can bypass EVC, then trustworthiness discrimination might remain intact.

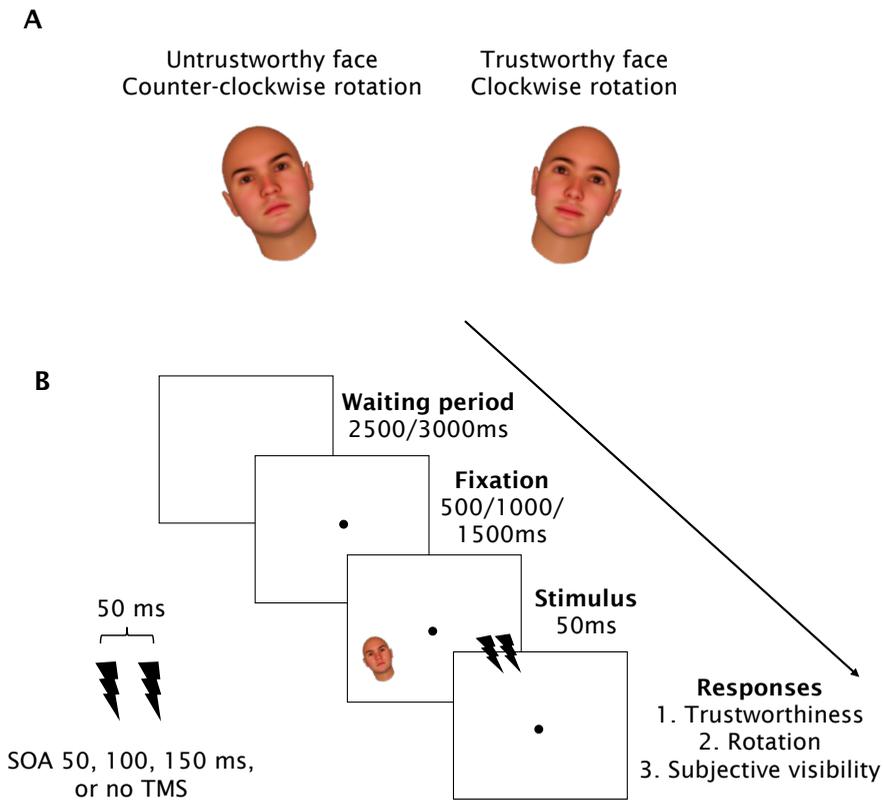
## 7.3 Methods

### Participants

Twenty volunteers participated in this experiment (9 males, ages 18–29). Participants were screened for transcranial magnetic stimulation (TMS) contraindications, provided written informed consent and had (corrected-to-)normal vision. The experiment was approved by the local ethical committee. Participants were compensated with either participation credits or 10 euros in vouchers per hour.

### Stimuli, Tasks, and Design

In one 2-hour session, participants performed several tasks in response to face stimuli (see Figure 7.1). We selected 25 male Caucasian faces from an existing database (Oosterhof and Todorov, 2008; Todorov et al., 2018). For each face, we used a version classified as untrustworthy (-3 SD from the average neutral face) and a version classified as trustworthy (+3 SD from the average neutral face) (Oosterhof and Todorov, 2008), leading to 50 different faces in total. We disrupted early visual cortex (EVC) of the right hemisphere with 20-Hertz double-pulse TMS at different stimulus-onset-asynchronies (SOAs). Trials without TMS served as a control condition (factor “TMS”: 50 ms, 100 ms, 150 ms, no TMS). Faces were presented in the left or right (control) hemifield (factor “Hemifield”), varying in trustworthiness and rotation (from the vertical meridian). To prevent floor and ceiling performance, face opacity and rotation angle were individually calibrated prior to the main task. Participants performed three tasks, capturing three visual processing mechanisms: 1) trustworthiness discrimination, 2) rotation discrimination, and 3) subjective rating of trustworthiness visibility.



**Figure 7.1: Stimuli and design.** **A) Example stimuli.** We presented faces which are either untrustworthy or trustworthy from a stimulus set created by Oosterhof and Todorov, 2008. The faces were rotated either clockwise or counterclockwise. **B) Experimental design.** In each trial, either no TMS was applied, or double-pulse TMS with an inter-pulse interval of 50 ms was applied at a stimulus-onset asynchrony (SOA) of 50 ms, 100 ms, or 150 ms (factor TMS). Faces were presented either to the lower left or right of fixation (factor Hemifield). After each stimulus, participants first indicated the trustworthiness of the stimulus (2AFC: trustworthy vs untrustworthy), then the rotation of the stimulus (2AFC: clockwise vs counterclockwise), and then the subjective visibility of the trustworthiness of the stimulus (4-point scale).

Trustworthiness discrimination was a 2AFC task (trustworthy vs untrustworthy). Rotation discrimination involved a two-alternative forced choice (2AFC) task, indicating by button press whether faces were rotated clockwise or counterclockwise from vertical. We hypothesized that performance could be impaired by TMS pulses around 100 ms, if this task relies on orientation processing (de Graaf, Cornelsen, et al., 2011; de Graaf et al., 2015; de Graaf, Herring, et al., 2011; de Graaf et al., 2014; Jacobs et al., 2014) (“neural efficacy check”; de Graaf and Sack, 2011, 2018). Note, however, that some previous studies

showed that orientation processing can survive TMS disruption of early visual cortex (Boyer et al., 2005; Koenig and Ro, 2018). Also, our current stimuli were larger and more complex than orientation stimuli typically used in previous studies investigating orientation processing. Subjective trustworthiness visibility ratings were given on a 4-point scale (1 (“not perceived”) to 4 (“clearly perceived”), with 2 and 3 parametrically in between). This scale was inspired by other 4-point subjective scales (e.g., perceptual awareness scale; Ramsøy and Overgaard, 2004), and was the same as in our previous studies (de Graaf, Cornelsen, et al., 2011; de Graaf et al., 2012; de Graaf, Herring, et al., 2011; Jacobs et al., 2014; Jacobs et al., 2012). Participants were explicitly instructed that subjective visibility ratings should reflect how well the trustworthiness was perceived, not the stimulus itself. Note that this scale does not actually measure whether participants perceived trustworthiness or untrustworthiness. Instead, this scale is explicitly meant to capture the extent to which, subjectively, the participants could consciously make out the trustworthiness of the face.

### TMS parameters

Biphasic TMS pulses were delivered to right EVC, using a MagPro R30 stimulator (MagVenture, Farum, Denmark) and a figure-of-eight coil (MC-B70). Stimulation intensity was 60% maximum stimulator output (MSO), unless this exceeded 200% of phosphene threshold (PT), in which case stimulation was at 200% PT (45% MSO, one case), or participants indicated discomfort in which case stimulation intensity was set to a tolerable level (five cases: 45% MSO (1), 50% MSO (2), 55% MSO (2)). PT was defined as the stimulation intensity at which phosphenes were reported in half of trials, in an informal procedure ( $M = 39\%$ , range = 23–47% MSO). We failed to record phosphene perception in four participants, we recorded that eight participants saw phosphenes, and eight participants did not see phosphenes. If phosphenes could not be elicited, the coil was positioned 2 cm above and to the right of theinion. If the participant perceived phosphenes overlapping with the left stimulus location, the coil was positioned on the phosphene hotspot; the location over right EVC with lowest PT. During the main task, coil position was fixed with lateral handle orientation using a mechanical arm. On each trial, double-pulse TMS with an inter-pulse interval of 50 ms was delivered at 50 ms, 100 ms, 150 ms, or not at all (no TMS) (see Figure 7.1b). Note that the different SOA conditions were connected: the second pulse for

one SOA was at the same time relative to visual stimulus onset as the first pulse of the next SOA condition. The waiting period between trials was either 2.5 or 3 sec. The total number of pulses (excluding PT determination) was 360. Note that, since we positioned the TMS coil over right EVC, if possible in a position that elicited phosphenes in left hemifield at the (later) stimulus location, we should specifically suppress processing of visual stimuli in the left hemifield, not the right hemifield (de Graaf et al., 2012; Railo and Koivisto, 2012; Tapia et al., 2014).

### Procedures

Stimuli were presented using MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) with Psychophysics Toolbox (Brainard, 1997) on a 24-inch monitor with a refresh rate of 60 Hertz. Faces were 4 degrees visual angle (DVA) high and were presented in the left or right hemifield, 3 DVA diagonally below central fixation, for 50 ms. A black fixation dot of 0.3 DVA was presented in the middle of a grey screen with a background luminance of  $156 \text{ cd/m}^2$ . Participants rested their heads in a chin rest, eyes 57 cm from screen, fixating continuously.

We calibrated task difficulty for both the rotation and trustworthiness task, using psychophysical staircases. We determined required face rotation (in degrees) for 80% discrimination accuracy. Quest (Watson and Pelli, 1983) was used with the following parameters:  $t_{\text{Guess}} = {}^{10}\log(4)$ ,  $t_{\text{SD}} = {}^{10}\log(10)$ ,  $\beta = 3.5$ ,  $\delta = 0.01$ ,  $\gamma = 0.5$ . In each trial, after 0.5, 1 or 1.5 sec fixation, a face appeared lower left of fixation. Participants reported as quickly and as accurately as possible the (counter-)clockwise rotation of the face. The task lasted 3 minutes and included 5 practice trials with feedback, and 50 main trials. We plotted rotation test values over trials: if staircases did not converge to a stable value they were repeated.

Another staircase determined required face opacity for 80% correct (un-)trustworthy discrimination. Staircase procedures and parameters were the same as above, but preceded by 10 practice trials in which stimuli were shown at full contrast for 500 ms. Quest here was provided with  $t_{\text{Guess}} ({}^{10}\log(125))$  and  $t_{\text{SD}} ({}^{10}\log(255))$ . In four participants, the task proved too difficult, and stimulus duration was increased to 67 ms throughout the experiment.

The “performance check” included 5 practice and 40 main trials, using rotation and opacity values resulting from the staircases. As in the main experiment, subjects provided three responses per stimulus: first they indicated the trustworthiness, then rotation of the face. Lastly, they rated subjective visibility of (how clearly they could perceive) the trustworthiness of the face on a four-point scale. As in the main experiment, response options and corresponding keys for rotation discrimination and subjective visibility ratings were prompted on screen on each trial. The performance check took 5 minutes, including one break. With now three required responses per trial, participants sometimes needed more practice. Therefore, if performance for either of the 2AFC tasks was close to floor (<55%) or ceiling level (>95%), the performance check was repeated.

The main experiment was described above (see Figure 7.1). With factors TMS (50 ms, 100 ms, 150 ms, no TMS) and target hemifield (left, right), 30 trials per condition cell randomized across 240 trials in total, preceded by 5 practice trials, offered 9 breaks at regular intervals, the task lasted 45 minutes.

## Analyses

Dependent variables for the 2AFC tasks were proportion correct, and average rating for the subjective trustworthiness visibility task. If participants performed too close to ceiling (>95%) or floor (<55%) in the no TMS control condition, they were excluded from the analyses for that task: three participants were excluded from the trustworthiness task and three from the rotation task (of those, one participant was excluded from both tasks). This was in accordance with our planned analysis approach; to evaluate TMS effects on each task separately. But, importantly, our conclusions did not change when all five outliers were excluded from all three tasks (see *Supplementary Materials I*).

In line with prior studies investigating the effect of TMS on objective versus subjective processing, our hypotheses pertain to each of the three tasks separately (de Graaf, Herring, et al., 2011; Jacobs et al., 2014; Koivisto, Railo, and Salminen-Vaparanta, 2011). The condition means of the three dependent variables were therefore compared with three separate two-way repeated measures ANOVAs with the factors “Hemifield” (left, right) and “TMS” (50ms, 100ms, 150ms, no TMS), in SPSS Version 24.0 (IBM Corp., Armonk, New York, United States).

Greenhouse-Geisser correction was applied. Significant interactions were followed by simple effects analyses. Since we targeted EVC in the right hemisphere, which processes stimuli in the left hemifield, we expected effects to occur specifically in the left hemifield. The right hemifield should not show any significant effect of “TMS” and therefore served as control condition (e.g., Amassian et al., 1989; Koivisto, Railo, Revonsuo, et al., 2011; Railo and Koivisto, 2012). Additionally, TMS SOA conditions were contrasted to no-TMS in Bonferroni-corrected one-sided planned comparisons, since we expected TMS to decrease performance as compared to baseline based on the TMS suppression literature (for reviews see de Graaf et al., 2014; Kammer, 2007a, 2007b). To provide more direct evidence for specific null or alternative hypotheses, we performed equivalent non-parametric Bayesian analyses (JASP software version 0.8.6.0, JASP Team, 2018). The Bayes factor (BF) contrasts the likelihood of the data fitting under the null hypothesis (H0) versus the alternative hypothesis (HA) (Wagenmakers, Love, et al., 2018; Wagenmakers, Marsman, et al., 2018). For “BF10”, values above 1 constitute anecdotal, above 3 moderate, and above 10 strong evidence for the HA (Wagenmakers, Love, et al., 2018; Wagenmakers, Marsman, et al., 2018). To evaluate the evidence for or against an interaction term, we included the main effects in the null model (Wagenmakers, Love, et al., 2018).

## 7.4 Results

In a TMS (50, 100, 150ms, no-TMS) by stimulus hemifield (left, right) within-subjects design, participants reported, on each trial, face trustworthiness (trustworthy vs untrustworthy), rotation (clockwise vs counter-clockwise), and subjective trustworthiness visibility (1-4 scale) (see sections 2.2 and 2.4). We report the results sequentially, in this same order, directly below.

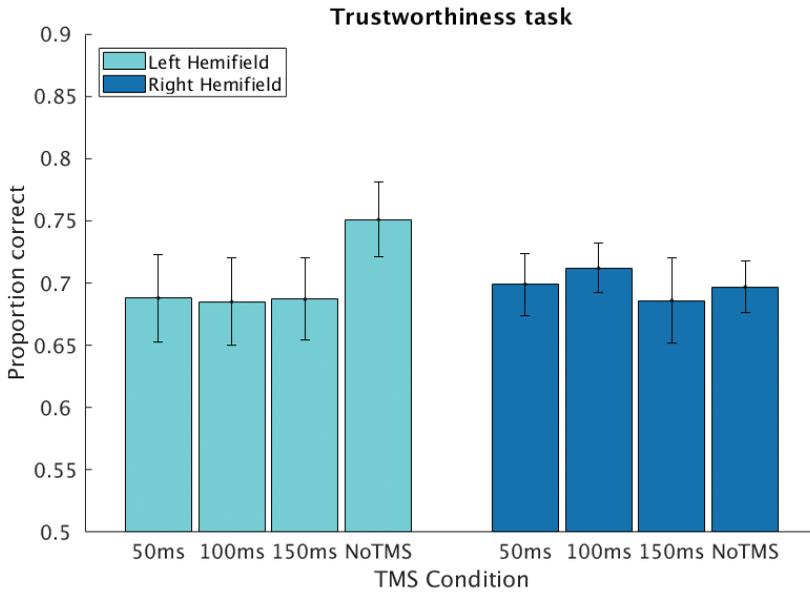
### Trustworthiness task

Figure 7.2 shows the mean proportions correct on trustworthiness judgments of faces (trustworthy vs untrustworthy) presented in left or right hemifield in different TMS conditions. A two-way repeated measures ANOVA showed no significant main or interaction effects (all  $p$ 's > 0.10). This suggests there is insufficient evidence to reject any of the null hypotheses. To investigate how much evidence there is for a specific null hypothesis, Bayesian statistics (i.e., the Inverse Bayes Factor;  $BF01$ ) can be used. A two-way Bayesian repeated measures ANOVA showed that the data are 3.49 times more likely under the  $H_0$  (i.e., no “Hemifield”  $\times$  “TMS” interaction effect exists) than the  $H_A$  (i.e., the interaction effect exists). This result gives moderate evidence for the *absence* of a “Hemifield”  $\times$  “TMS” interaction.

Despite this lack of an interaction, and evidence for absence of such interaction, we evaluated the support for a potential TMS effect on left hemifield targets for full transparency. A one-way repeated measures ANOVA did not reveal a significant effect of TMS SOA (uncorrected  $p = 0.09$ ). According to the Bayesian ANOVA equivalent, our data were equally likely ( $BF01 = 0.99$ ) under the  $H_0$  (i.e., no effect of TMS SOAs) and the  $H_A$  (i.e., a TMS effect). Thus, there was no evidence for an effect of TMS in the left hemifield.

Although not statistically significant, in Figure 7.2 it might seem as if TMS decreases performance in the left hemifield. However, this pattern appears to be driven exclusively by higher performance in the no-TMS control condition, rather than a potential suppressive effect of TMS. After all, as we elaborate in the sections below, TMS suppression effects are generally temporally specific, as we indeed observe for the rotation discrimination task and subjective visibility ratings (as shown in Figures 7.3 and 7.4). Altogether, these results do not convincingly support

the notion that trustworthiness discrimination in the left hemifield was impaired by TMS to right EVC. In other words, we cannot reject the null hypothesis that EVC is not necessary for objective (forced-choice) trustworthiness judgments.

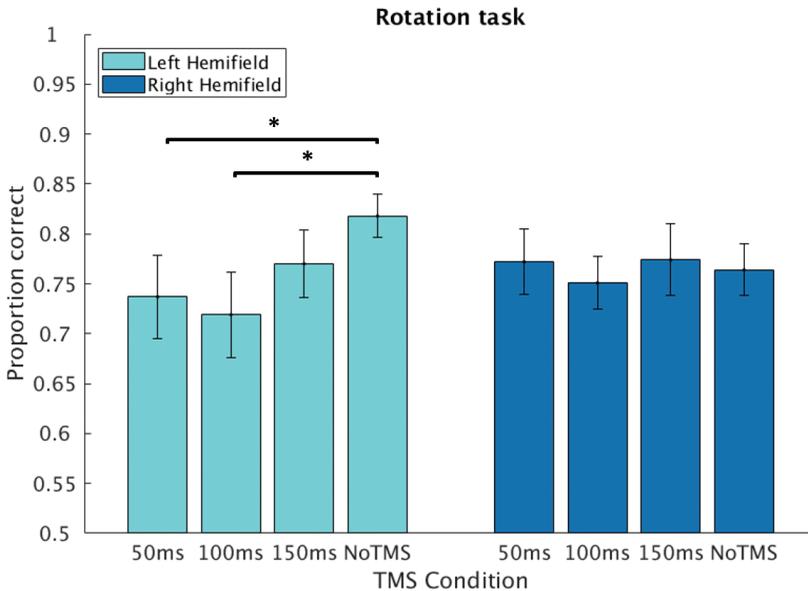


**Figure 7.2: Average trustworthiness discrimination accuracies.** Error bars are standard error of the mean (SEM).

### Rotation task

Figure 7.3 shows the mean proportions of correct trials over TMS conditions per hemifield. A two-way repeated measures ANOVA showed no significant effects (all  $p$ 's  $> 0.10$ ). However, since we expected an effect of TMS for the left hemifield, we performed a more direct test for this hypothesis. A one-way repeated measures ANOVA indeed showed a significant effect of "TMS" on accuracy only for the left hemifield ( $F(2.74,43.75) = 3.85$ ,  $p = .020$ ,  $\eta_p^2 = 0.19$ ). Rotation discrimination was impaired, as compared to no TMS ( $M = 0.82$ ,  $SD = 0.09$ ), by TMS at 50 ms ( $M = 0.74$ ,  $SD = 0.17$ ,  $t(16) = 2.53$ , one-tailed corrected  $p = 0.02$ ) and by TMS at 100 ms ( $M = 0.72$ ,  $SD = 0.18$ ,  $t(16) = 4.64$ , one-tailed corrected  $p = 0.02$ ), but not by TMS at 150 ms ( $M = 0.77$ ,  $SD = 0.82$ ,  $p > 0.10$ ).

We again supplemented our parametric analyses with Bayesian analyses, to investigate how likely the expected effects are given our data. Bayesian analysis provided moderate evidence against a “Hemifield”  $\times$  “TMS” interaction ( $BF_{10} = 0.22$ ), but provided moderate evidence for a left hemifield TMS effect ( $BF_{10} = 3.41$ ), and supported an impairment of rotation discrimination compared to no TMS at specifically early SOAs (50 ms:  $BF_{10} = 2.91$ , 100 ms:  $BF_{10} = 3.40$ , 150 ms:  $BF_{10} = 0.72$ ).



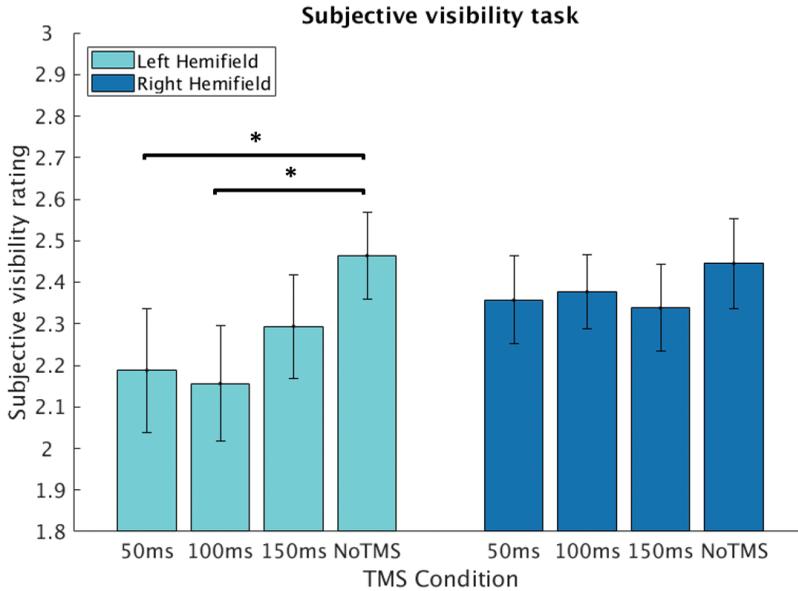
**Figure 7.3: Average accuracies for the rotation discrimination task.** Error bars are standard error of the mean (SEM). \* corrected  $p < 0.05$ .

Taken together, these results suggest that rotation discrimination performance is disrupted by TMS to right EVC. Though the statistical strength of this result is somewhat limited, the results follow precisely the hypothesized pattern of performance over SOAs, which is in accordance with a large body of previous research (the classical masking “dip”; see de Graaf et al., 2014; Kammer, 2007a, 2007b for reviews). This established temporal pattern stands in stark contrast to the results for the objective trustworthiness discrimination task where no such pattern can be discerned (compare Figures 7.3 and 7.4 to Figure 7.2). Overall, the rotation discrimination results suggest that our TMS protocol could impair forced-choice behavior in our subject sample.

### Subjective visibility task

Figure 7.4 shows mean subjective visibility ratings per hemifield and TMS condition. A two-way repeated measures ANOVA showed a significant “Hemifield”  $\times$  “TMS” interaction ( $F(2.07,39.35) = 3.59, p = .040, \eta_p^2 = 0.16$ ), suggesting that the effect of TMS differs between hemifields. Follow-up simple effects analyses showed a significant effect of “TMS” only for the left hemifield ( $F(1.46,27.64) = 6.16, p = .010, \eta_p^2 = 0.25$ ). Subjective visibility of trustworthiness was suppressed, as compared to no TMS ( $M = 2.46, SD = 0.10$ ), by TMS at 50 ms ( $M = 2.19, SD = 0.15, t(19) = 2.53, \text{one-tailed corrected } p = 0.03$ ) and 100 ms ( $M = 2.16, SD = 0.14, t(19) = 2.94, \text{one-tailed corrected } p = 0.01$ ), but not 150 ms ( $M = 2.29, SD = 0.56, p > 0.10$ ). These results are in line with our hypothesis that subjective trustworthiness processing is impaired after TMS to right EVC.

A two-way Bayesian repeated measures ANOVA could not reveal a reliable result for the “Hemifield”  $\times$  “TMS” interaction (due to a 11.13%-error of the BF estimate [ $BF10 = 0.51$ ]). However, Bayesian analysis provided strong support for an effect of TMS specifically for the left hemifield ( $BF10 = 29.10$ ). Follow-up analyses provided anecdotal evidence for a suppression effect after TMS at 50 ms ( $BF10 = 2.83$ ), moderate evidence for TMS at 100 ms ( $BF10 = 6.02$ ), and no evidence for TMS at 150 ms ( $BF10 = 0.87$ ). This is in agreement with the previously reported parametric test results. See *Supplementary Materials II* for a visualization and details on the proportions of subjective visibility ratings 1, 2, 3 and 4 across TMS conditions and hemifields. Overall, it appears that TMS primarily affected the proportions of trials with lower ratings, e.g. increasing the number of trials in which targets were reported as “not perceived” (subjective visibility rating 1).



**Figure 7.4:** Average subjective trustworthiness visibility ratings on a scale from 1 (“not perceived”) to 4 (“clearly perceived”), with 2 and 3 parametrically in between. Error bars are standard error of the mean (SEM). \* corrected  $p < 0.05$ .

Altogether, these results show that there was a significant “Hemifield”  $\times$  “TMS” interaction, due to TMS suppression of specifically left hemifield targets. Moreover, as in the rotation discrimination results (Figure 7.3), and in contrast to the trustworthiness discrimination results (Figure 7.2), the pattern of visibility ratings over SOA conditions followed the hypothesized TMS suppression pattern (Figure 7.4). Subjective visibility ratings were suppressed in the 50 and 100 ms conditions as compared to the no TMS condition. These results suggest that subjective (conscious) perception of trustworthiness relies on intact EVC at the hypothesized SOAs.

## 7.5 Discussion

We investigated whether objective trustworthiness discrimination, face rotation discrimination, and subjective trustworthiness visibility ratings require a functioning early visual cortex (EVC). We disrupted right EVC with double-pulse TMS at different SOAs. There was no evidence for an impairment of forced-choice trustworthiness discrimination. Yet, at specifically early SOAs (50 and 100 ms), TMS to EVC impaired rotation discrimination and decreased subjective trustworthiness visibility ratings in the left hemifield. These results are in line with the hypothesis that EVC is necessary for subjective perception of face trustworthiness, but do not support a role for EVC involvement in objective processing of face trustworthiness.

These results are in agreement with previous studies showing that objective trustworthiness can occur outside of awareness (Getov et al., 2015; Stewart et al., 2012; Todorov et al., 2009). This suggests that the underlying neural processes can act on our behavior, assessing the trustworthiness of others, without us being aware of it. Although counter-intuitive, such automatic processes have also been shown for other types of information (see below). While conscious processing allows reflection and flexibility, for ecologically relevant information quick and automatic processes may be at least as important. Interestingly, the intrinsically social process of trustworthiness evaluation might fall in this category, further highlighting its ecological relevance.

This line of reasoning converges with several previous reports. For instance, in 7-month-old infants, differences in event-related potentials (ERPs) elicited by unconscious (un)trustworthy faces were found for central and frontal but not occipital electrodes (Jessen and Grossmann, 2017). Moreover, the amygdala and insula but not the EVC were differentially activated by (un)trustworthy faces during an implicit trustworthiness discrimination task (Winston et al., 2002). Furthermore, unconscious trustworthiness evaluation affected amygdala activity but did not affect activity in fusiform areas (Freeman et al., 2014). This resembles the mechanisms assumed to underlie unconscious emotion processing, where several studies suggest that strong emotional signals such as facial expressions can influence amygdala activation via a subcortical route in the absence of conscious awareness (Celeghin et al., 2015; Tamietto and de Gelder, 2010). In emotional

expressions, single features such as wide eyes are sufficient to elicit emotion-related differences in neural activation (Whalen et al., 2004). Crucially, though, face trustworthiness is characterized by more complex feature arrangement (Todorov et al., 2015). Hence, the question arises to what degree subcortical mechanisms are sufficient to evaluate the complex feature arrangements necessary to differentiate face trustworthiness.

The debate about whether the neural pathway underlying unconscious face trustworthiness processing is entirely sub-cortical, is ongoing. In prior work, two higher order visual areas, namely the superior temporal sulcus (STS) and the fusiform gyrus, were differentially activated by unconscious (un)trustworthy faces (Winston et al., 2002). However, the STS contrast was mostly seen during an explicit task, and the fusiform gyrus contrast might be explained by modulatory feedback responses from the amygdala (Morris et al., 1998). There is some indirect evidence against a solely sub-cortical route. While sub-cortical emotion processing is assumed to involve predominantly low spatial frequencies, i.e. coarse information (Vuilleumier et al., 2003), amygdala activation was modulated by face trustworthiness for both images containing only low and images containing only high spatial frequencies (Said et al., 2009). Future studies are necessary to elucidate this issue.

Faces seem to be processed differently between the two cerebral hemispheres. Previous studies have established the right hemispheric dominance for face perception in general (Gainotti and Marra, 2011; Heering and Rossion, 2015; Pitcher et al., 2007; Rangarajan et al., 2014; Rossion et al., 2012; Van Belle et al., 2011). More specifically, some evidence suggests that especially the right hemisphere is involved in the processing of emotional expressions (Demaree et al., 2005) and face trustworthiness (Dzhelyova et al., 2012; Okubo et al., 2013). In line with this strong right-lateralization of face processing, we targeted only the right EVC. However, the right hemisphere is not exclusively involved in this type of processing. There is some evidence suggesting that the left vs right hemispheres are preferentially processing positive and negative emotions, respectively (Okubo et al., 2017). Moreover, faces presented in the right visual field (and thus processed by the left hemisphere) were rated as more trustworthy compared to faces presented in the left visual field (Slepian et al., 2017). It thus remains unclear what is the exact role of the left EVC in the processing of face trustworthiness.

Although our analyses did not support a TMS effect on objective trustworthiness processing, one might have the impression (see Figure 7.2) that performance in no-TMS trials in the left hemifield differed from performance in the three TMS conditions (the three SOAs). This pattern might be interpreted as a general, temporally unspecific, decrease in performance after TMS. While we cannot exclude this possibility, aside from the lack of statistical support in our view this seems unlikely; given that TMS masking effects generally display a particular temporal pattern with a maximal suppression effect around 100 ms (“the classical dip”; original finding by Amassian et al., 1989, for reviews see de Graaf et al., 2014; Kammer, 2007a, 2007b). And indeed, specifically in the left hemifield, task performance in the rotation discrimination and subjective visibility tasks precisely matched this hypothesized temporal pattern over SOAs (see Figures 7.3 and 7.4). There is some evidence suggesting that EVC may be functionally relevant for face processing for a longer period of time. We previously observed delayed or prolonged TMS suppression of face stimuli (de Graaf et al., 2012), though not with SOAs as late as 150-200 ms. There are reports of TMS masking at later (> 150ms) SOAs for more complex tasks such as categorization of natural scenes (Camprodon et al., 2009; Koivisto, Railo, Revonsuo, et al., 2011), figure-ground segregation (Heinen et al., 2005), and complex visual search (Dugué et al., 2011; Juan and Walsh, 2003). Still, a temporally unspecific TMS masking effect seems to us unlikely.

So alternatively, perhaps performance in the no-TMS trials was slightly enhanced. We have previously discussed the possible complications of no-TMS trials in randomized event-related experimental TMS designs. Since the majority of trials includes TMS pulses, the unexpected omission of pulses can be surprising, with varying consequences on performance (de Graaf, Cornelsen, et al., 2011; de Graaf and Sack, 2011; Duecker and Sack, 2013). This might have caused response biases which we cannot address given that we did not use a signal detection paradigm (Stanislaw and Todorov, 1999). For instance, we cannot exclude the possibility that the presence/absence of TMS pulses might have caused participants to indicate lower/higher subjective trustworthiness visibility, because they might believe that something should happen. Although, note that participants were naïve to the hypotheses of our experiment. In addition, the SOA conditions were probably not distinguishable and thus the classical TMS pattern with the dips at early SOAs is not easily explained by this sort of response bias. This, the lack of

statistical support for TMS effects, and the fact that there was no difference in performance across the three TMS SOAs, leads us to the interpretation that trustworthiness judgments were unimpaired by TMS in our experiment.

Since this was the first attempt to disrupt processing of face trustworthiness using TMS, we did not design the experiment to achieve high temporal resolution chronometry. Rather, we included several SOAs, covering the full extent of the classical TMS masking window, to ensure we did not miss the relevant processing window (de Graaf et al., 2014) as has been reported previously (e.g. Boyer et al., 2005). We used double-pulse TMS because of its strong impact on EVC (although the difference with single pulse TMS is small (Gerwig et al., 2005; Kammer and Baumann, 2010; Ray et al., 1998). The results do suggest that our SOAs were sufficiently separated to find temporally specific masking effects, since we found suppression by TMS only at early (50 and 100 ms) SOAs. But, also due to the implementation of connecting SOAs (see Figure 7.1b), temporal resolution was limited and we refrain from interpretations about when exactly EVC is crucially involved in subjective processing of face trustworthiness. Future studies might replicate and extend the current findings with higher temporal specificity and a broader range of SOAs.

Another limitation of the current report involves the unusually large size of our visual stimuli. Often in occipital TMS suppression studies, stimuli are small so as to fully suppress their perception with TMS pulses. However, our goal here was not to make the stimuli invisible, but to disrupt specific aspects of their processing, including rotation judgments and the subjective visibility of trustworthiness (as opposed to visibility of the face itself). The magnitudes of effect here do not deviate strongly from those reported in some previous work. We designed this project with the explicit *a priori* determined approach of evaluating separately the potential TMS effects on rotation judgment, 2AFC trustworthiness judgment, and subjective visibility of trustworthiness. To our knowledge, this was the first such TMS study in trustworthiness processing, and a meaningful first step. Results are in line with the hypothesis that objective trustworthiness processing does not require EVC, while subjective (conscious) trustworthiness perception does. But the analyses did not directly assess whether trustworthiness discrimination can take place in the absence of conscious perception (i.e. a direct test for unconscious processing). This requires a different design and analysis approach. Future studies

could evaluate such blindsight-like performance for trustworthiness information directly, by asking per trial whether trustworthiness was perceived and evaluating 2AFC judgments on specifically unseen trials (Boyer et al., 2005; Christensen et al., 2008; Jacobs et al., 2012; Jolij and Lamme, 2005; Koenig and Ro, 2018; Ro et al., 2004).

In TMS masking studies, subjective visibility ratings are generally reported after performing an objective task (de Graaf, Cornelsen, et al., 2011; Jacobs et al., 2014; Koivisto, Railo, Revonsuo, et al., 2011). Jolij and Lamme, 2005 asked participants to first as quickly as possible discriminate the emotional expressions, followed by the localization task response without time pressure. Also in the current study, task order was not counterbalanced between trials. If there is unconscious processing to be captured by our 2AFC task, it seems plausible that responses should be given quickly and instinctively (reflexive), in case the neuronal representation is fleeting. This seems less relevant for subjective visibility ratings which can be more deliberate (reflective). By this logic, we cannot rule out that the current suppression effects on stimulus rotation judgment were (partly) attributable to task order, though we repeatedly observed similar suppression effects on 2AFC orientation judgments in the past even if the orientation judgment was the first required response (de Graaf, Cornelsen, et al., 2011; de Graaf et al., 2015; de Graaf, Herring, et al., 2011; Jacobs et al., 2014; Koivisto, Railo, Revonsuo, et al., 2011). Although note that others have indeed reported above-chance orientation discrimination performance in the absence of conscious (subjective) perception (Boyer et al., 2005; Koenig and Ro, 2018), so this certainly does not mean that unconscious orientation processing is not possible. In any case, none of this affects the more poignant dissociation between the subjective and objective trustworthiness tasks.

Possibly, different tasks are differentially susceptible to disruption by TMS. This is often difficult to evaluate in TMS studies and we cannot exclude the possibility here. In this study, we did not only compare TMS effects on a subjective task with effects on an objective task (e.g. de Graaf, Herring, et al., 2011; Jacobs et al., 2014; Koenig and Ro, 2018), but also included an additional objective task (e.g. Jolij and Lamme, 2005). Moreover, we calibrated baseline performance in the two objective tasks with staircase procedures. Yet, one task was affected (rotation discrimination) and the other was not (trustworthiness discrimination). Moreover, we do not seem to find any time-specific effect on performance in the objective

trustworthiness task, while we previously found suppression of both subjective and objective task performance across many intensities (de Graaf, Cornelsen, et al., 2011; de Graaf et al., 2012; Jacobs et al., 2014).

Finding no TMS suppression of trustworthiness judgment is a null result. Generally, null results in TMS are difficult to interpret (de Graaf and Sack, 2018), since the complex combination of TMS stimulation parameters and stimulus characteristics determines whether effects are detected or not. Perhaps different or individualized cortical targeting, stimulation intensity, or face stimulus duration procedures would impair trustworthiness judgment after all. We recently presented a taxonomy for null result interpretation, with guidelines on design and interpretation (de Graaf and Sack, 2018). In the current study, we included a “neural efficacy check” (rotation discrimination task effects) and Bayesian support for the null finding (Wagenmakers, Love, et al., 2018; Wagenmakers, Marsman, et al., 2018). This makes the collection of results on the rotation task, subjective visibility, and forced-choice trustworthiness judgments, of interest. The positive support for a role of EVC in rotation and conscious trustworthiness processing, and negative result for forced-choice trustworthiness processing, were all in line with the hypothesis and prior research.

## 7.6 Conclusion

TMS is ideally suitable to investigate whether and when specific cortical areas are necessary for certain processes (Pascual-Leone et al., 2000). We extend the existing literature by showing that subjective processing (conscious perception) of face trustworthiness can be, but objective (forced-choice) trustworthiness processing may not be, disrupted by TMS to EVC. It remains to be investigated whether true “blindsight-like” performance (i.e., above-chance trustworthiness discrimination after completely abolishing conscious perception of face trustworthiness) can be achieved. We here evaluated the functional relevance of EVC for objective versus subjective trustworthiness processing separately. Our results regarding the EVC, the lowest level in the cortical visual hierarchy, pave the way for a more in-depth exploration of the underlying neural pathways. A fruitful next step would be to investigate the relevance of higher order cortical visual areas such as the STS for the processing of face trustworthiness. Moreover, it would be highly interesting to

study which subcortical areas are involved. Although it is not possible to directly stimulate subcortical regions with TMS, they could be indirectly stimulated via cortical areas (Wagner et al., 2009; Wang et al., 2014). Lastly, TMS could be used in combination with neuroimaging methods such as fMRI and EEG, to visualize the entire network underlying processing of face trustworthiness.

## 7.7 Supplementary Materials I: Excluding outliers on all tasks

Outliers were excluded per task, since we performed separate statistical analyses for each of the three tasks. Here we assess whether excluding five outliers on all tasks alters our conclusions. For the trustworthiness task, the evidence in favor of our hypothesis (i.e., no “TMS”  $\times$  “Hemifield” interaction and, more specifically, no effect of “TMS” in the left hemifield) has become slightly stronger. The statistical strength of the effects on the rotation task is decreased slightly. The same was true for the results on the subjective visibility task. The exact statistical values are reported below. Crucially, though, none of the main conclusions were altered by excluding five participants from all tasks instead of excluding participants per task.

### Trustworthiness task

A two-way repeated measures ANOVA showed no significant main or interaction effects (all  $p$ 's  $> 0.10$ ). A two-way Bayesian repeated measures ANOVA showed that the data are 5.98 times more likely under the H0 (i.e., no “TMS”  $\times$  “Hemifield” interaction effect exists) than the HA (i.e., the interaction effect exists). A one-way repeated measures ANOVA revealed no significant effect of “TMS” for the left hemifield (uncorrected  $p = 0.13$ ). According to the Bayesian ANOVA equivalent, our data were slightly more likely ( $BF_{01} = 1.44$ ) under the H0 (i.e., no effect of “TMS”) compared to the HA (i.e., a “TMS” effect). In sum, the results after excluding three participants (Figure 7.2) versus five participants (Figure 7.5) are highly similar.

### Rotation task

A two-way repeated measures ANOVA showed a trending “Hemifield”  $\times$  “TMS” interaction ( $F(2.52,35.31) = 2.72$ ,  $p = .070$ ,  $\eta_p^2 = 0.16$ ). A one-way repeated measures ANOVA univariate follow-up test showed a significant effect of “TMS” on accuracy only for the left hemifield ( $F(2.73,38.24) = 4.12$ ,  $p = .030$ ,  $\eta_p^2 = 0.23$ ). Rotation discrimination was impaired, as compared to no TMS ( $M = 0.81$ ,  $SD = 0.09$ ), by TMS at 50 ms ( $M = 0.73$ ,  $SD = 0.18$ ,  $t(14) = 2.49$ , one-tailed corrected  $p = 0.04$ ) and by TMS at 100 ms ( $M = 0.70$ ,  $SD = 0.18$ ,  $t(14) = 2.73$ , one-tailed corrected  $p = 0.02$ ), but not by TMS at 150 ms ( $M = 0.77$ ,  $SD = 0.15$ ,  $p > 0.10$ ). Bayesian analysis provided anecdotal evidence against a “Hemifield”  $\times$  “TMS”

interaction ( $BF10 = 0.63$ ), but provided moderate evidence for a left hemifield TMS effect ( $BF10 = 4.22$ ), and supported an impairment of rotation discrimination compared to no TMS at specifically early SOAs (50 ms:  $BF10 = 2.70$ , 100 ms:  $BF10 = 3.73$ , 150 ms:  $BF10 = 0.57$ ). Thus, our conclusions did not change after excluding five participants (see Figure 7.6) as compared to three participants (see Figure 7.3).

### Subjective visibility task

A two-way repeated measures ANOVA showed a significant “Hemifield”  $\times$  “TMS” interaction ( $F(1.85,25.89) = 3.58$ ,  $p = .050$ ,  $\eta_p^2 = 0.20$ ), indicating that the effect of “TMS” differs between hemifields. Follow-up simple effects analyses showed a significant effect of “TMS” only for the left hemifield ( $F(1.40,19.57) = 4.69$ ,  $p = .030$ ,  $\eta_p^2 = 0.25$ ). Subjective visibility of trustworthiness was suppressed, as compared to no TMS ( $M = 2.52$ ,  $SD = 0.49$ ), by TMS at 50 ms ( $M = 2.21$ ,  $SD = 0.72$ ,  $t(14) = 2.26$ , one-tailed corrected  $p = 0.06$ ) and 100 ms ( $M = 2.20$ ,  $SD = 0.68$ ,  $t(14) = 2.94$ , one-tailed corrected  $p = 0.04$ ), but not 150 ms ( $M = 2.37$ ,  $SD = 0.49$ ,  $p > 0.10$ ). A two-way Bayesian repeated measures ANOVA provided anecdotal evidence against a “Hemifield”  $\times$  “TMS” interaction ( $BF10 = 0.44$ , but note that 11.13 %-error of this BF estimate was rather high, limiting its interpretability). Furthermore, Bayesian analysis provided moderate support for an effect of TMS specifically for the left hemifield ( $BF10 = 6.75$ ). Follow-up analyses provided anecdotal evidence for a suppression effect after TMS at 50 ms ( $BF10 = 1.86$  and 100 ms ( $BF10 = 2.45$ ), but no evidence for TMS at 150 ms ( $BF10 = 0.53$ ). In sum, our conclusions did not change after excluding five participants (see Figure 7.7) as compared to excluding no participants (see Figure 7.4).

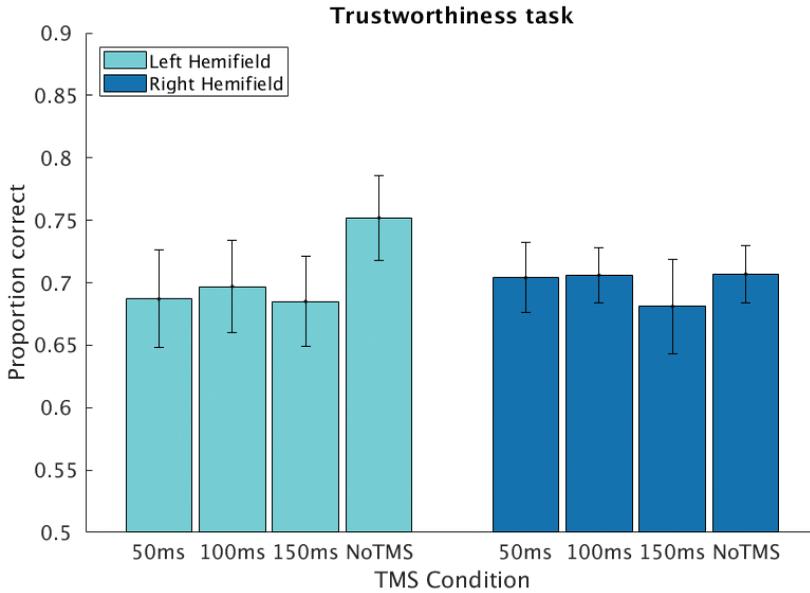


Figure 7.5: Average trustworthiness discrimination accuracies after excluding five participants. Error bars are standard error of the mean (SEM).

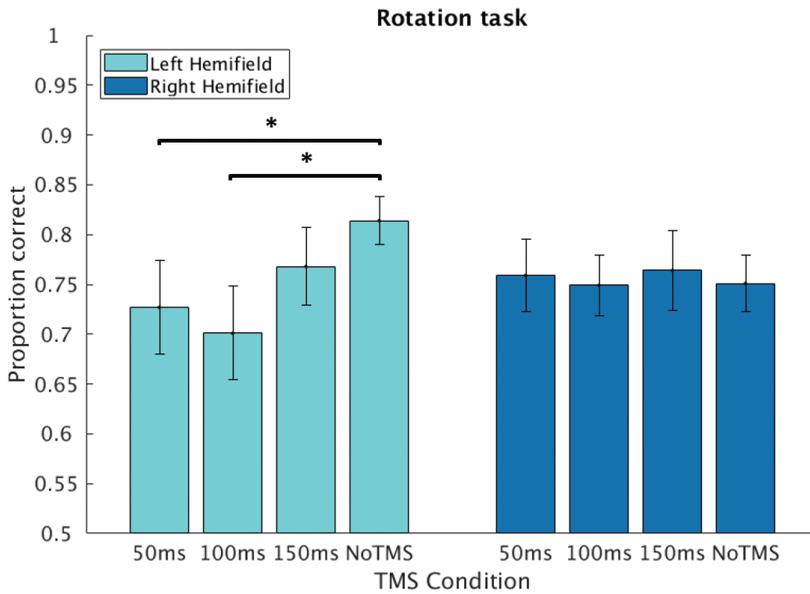
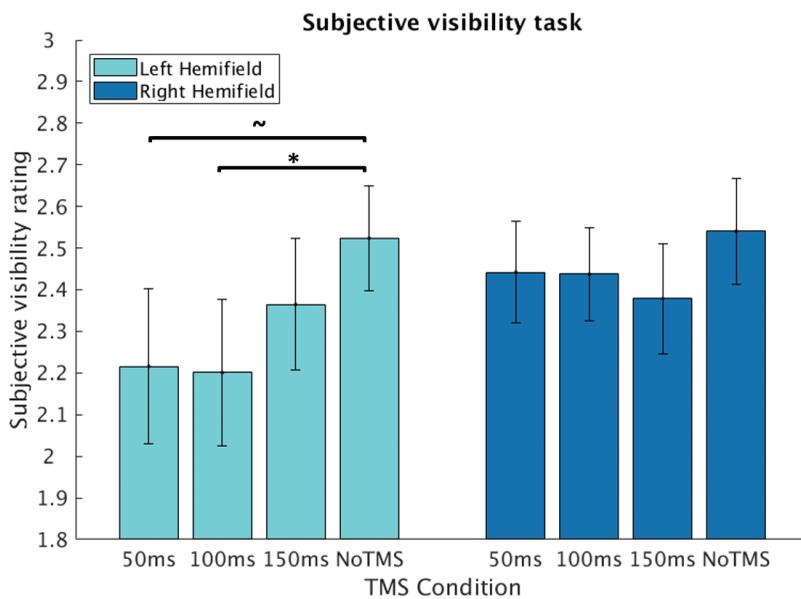


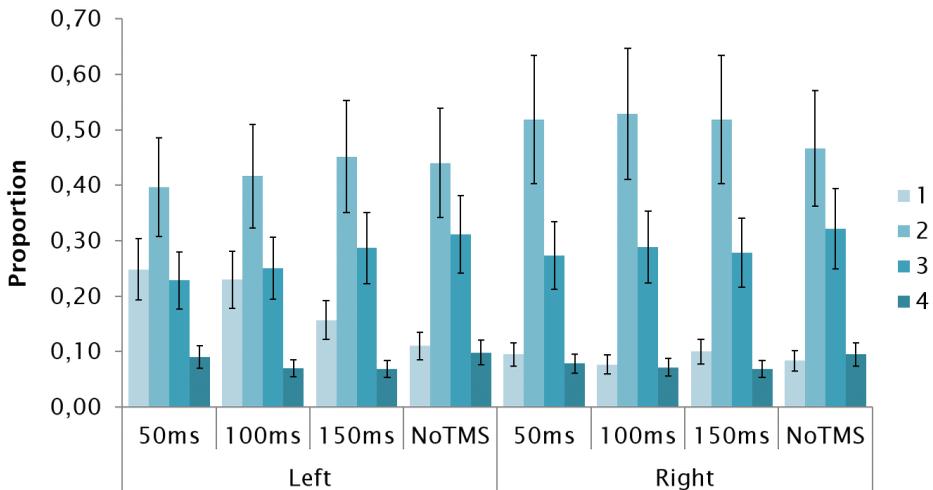
Figure 7.6: Average accuracies for the rotation discrimination task after excluding five participants. Error bars are standard error of the mean (SEM). \* corrected  $p < 0.05$ .



**Figure 7.7:** Average subjective trustworthiness visibility ratings on a scale from 1 (“not perceived”) to 4 (“clearly perceived”), with 2 and 3 parametrically in between. Five participants were excluded. Error bars are standard error of the mean (SEM). \* corrected  $p < 0.05$ , corrected  $p = 0.06$ .

## 7.8 Supplementary Materials II: Proportion of subjective ratings

We found decreased subjective trustworthiness visibility ratings in the left hemifield after TMS at 50 ms and 100 ms (see “Subjective visibility task” under “Results”). The question arises where this suppressive effect of TMS is coming from: does TMS only influence trustworthiness visibility in the higher part of the scale, having an effect on the clarity of perception? Or does TMS also have an effect in the lower part of the scale, increasing the number of trials in which trustworthiness is not perceived at all? To investigate how TMS affected subjective trustworthiness visibility, we calculated the proportion of trials in each level of the 4-point scale as a function of TMS and hemifield. Inspection of Figure 7.8 shows that the proportion of trials in which participants indicated not having perceived the trustworthiness at all (visibility rating 1) seems to be increased specifically for the left hemifield 50 ms and 100 ms conditions. However, no significant differences in proportions were found across conditions when comparing them in a 4 (visibility rating)  $\times$  4 (TMS)  $\times$  2 (hemifield) repeated-measures ANOVA (all  $p$ 's  $>$  0.10).



**Figure 7.8: Proportion of trials in each level of the 4-point subjective trustworthiness visibility scale, separately per TMS condition and hemifield.** For each condition, the leftmost bar indicates the proportion of trials with subjective visibility rating 1 (trustworthiness “not perceived”) and the rightmost bar indicates the proportion of trials with subjective visibility rating 4 (trustworthiness “clearly perceived”), with rating 2 and 3 in between. Error bars are standard error of the mean (SEM).

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The background of the page is a watercolor wash in various shades of blue, ranging from light sky blue to deep, dark navy blue. The wash is applied in a way that creates soft, blended edges and some darker, more saturated areas, giving it a textured, artistic appearance. The text is centered in the upper half of the page.

*Chapter 8*

**General Discussion**

Visual perception and attention rely on information exchange between higher-order frontoparietal areas and lower-level visual areas. The main goals of this thesis were to 1) investigate how signals propagate within this vision-attention network, 2) explore how neuronal alpha oscillations may be involved in visuospatial attention, and 3) evaluate the causal relevance of the early visual cortex (EVC) for the perception of evolutionarily relevant visual stimuli. The work outlined in this thesis presents a multimodal approach, since multiple (combinations of) neuroscientific methods were used to tackle these issues from various angles. Below, I will first provide an overview of the findings from the separate parts of this thesis. I will then dive into the recurring themes of this thesis to better understand them in the context of the existing non-invasive brain stimulation (NIBS) and cognitive neuroscience literature.

## 8.1 Part I: Signal propagation in the vision-attention network

Neuroscientific research into brain networks is popular – not only in the fundamental domain (Betzler and Bassett, 2017; Lynn and Bassett, 2019; Zabelina and Andrews-Hanna, 2016), but also in the clinical domain (Blanken et al., 2021; Fornito et al., 2015; Wen et al., 2011). Changes in network interactions can be related to changes in task performance and consequently be linked to specific cognitive processes (Bressler and Menon, 2010; Park and Friston, 2013). More severe or permanent alterations in network interactions can be linked to complex disorders such as depression and schizophrenia (Mulders et al., 2015; Sheffield and Barch, 2016). As mentioned above, the work presented in this thesis focuses on interactions within the vision-attention network. In **Chapter 1**, we discussed neuroimaging studies that seemed to suggest that frontoparietal areas exert control over lower-level visual areas during spatial attention, to subsequently improve visual perception at the currently relevant (i.e., attended) location (Bressler et al., 2008; Lauritzen et al., 2009; Mayrhofer et al., 2019). However, the evidence provided in these studies is merely correlational, since neuroimaging methods were used to measure network interactions and relate them to behavior, cognition, and dysfunction.

This begs the question: how can we disentangle those functional connections that are crucial for a certain process from those that are merely correlated with that process? The causal relevance of network interactions can be established by experimentally manipulating them, and by subsequently observing whether the

process of interest is affected. The first part of this thesis explored how top-down interactions in the vision-attention network can be experimentally manipulated to establish their causal relevance for cognition. For this, we made use of a novel behavioral paradigm and a non-invasive brain stimulation (NIBS) method. In **Chapter 2**, we developed an “attention adaptation” paradigm with the aim of isolating the top-down neuronal pathways underlying attention shifts to specific locations in visual space. In **Chapters 3 and 4**, we outline how transcranial magnetic stimulation (TMS) may be used to study causal interactions between brain areas, especially when combined with functional magnetic resonance imaging (fMRI) and electroencephalography (EEG).

The “attention adaptation” paradigm builds upon the concept of neuronal adaptation (**Chapter 2**). Neurons can adapt after prolonged exposure to a stimulus that drives them, by lowering their baseline firing rates (Engel, 2005; Kohn, 2007; Webster, 2011, 2012). This change in neuronal activity can cause perceptual and behavioral effects (Clifford et al., 2007). For instance, after observing a leftward moving stimulus for an extended duration, we tend to perceive a still image as moving in the opposite (rightward) direction, and we become worse at detecting the adapted (leftward) motion direction (Cattaneo and Silvanto, 2008). This process makes sense from an evolutionary perspective, since our brains can conserve energy by not constantly reacting to stimuli that stay the same (and are therefore likely irrelevant), but rather responding to stimuli that suddenly change or appear (and may therefore be harmful or relevant in another way).

In theory, it should be possible to over-stimulate and consequently adapt the frontoparietal neurons responsible for voluntary attention shifts. The adaptation effect within those frontoparietal neurons may then also extend to interconnected downstream visual neurons. In other words, if there is less top-down input from frontoparietal areas, visual areas may also show decreased baseline firing rates. If this neuronal adaptation effect would be sufficiently strong, then this should also be detectable in a behavioral task that requires the adapted neurons. Across three behavioral experiments, we could not reveal consistent adaptation effects. These inconsistent findings will be further discussed below, in the context of the limited consistency of cognitive neuroscience data in general.

It is important to mention that the absence of a consistent behavioral attention adaptation effect does not prove the absence of an underlying neuronal attention

adaptation effect. It is possible that our experimental (Posner) task was insufficiently sensitive to detect a weak behavioral effect. On the other hand, our adaptation manipulation may have caused a neuronal adaptation effect that was simply too weak to impact behavioral performance. Currently, we can only conclude that we have not (yet) been able to provide evidence for the efficacy of our paradigm. It could still be worthwhile to further pursue this paradigm. A potentially interesting application would be to combine the “attention adaptation” paradigm with TMS. In essence, neuronal adaptation suppresses a select group of neurons. This manipulation of their state makes these neurons more susceptible to external stimulation by TMS. In other words, TMS can reactivate the adapted neuronal population beyond their original (baseline) activation state, and subsequently cause improvements in behavioral performance (Silvanto and Cattaneo, 2017; Silvanto et al., 2007; Silvanto et al., 2008). Perhaps, a “TMS attention adaptation” paradigm could be used to reactivate specific top-down pathways to improve attention task performance at certain locations in space.

Despite its widespread use in both research and clinical settings, TMS effects are not always consistent (see the section on inconsistent conclusions in the cognitive neuroscience literature below). Evidence suggests that the flow of information through the brain can be “gated” or directed by synchronized neuronal oscillations, especially in the 7 – 13 Hertz alpha band (Salinas and Sejnowski, 2001). It was recently shown that TMS pulses applied to the premotor area propagated differently throughout an interconnected cortico-subcortical motor network, depending on pre-TMS alpha power (Peters et al., 2020). In other words, signal propagation depended on the momentary oscillatory state at the time of TMS. Furthermore, TMS signal propagation may depend on what the participant is doing (“neurocognitive state”) (Blankenburg et al., 2010; Heinen et al., 2014; Leitão et al., 2013; Ruff et al., 2008). In **Chapter 4**, we combined these different research lines for the first time. Using the innovative simultaneous TMS-EEG-fMRI paradigm, we evaluated whether TMS signal propagation from the right posterior parietal cortex to other brain areas depended on the oscillatory (alpha power) and/or neurocognitive (eye closure) state at the time of TMS.

We found fMRI activations in sensorimotor areas for high- compared to low-intensity TMS, which are likely due to the non-specific (i.e., auditory and somatosensory) side effects of TMS (Jung et al., 2016; Leitão et al., 2017; Leitão

et al., 2013; Ruff et al., 2006). Unfortunately, we did not obtain the key hypothesized finding of brain state-dependent TMS-induced signal propagation. This could be due to several reasons. We performed group analyses on a limited set of data in 8 participants due to the challenges associated with the simultaneous TMS-EEG-fMRI set-up (e.g., participant discomfort, long preparation time, and technical difficulties). It is possible that brain state-dependent signals were simply too subtle to be detected with our experimental set-up, design, and/or analyses. There is generally a tradeoff between statistical power within individual subjects and statistical power in group-based analyses. Perhaps, brain-state dependent effects are easier to detect in single subjects with larger amounts of data (as in Peters et al., 2020). But even when collecting a large amount of data in a single participant, the fMRI correlates of a real (neural) TMS effect can be difficult to detect (de Graaf et al., 2018). It is furthermore possible that the detection of brain state-dependent TMS effects in cognitive networks requires some sort of visual/other input. In the future, it should be explored whether brain state-dependent TMS effects can be obtained in the vision-attention (or other cognitive) networks with our experimental set-up, by acquiring a larger amount of data in a few participants and by including a visual (or other cognitive) task.

Interestingly, we did find differential fMRI activations for eyes open compared to eyes closed resting state in response to TMS pulses irrespective of their stimulation intensity. We found increases for eyes open resting state in the supplementary motor area, thalamus, right frontal eye fields, and left inferior parietal lobe, and decreases for several visual cortex clusters. These brain areas may respond to the non-specific effects of TMS (e.g., auditory stimulation, somatosensory stimulation, or expectancy effects associated with upcoming TMS pulses) in a neurocognitive state-dependent manner. The fMRI activations that we found were in line with prior studies revealing a dominant “exteroceptive” versus “interoceptive” brain network during eyes open compared to eyes closed resting state, respectively (Marx et al., 2003; Wei et al., 2018; Xu et al., 2014). Our findings also make sense in light of the fact that eye opening/closure can influence auditory and somatosensory processing (Brodoehl, Klingner, Stieglitz, et al., 2015; Brodoehl et al., 2016; Brodoehl, Klingner, and Witte, 2015; Götz et al., 2017). Though not entirely as expected, these findings from **Chapter 4** are exciting and open the door to future exploration of brain-state-dependent TMS effects in cognitive brain networks.

## 8.2 Part II: Neuronal alpha oscillations in the vision-attention network

Different brain areas may communicate through synchronized neuronal oscillations (Salinas and Sejnowski, 2001). Different cognitive processes may rely on different oscillatory frequency bands (Ward, 2003). Neuronal oscillations in the 7 – 13 Hertz alpha band have been linked to visual perception and attention (de Graaf et al., 2020; Diepen et al., 2016; Klimesch, 2012; Nelli et al., 2017; Ruzzoli et al., 2019). Following the same logic as described previously, these studies could only provide correlational evidence for the involvement of neuronal alpha oscillations in visual perception and attention, because the oscillations were merely measured rather than experimentally manipulated. This issue can be circumvented by using another form of NIBS, namely, transcranial alternating current stimulation (tACS) (Antal and Herrmann, 2016; Antal and Paulus, 2013).

TACS applied to posterior parietal cortex at alpha frequency has been shown to enhance the power of posterior alpha oscillations (Helfrich et al., 2014; Huang et al., 2021; Kasten et al., 2016; Kasten and Herrmann, 2017; Neuling et al., 2013; Stecher et al., 2017; Vossen et al., 2015; Witkowski et al., 2016; Zaehle et al., 2010) and to affect task performance in the classic endogenous Posner paradigm (Kasten et al., 2020; Kemmerer et al., 2020; Schuhmann et al., 2019). Unfortunately, similar to the effects of TMS, the effects of tACS have also been inconsistent and difficult to replicate (Coldea et al., 2021; Veniero et al., 2017). This may in part be due to ineffective stimulation frequencies, if the standard (10 Hertz) stimulation frequency differs from the dominant “individual alpha frequency” (IAF) (Haegens et al., 2014; Janssens et al., 2021; Kemmerer et al., 2020). To circumvent this problem, tACS protocols are therefore increasingly calibrated to the relevant individual peak frequency (see the section on multimodal NIBS approaches below) (Fresnoza et al., 2018; Kasten et al., 2016; Kasten et al., 2020; Vossen et al., 2015; Zaehle et al., 2010). In such studies, the IAF is often based on a short EEG measurement from a few electrodes during eyes closed resting state. Typically, IAF-tACS is then applied in multiple sessions and during a different neurocognitive state (i.e., during cognitive task performance) (Kemmerer et al., 2020; Mioni et al., 2020; Ronconi et al., 2018; Ronconi et al., 2020). Though IAF tends to be reliable within the same individual over time during resting state (Grandy, Werkle-Bergner, Chicherio, Lövdén, et al., 2013; Grandy, Werkle-Bergner, Chicherio, Schmiedek, et al., 2013),

it can fluctuate considerably during visual task performance (Benwell et al., 2019). It was therefore essential to assess to what extent a single, practically limited resting-state EEG measurement can be used to accurately target the relevant IAF during cognitive task performance (**Chapter 5**).

We found that the IAF showed good test-retest reliability within- and between-days. In general, we found that the relevant “true IAF” during attention task performance was approximated more accurately when individually calibrating the stimulation frequency based on EEG data, compared to simply using a standard (i.e., 10 Hertz) frequency for all participants. Notably, the “Gaussian fit” estimation method led to more reliable results than the “maximum” estimation method, especially for EEG data measured during attention task performance. Alpha power is typically suppressed during cognitive task performance compared to resting state, which makes it more difficult to reliably detect an alpha peak (Yamagishi et al., 2008). The “Gaussian fit” method seems to be less vulnerable to this issue. In our experiment, the “true” IAF during attention task performance was approximated most accurately using resting-state EEG data along with a “Gaussian fit” approach.

An important side note is that **Chapter 5** focused on a single oscillatory frequency band and a single cognitive task. Our recommendation of using resting-state EEG data along with a “Gaussian fit” approach for estimating individual peak frequencies still needs to be validated for other oscillatory frequency bands and cognitive tasks. It is furthermore noteworthy to mention that our findings are applicable to those rhythmic stimulation experiments that aim to enhance the power of an intrinsic (dominant) peak frequency, rather than shifting the dominant frequency upwards or downwards (Cecere et al., 2015; Mioni et al., 2020; Ronconi et al., 2020). Our results may furthermore be useful for personalizing neurofeedback trainings (Arns et al., 2012; Bazanova and Aftanas, 2010; Nan et al., 2012) and for personalizing NIBS treatment of depression (Corlier et al., 2019; Garnaat et al., 2019; Leuchter et al., 2017; Roelofs et al., 2020).

Even though IAF-tACS is superior to standard 10 Hertz tACS, its effects have still been inconsistent (Fekete et al., 2018; Veniero et al., 2017). The standard single frequency tACS protocols do not capture the full complexity of intrinsic oscillatory activity. Typically, human M/EEG power spectra show enhanced power over a range of frequencies in the alpha band. Some of these broadband signals

could reflect meaningful neuronal processes. For instance, there may be several functionally relevant alpha oscillators that oscillate at slightly different frequencies (Benwell et al., 2019; Klimesch et al., 1997; Klimesch, 1999). It is theoretically possible that tACS targeting a wider range of frequencies (rather than a single peak frequency) might impact a larger range of functionally relevant oscillators/circuits, which may yield stronger effects on oscillatory activity and/or behavior.

We evaluated this idea in **Chapter 6**, by developing such a “broadband-alpha” tACS protocol and an “alpha-removed” control tACS protocol. Broadband-alpha tACS reduced the rightward attention bias (compared to sham tACS) in an endogenous Posner task (Posner, 1980; Posner et al., 1980). Unexpectedly, alpha-removed tACS also reduced the rightward attention bias compared to sham tACS. It is possible that our unexpected behavioral finding was caused directly by an increase in oscillatory power in the theta, beta, or gamma band (Battaglini, Ghiani, et al., 2020; Samaha et al., 2017). It is difficult to establish what alpha-removed tACS did to oscillatory power because we cannot analyze the online EEG data. We did not find statistically significant (immediate) aftereffects of any active tACS condition (compared to sham tACS) on oscillatory power in any of the frequency bands. It is therefore difficult to explain why broadband-alpha tACS and alpha-removed tACS led to the same behavioral finding in this analysis. Future studies are needed to establish whether any multi-frequency tACS protocol may cause a reduction in the rightward attention bias, for instance by including a “broadband-beta tACS” condition.

Attention benefits were significantly decreased only after broadband-alpha tACS compared to sham tACS. Broadband-alpha tACS was hypothesized to synchronize alpha band oscillators, and may therefore counteract the alpha desynchronization that is associated with attention allocation (Gould et al., 2011). This behavioral effect did not interact with the factor “hemifield”, which is puzzling given that we stimulated only the left hemisphere. The exact reason for this is currently unknown, but it may be related to the spatial specificity of our tACS stimulation or to interhemispheric interactions. One limitation of the tACS ring electrode montage is that the current flow cannot be modeled exactly. Future studies could opt for a small central electrode surrounded by multiple small electrodes to overcome this issue. In any case, our findings in the broadband-alpha tACS condition cannot be explained by somatosensory side effects (Asamoah

et al., 2019; Matsumoto and Ugawa, 2017; Raco et al., 2014; Vieira et al., 2020), because IAF-tACS led to no statistically significant behavioral effects even though it was typically perceived as involving stronger somatosensory stimulation.

One crucial difference between the IAF-tACS protocol and the broadband-alpha and alpha-removed tACS protocols is that IAF-tACS contains larger amplitude variations over time compared to the other two protocols. This is due to the nature of multi-frequency time series and could thus not be prevented. Note that although a direct statistical comparison did not show any significant differences between IAF-tACS and broadband-alpha tACS, our newly developed protocol could detect a behavioral effect in the same participants with the same montage, while IAF-tACS could not. Single-subject data revealed that most participants showed behavioral effects in the expected direction after broadband-alpha tACS but not after IAF-tACS. In sum, these first effects of broadband-alpha tACS were statistically strong and consistent, and therefore exciting to pursue further. Still, not all effects could be easily interpreted, and therefore caution is warranted. Future studies are necessary to systematically investigate whether broadband-alpha tACS indeed leads to more consistent effects compared to IAF-tACS and/or whether it is associated with fewer side effects.

The work presented in **Chapter 6** paves the way towards novel explorations of individualized tACS protocols (see section on multimodal NIBS approaches below). From a clinical perspective, more robust or powerful tACS protocols would be highly meaningful. Alpha-tACS has already been suggested as a treatment strategy for depression (Alexander et al., 2019; Riddle et al., 2020) and substance use disorder (Daughters et al., 2020). Another future perspective would be to decrease neuronal oscillations within a specific frequency band (which we originally intended to achieve with our alpha-removed tACS protocol). It may be possible to alleviate spatial neglect symptoms by decreasing alpha power in the damaged hemisphere (Lasaponara et al., 2019; Pirondini et al., 2020). Similarly, depression symptoms may potentially be improved by reducing gamma power in fronto-temporal brain areas (Strelets et al., 2007).

### 8.3 Part III: The causal relevance of the early visual cortex for visual perception

The EVC has traditionally been implicated in visual awareness (Ro et al., 2003). TMS can be used to establish whether and when the EVC is needed to process a certain visual feature (for reviews see de Graaf et al., 2014; Kammer, 2007a, 2007b). Using this so-called “TMS masking paradigm”, it has been shown that the EVC is causally involved in the processing of basic visual features at around 70 – 130 msec after stimulus onset (Amassian et al., 1989; Masur et al., 1993; Potts et al., 1998). Some studies found a suppression of both objective and subjective processing visual stimuli after TMS to EVC (Jacobs et al., 2014; Jacobs et al., 2012; Koivisto et al., 2011). Other studies instead specifically looked at trials without conscious visual perception (subjective processing), observing that forced-choice task performance (objective processing) can remain above chance (Boyer et al., 2005; Koenig and Ro, 2018; Ro et al., 2004). One study reported that discrimination of (schematic) emotional expressions remained above chance after TMS to EVC, while participants were impaired at localizing the emotional expression and indicated not being aware of the stimuli (Jolij and Lamme, 2005). This finding is especially interesting as it shows a dissociation between two different objective visual tasks performed on the same face stimuli, with emotion processing being preserved after TMS to EVC. Apparently, the emotional content of face stimuli can be processed outside of visual awareness and without the involvement of the EVC. This makes sense from an evolutionary perspective because emotional expressions are ecologically highly relevant stimuli. They should thus be processed as quickly as possible, perhaps taking a “shortcut” pathway that bypasses the EVC (de Gelder et al., 2001).

The same principle might hold for other evolutionarily relevant visual stimuli, such as the trustworthiness of faces (Todorov et al., 2015; Todorov et al., 2008). We tested this hypothesis in **Chapter 7**. We found no evidence for an impairment of objective trustworthiness processing after TMS to EVC. Performance in a control (rotation discrimination) task was impaired by TMS to EVC in a temporally specific manner, which validates the neural efficacy of our TMS protocol (de Graaf et al., 2011; de Graaf et al., 2018). Subjective trustworthiness processing was also impaired by TMS to EVC. Our results support the hypothesis that EVC is required for the subjective perception of face trustworthiness, but do not support a role of the EVC

in the objective processing of face trustworthiness. It is currently unclear whether the same applies to the (here untested) left EVC, since the right hemisphere seems to be dominant for the processing of faces (De Heering and Rossion, 2015; Gainotti and Marra, 2011; Rangarajan et al., 2014; Rossion et al., 2012), emotional expressions (Demaree et al., 2005), and even face trustworthiness (Dzhelyova et al., 2012; Okubo et al., 2013).

This was the first attempted study to disrupt the processing of face trustworthiness using TMS, and we therefore did not design the experiment to achieve high temporal resolution chronometry. We rather included several TMS timings to cover the full extent of the classic TMS masking window, to ensure that we did not miss the crucial processing time as reported previously (Boyer et al., 2005; de Graaf et al., 2014). We used double pulse TMS rather than single pulse TMS to achieve a strong disruptive impact while keeping some temporal resolution to detect a temporally specific masking effect. Another limitation is that different tasks may be differentially susceptible to disruption by TMS. We therefore not only compared TMS effects on a subjective task with effects on an objective task, but included an additional objective task (all on the same stimuli). We did not seem to find any time-specific effect on the objective trustworthiness task, while we previously found suppression of both subjective and objective processing with many TMS intensities (de Graaf et al., 2011; de Graaf et al., 2012; Jacobs et al., 2014). It furthermore remains to be investigated whether above-chance trustworthiness discrimination performance can be obtained after completely abolishing conscious perception of face trustworthiness, rather than merely decreasing the subjective visibility of it.

## 8.4 The cognitive neuroscience field suffers from noisy data

As cognitive neuroscientists, we have the difficult task of establishing regularities based on measured responses from a noisy system (i.e., the human brain) (Huber et al., 2019). The noise in our data comes from various sources. Firstly, each individual and each brain is different (Beaty et al., 2019; Gu and Kanai, 2014; Kanai and Rees, 2011). Secondly, the same brain may respond differently over time, with variations on different temporal scales (e.g., weeks, days, or even (milli)seconds) (Dinstein et al., 2015). In other words, the state of the brain

changes constantly. The brain state may change because of current environmental/task demands (“neurocognitive state”) (**Chapters 2 and 4**). The brain state may also change because of spontaneous fluctuations in neuronal oscillations (“oscillatory state”) (**Chapters 3 and 4**). Although different neurocognitive states may be associated with different oscillatory states on average (Berger, 1929, 1933; Haegens et al., 2014; Quigley, 2021), the oscillatory state can fluctuate considerably within the same neurocognitive state (Benwell et al., 2019). Both the neurocognitive and oscillatory brain state might thus partially explain the variability in the way information is processed in the brain.

Besides the noise that arises within the system (i.e., brain) itself, our methods of measurement may create additional noise. The experimental method may introduce noise by changing the participant’s state of mind (e.g., placebo effects) or may have other unwanted side effects. For instance, sham (“ineffective”) TMS can have measurable effects on behavior (Duecker et al., 2013; Duecker and Sack, 2013, 2015). We discussed this complication in the context of our TMS masking paradigm in **Chapter 7**, where different TMS conditions were compared to an interleaved “no TMS” control condition. This issue also arises in experiments that compare low (“inactive”) versus high (“active”) intensity TMS (**Chapter 4**), since low intensity stimulation may still have effects on the brain (Zmeykina et al., 2020) and on behavior (Abrahamyan et al., 2015). This problem might be worsened when an individual’s brain is in a highly excitable state (Silvanto and Cattaneo, 2017). Multimodal TMS experiments could be especially prone to this, for instance because of the associated excitement, novelty, or even anxiety. Previous work already assessed the effects of TMS on heart rate, heart rate variability, and galvanic skin responses (Iseger et al., 2019; Iseger et al., 2017; Wang et al., 2016). But it could also be worthwhile to turn this question around: how does a participant’s current physiological/visceral state determine the brain’s response to TMS? Furthermore, future studies should systematically compare the efficacy of different TMS control conditions, such as the inclusion of a control stimulation site (e.g., “vertex”; Jung et al., 2016) and the blocking of sensory inputs (Biabani et al., 2019). Each experimental design and (combination of) neuroscientific method(s) suffers from a unique set of confounding factors, and the TMS control condition should be tailored to address those factors.

Similarly, when comparing different tACS protocols, we should consider the possibility that tACS effects may be due to non-specific side effects such as somatosensory stimulation (Asamoah et al., 2019; Raco et al., 2014). Importantly, tACS can still impact neuronal activity even when somatosensory side effects are blocked using a topical anesthetic (Vieira et al., 2020). TACS side effects can be effectively controlled such that double-blind designs are possible (Fröhlich and Riddle, 2021), but using a topical anesthetic may not always be desirable from an ethical perspective (considering the risk of skin burn; Antal et al., 2017). Especially when testing new tACS protocols, the blocking of skin sensations should be avoided. In **Chapter 6**, participants generally indicated that the standard IAF-tACS protocol led to the strongest somatosensory stimulation. Yet only our newly developed “broadband-alpha” and “alpha-removed” tACS protocols led to statistically significant behavioral effects. We concluded that these behavioral effects cannot solely be due to somatosensory side effects, but with the side note that this should be systematically addressed and replicated in future studies.

Not only NIBS methods introduce noise into the brain. The mere presence within an MRI scanner environment may affect perceptual decision making (Maanen et al., 2016) and cognitive control (Hommel et al., 2012). MRI scanning can cause vestibular stimulation (Roberts et al., 2011) which may lead to spatial attention biases (Lindner et al., 2021). The MRI environment may furthermore impact EEG (Assecondi et al., 2010) and eyetracking measures (Mack et al., 2021), and can in some cases lead to changed reaction times (Koch et al., 2003; Koten et al., 2013). Clinical populations may be especially prone to influences from the MRI scanner environment (Ellerbrock and May, 2015; Kolodny et al., 2021). The same holds for children and adolescents (Eatough et al., 2009). For such vulnerable populations, we should be especially careful in generalizing our conclusions from the MRI environment to real-world scenarios. It is furthermore well-known that an experimenter may unwillingly influence the participant’s behavior (so-called “demand characteristics”) (Sharpe and Whelton, 2016), which could be a confounding factor in the cognitive neuroscience literature at large.

A final factor to consider is that the actual measurement of the underlying brain data is imperfect. As described in **Chapter 1**, each method of cognitive neuroscience captures different properties and has its own strengths and weaknesses. While fMRI can only provide an indirect measure of neuronal activity, EEG suffers from volume

conduction effects and thus cannot provide spatially precise information (Gazzaniga et al., 2014). Behavioral measures such as reaction times may need a large number of trials in order to provide reliable results (Shahar et al., 2019). Altogether, these different sources of noise obscure the underlying brain mechanisms and cognitive processes of interest. Considering this, it is perhaps unsurprising that the field of cognitive neuroscience often suffers from inconsistent conclusions across studies.

## 8.5 The cognitive neuroscience field suffers from inconsistent conclusions

One example of such inconsistent findings is presented in **Chapter 2**, in which we aimed to develop a novel behavioral “attention adaptation” paradigm. We found statistically significant yet opposing findings across two direct replication studies. Not only was the direction of the effects different across these two studies, the effects were also inconsistent across three dependent variables that are often used to measure attention task performance (i.e., reaction times, proportion of correct trials, and inverse efficiency). The results from a third behavioral study with an improved experimental design came out negative, and thus could not help us make sense out of the other findings. Hypothesized results may not always be revealed when analyzing scores on a particular dependent variable of interest (e.g., response accuracy), but may appear only for another dependent variable that is assumed to measure performance in the same experimental task (e.g., reaction times; de Graaf et al., 2020). This not only raises questions as to what exactly those different dependent variables are measuring, but also about the robustness of our conclusions. In this context, it could be worthwhile to model the different perceptual decision-making components by applying drift diffusion models to reaction time scores (Ratcliff et al., 2015; Tavares et al., 2017), and to model the reliability of reaction time scores (Miller and Ulrich, 2013).

Unfortunately, failed replication studies are not uncommon in the attention literature, even when a direct application attempt is performed by the same researchers (Schouwenburg et al., 2018; Schouwenburg et al., 2017; Veniero et al., 2017). For instance, cathodal transcranial direct current stimulation (tDCS) to parietal cortex led to a shift in spatial attention bias in some (Benwell et al., 2015; Giglia et al., 2011), but not all studies (Veniero et al., 2017). Similarly, 10 Hertz

tACS to posterior parietal cortex affected endogenous attention task performance in some studies (Kasten et al., 2020; Kemmerer et al., 2020; Schuhmann et al., 2019, but failed to do so in a recent study (Coldea et al., 2021). Along the same lines, alpha-tACS does not always lead to a detectable increase in oscillatory alpha power (Battaglini, Mena, et al., 2020; Fekete et al., 2018). There is also ongoing debate regarding the causal involvement of neuronal alpha oscillations in active distractor suppression (Antonov et al., 2020; Noonan et al., 2016; Schneider et al., 2021; Wöstmann et al., 2019). The roles of the parietal cortex and neuronal alpha oscillations in visuospatial attention are thus not well understood yet. In **Chapters 5 and 6**, we therefore investigated to what extent individually calibrated alpha-tACS may help shed light on these issues (see the section on multimodal NIBS approaches below).

Such contradicting findings are not limited to the vision-attention network. Some studies reported aftereffects of beta-tACS applied to primary motor cortex on corticospinal excitability (Wischniewski, Schutter, et al., 2019), while others did not (Wach et al., 2013). Four studies failed to find a significant modulation of alpha or beta power following 10 Hertz- and 20 Hertz-tACS to motor cortex (Harada et al., 2020; Lafleur et al., 2021; Sugata et al., 2018; Wach et al., 2013). In contrast, another study using a more focal stimulation montage and a higher stimulation intensity did find a significant increase in beta oscillations lasting until 60 minutes after beta-tACS to primary motor cortex (Wischniewski, Engelhardt, et al., 2019). From **Chapter 3**, it became clear that both immediate and aftereffects of TMS also show substantial between- and within-subject variability (Corp et al., 2020, 2021). For instance, the reactivity of the motor cortex to single pulse TMS (as measured with motor-evoked potentials; MEPs) varies considerably over trials (Burke et al., 1995; Goetz et al., 2014; Goldsworthy et al., 2016; Kiers et al., 1993; Rösler et al., 2008; Wassermann, 2002). Moreover, the effects of repetitive TMS and theta burst stimulation (TBS) on neuroplasticity are inconsistent across individuals (Cheeran et al., 2008; Goldsworthy et al., 2012; Hamada et al., 2013; Hordacre et al., 2017; Maeda et al., 2000; Nettekoven et al., 2015; Schilberg et al., 2017).

The replication problem is pervasive also beyond the NIBS literature. Failed replication studies emerge for diverse scientific topics, including memory processes (Schie and Leer, 2019), emotional processes (Lane et al., 2015), and decision making (Röseler et al., 2021). In the psychology domain, only approximately one

in three replication studies leads to statistically significant results (despite sufficient statistical power to detect the original effect sizes) (Aarts et al., 2015). The replication probability might even be worse in the cognitive neuroscience field, given the low power to detect medium and large effects (Szucs and Ioannidis, 2017). This made me wonder: in this stream of noisy and inconsistent data, how can we find our way towards the truth?

## 8.6 Increasing the credibility of our conclusions

The replication crisis in cognitive neuroscience is a multi-faceted problem. Firstly, there is a lack of direct replication studies. While the number of replication studies is increasing in the psychology domain, the cognitive neuroscience field seems to be lacking behind (Huber et al., 2019). The competition for funding is fierce, and funding bodies tend to place great emphasis on the importance of novelty and innovation in our work (Romero, 2017). There are some initiatives for funding replication studies (e.g., the Dutch Research Council allotted 3 million euros in their 2016 – 2019 pilot program), but they are scarce. Prestigious scientific journals also show a preference for novel findings. In fact, there seems to be a negative relation between the journal impact factor and the reliability of the published results (Brembs, 2019). While exploratory studies are needed to advance scientific knowledge, we cannot truly move forward unless the foundations that we are building on are solid. As a middle way, it may be possible to combine replication with exploration in a single experimental design (as in **Chapter 6**).

A related problem is that positive results tend to be published more often than negative results (Kühberger et al., 2014). This “file drawer problem” makes it difficult to detect false positive findings in the published literature. It may also lead to a waste of time and money, since several researchers may have already conducted similar experiments and failed to find an effect – without anyone being aware of it. This may also lead to biased conclusions in literature reviews. Systematic reviews could be supplemented with meta-analyses to quantify the publication bias (Sutton et al., 2000). Another potential solution is experiment preregistration (Hales et al., 2018; Locey, 2020; Poldrack et al., 2017). This may also help prevent other problems such as low statistical power (Button et al., 2013; Szucs and Ioannidis, 2017).

Other initiatives may also help us distinguish between real and spurious effects. For instance, openly sharing code for stimulus presentation and data analysis will facilitate the replication process. Thankfully, there are ongoing initiatives for investigating the reliability of cognitive neuroscience research across labs, such as the “EEGManyLabs” project (Pavlov et al., 2021). Given the complexity of neuroscientific data, there is also a need to investigate to what extent our conclusions depend on the exact preprocessing and analysis steps (such as in the ongoing “EEGManyPipelines” project; Poldrack et al., 2017). For instance, we showed that there are different ways to calculate the IAF, and that the relatively unknown “Gaussian fit” method led to more reliable results than the standard “maximum” method (**Chapter 5**). This underlines the importance of systematically evaluating whether “gold standard” research procedures are valid, rather than simply repeating them. Finally, Bayesian statistics may help us provide evidence for the absence or presence of effects (**Chapter 7**) (de Graaf et al., 2011; de Graaf et al., 2018; Janssens et al., 2020a; Wagenmakers et al., 2018), and can even be used to estimate the prevalence of an effect in the population based on the proportion of an effect in the sample (Ince et al., 2021).

Even if we were to apply all these changes, variability in research findings would likely remain. Since both tACS and TMS are increasingly being explored as treatment options for a variety of brain-based disorders including depression and schizophrenia (Alexander et al., 2019; de Graaf et al., 2021; Lefaucheur et al., 2020; Riddle et al., 2020), there is an urgent need to improve the efficacy and consistency of NIBS. Part of the variability in NIBS effects is likely due to suboptimal stimulation parameters in the “one size fits all” approach that has typically been used in research and clinical settings. There is a growing interest in the individual calibration of NIBS protocols based on neuroimaging data. Such multimodal NIBS approaches may help mitigate some of the variability in NIBS effects (**Chapter 3**).

## 8.7 Neuroimaging may help increase the efficacy of NIBS

NIBS is increasingly combined with neuroimaging, for two reasons (Bergmann et al., 2016). Firstly, neuroimaging can be used to evaluate the effects of NIBS. For instance, we used fMRI to visualize the effects of TMS during stimulation

(“online”, **Chapter 4**) and used EEG to evaluate the effects of tACS after stimulation (“offline”, **Chapter 6**). Secondly, neuroimaging can be used to individualize NIBS protocols to potentially increase their efficacy (**Chapters 3, 4 and 5**). NIBS experiments are characterized by many relevant parameters, such as the stimulation site, frequency, and intensity. Individually calibrating such parameters using a “trial and error” approach would be highly inefficient. Below, I discuss several ways in which neuroimaging data may guide us in determining the optimal stimulation parameters for each individual.

### 8.7.1 Stimulation site

In some cases, the NIBS target site can be determined based on some observable output. The classic example is targeting the motor cortex after finding the “motor hotspot” using single pulse TMS, which is the stimulation site that leads to the largest TMS-induced muscle response (e.g., Schilberg et al., 2018; Thomson et al., 2019). Another example is targeting the early visual cortex based on the subjective perception of “phosphenes”, though not all individuals can perceive phosphenes (e.g., **Chapter 7**). More precise targeting of for instance the primary visual cortex (V1) requires the use of (f)MRI data (Salminen-Vaparanta et al., 2012). In many cases, NIBS is applied to a standardized electrode position from the 10-20 EEG coordinate system (Herwig et al., 2003). In **Chapter 4**, we applied TMS to electrode position P4. Our goal was to target the right posterior parietal cortex as a cognitive network hub (Heuvel and Sporns, 2013), rather than to stimulate a particular sub-area of the intraparietal cortex (Szczepanski et al., 2010; Szczepanski et al., 2013). In **Chapter 6**, we aimed to modulate posterior parietal alpha oscillations and attention task performance by applying tACS to electrode position P3, using a stimulation montage that previously led to positive effects (Kemmerer et al., 2020; Schuhmann et al., 2019).

The decision for a specific NIBS targeting method typically involves a trade-off between accuracy and investment (in terms of time and money). Depending on the experimental aims, it may or may not be worthwhile to invest more resources into targeting a precisely defined brain area. If the goal is to stimulate a specific brain area with high spatial precision, it could be worthwhile to use individual anatomical MRI data or an fMRI localizer to determine the optimal stimulation target in the brain. Examples of such targets include the occipital face area (Ambrus et al., 2017), the

lateral occipital complex (Bona et al., 2014), and V5/MT+ (Sack et al., 2005). TMS neuronavigation can then be used to determine the optimal TMS coil location and orientation to reach the target brain area, which may increase TMS efficacy (Ahdab et al., 2010; Sack et al., 2009; Sparing et al., 2008). Similarly, electric field modeling techniques could be used to determine the optimal tACS electrode placement for targeting the brain area of interest (Kasten et al., 2019; Saturnino et al., 2018). Differences in tACS-induced electric fields can explain a large part of the between-subject variability in tACS-induced effects (Kasten et al., 2019; Zanto et al., 2021) and tDCS treatment response (Albizu et al., 2020). Although we modeled the tACS-induced electric field in **Chapter 6**, it should be mentioned that we used a standard brain rather than individual (f)MRI data to do so (similar to Kasten et al., 2020; Schuhmann et al., 2019).

In **Chapters 1 and 4**, we discussed that the effects of TMS can extend beyond the area directly underneath the coil towards other (even subcortical) brain areas (Bergmann et al., 2021). Deeper brain areas may thus be indirectly affected by the effects of TMS on cortical brain areas. This finding can be useful in a clinical context, for instance for individualizing TMS treatment for depression (Klooster et al., 2021). The structural (Klooster et al., 2020) and functional (Fox et al., 2013; Ge et al., 2020) connectivity between the cortical TMS targeting site in the left dorsolateral prefrontal cortex (DLPFC) and the deeper cingulate cortex can predict the clinical response to TMS. The functional connectivity between the DLPFC target site and the nucleus accumbens could predict the anti-depressant and anti-anxiety effects of TMS (Du et al., 2018). Individual connectivity measures derived from neuroimaging data may thus help us determine the optimal TMS site for achieving the largest clinical response to TMS (Klooster et al., 2021). This may also be feasible in other disorders such as obsessive-compulsive disorder (OCD) (Mantovani et al., 2021). As a future outlook, it would be interesting to investigate whether the optimal connectivity-based TMS target site may depend on the (neurocognitive or oscillatory) brain state (**Chapter 4**).

### 8.7.2 Stimulation frequency

Rhythmic TMS (Lin et al., 2021; Okazaki et al., 2021; Thut et al., 2011) and tACS (Helfrich et al., 2014; Vossen et al., 2015; Zaehle et al., 2010) have both been used to enhance endogenous neuronal oscillations at a particular frequency of interest.

Individuals differ considerably in terms of their dominant ongoing brain rhythms (Haegens et al., 2014; Janssens et al., 2020b; Ramsay et al., 2021). Neural and behavioral effects of rhythmic NIBS may be frequency specific (Herrmann et al., 2013; Kemmerer et al., 2020; Klink et al., 2020; Zaehle et al., 2010). For instance, the effects of rhythmic TMS on the motor cortex were maximal when applied at the individual beta frequency (Romei et al., 2016). Furthermore, a mismatch between the NIBS frequency (e.g., 10 Hertz) and the individual dominant frequency (e.g., the IAF) can be detrimental for the repetitive TMS treatment outcome in depression (Corlier et al., 2019; Roelofs et al., 2020). These findings demonstrate the importance of calibrating rhythmic NIBS protocols to individual peak frequencies. In **Chapter 5**, we concluded that short resting-state EEG measurements from limited electrodes are sufficient to reliably estimate the IAF.

In **Chapter 6**, we explored a new way of incorporating the individual oscillatory frequency content in tACS protocols. More specifically, we created multi-frequency tACS protocols based on the individual EEG power spectrum within the alpha range (“broadband-alpha tACS”) or outside the alpha range (“alpha-removed tACS”). Multi-frequency transcranial electric stimulation (TES) is not novel per se. Transcranial random noise stimulation (tRNS) targets a broad range of frequencies, typically between 100 and 700 Hertz (Paulus, 2011). It can increase cortical excitability (Chaieb et al., 2011; Moret et al., 2019; Terney et al., 2008), potentially by modulating the neuronal signal-to-noise ratio – a mechanism that is called “stochastic resonance” (Antal and Herrmann, 2016; Groen and Wenderoth, 2016; Pavan et al., 2019). TRNS has been shown to improve attention (Contò et al., 2021; Tyler et al., 2018), working memory (Mulquiney et al., 2011; Murphy et al., 2020), and face perception (Romanska et al., 2015). In contrast to tRNS, our tACS protocols were not designed to enhance cortical excitability by randomly stimulating with frequencies outside the typical EEG frequency range. Instead, we aimed to modulate the power of specific oscillatory frequency bands by “replaying” the frequency content that was present in the individual EEG power spectrum. Future studies are needed to compare the mechanisms and effects of “broadband-alpha” and “alpha-removed” tACS with those of tRNS.

### 8.7.3 Stimulation intensity

The TMS intensity can be determined in various ways. In some cases, a fixed stimulation intensity is used for all individuals (**Chapter 7**). In the majority of cases, the TMS intensity is set to a percentage of the individually determined resting motor threshold, active motor threshold, or phosphene threshold (for occipital stimulation) (Turi et al., 2021). The resting and active motor threshold are defined as the TMS stimulation intensity that is required to induce a muscle response in 50% of the cases when the muscle is relaxed versus contracted, respectively (Rossini et al., 2015). The phosphene threshold is defined as the TMS intensity required to induce a phosphene in 50% of the cases (de Graaf et al., 2017; Kammer et al., 2001). For non-motor areas, the TMS intensity is also often based on the motor threshold; but individual anatomical MRI scans should be used to take into account differences in scalp-to-cortex distance across brain areas (Stokes et al., 2007; Stokes et al., 2005). It seems that only three studies used electric field modeling to determine the intensity of repetitive TMS thus far (Beynel et al., 2020; Kraft et al., 2015; Zmeykina et al., 2020). Crucially, higher stimulation intensity is not necessarily better. There was an inverted u-shape relationship between the intermittent theta burst stimulation intensity and the subsequent neurophysiological effects (Chung et al., 2018). Furthermore, the same TMS protocol may have either excitatory or inhibitory effects depending on the stimulation intensity (Doeltgen and Ridding, 2011). The optimal stimulation intensity may furthermore depend on the current brain state (Silvanto and Cattaneo, 2017).

TES intensities typically range between 1 – 2 mA peak-to-peak (Bland and Sale, 2019), to ensure stimulation tolerability (Fertonani et al., 2015). Electric field modeling is increasingly used to visualize TES-induced electric fields for fixed stimulation frequencies (**Chapter 6**) (Saturnino et al., 2018). For a fixed stimulation intensity, the TES-induced electric field intensity can vary considerably across individuals (Evans et al., 2020). The consistency of TES effects may be improved by individually dosing the stimulation intensity based on electric field modeling (Datta et al., 2012). Similar to TMS effects, tACS effects can be intensity dependent (Johnson et al., 2020; Moliadze et al., 2012). The same is true for tRNS effects, which is in line with the supposed underlying mechanism of “stochastic resonance” (Antal and Herrmann, 2016; Groen and Wenderoth, 2016). More

research is needed to fully understand the relationship between TES intensity, induced electric fields, and subsequent effects on behavior and cognition (Klooster et al., 2016).

#### 8.7.4 Closed-loop NIBS

Thus far, this section focused on individualizing NIBS parameters per individual. While this can help improve the consistency of NIBS effects, this approach does not consider within-subject variations in the brain state. We previously discussed that spontaneous fluctuations in the oscillatory brain state can explain part of the variability in NIBS effects (**Chapter 3**). “Closed-loop” NIBS approaches can take into account such oscillatory state fluctuations by continuously measuring the M/EEG signal and adjusting the NIBS protocol accordingly (Bergmann et al., 2016; Guerra et al., 2020; Janssens and Sack, 2021; Thut et al., 2017; Zrenner, Tünnerhoff, et al., 2016; Zrenner, Belardinelli, et al., 2016). For instance, the timing of single TMS pulses may be adjusted to match the optimal oscillatory power or phase. As a first demonstration of this principle, it was shown that TMS-induced motor-evoked potentials were highest when TMS was applied to the motor cortex during the rising phase of slow oscillations (Bergmann et al., 2012). The development of the “brain electrophysiological recording stimulation” (BEST) toolbox further facilitates the application of “closed-loop” NIBS approaches (Hassan et al., 2022). A combination of “closed-loop” NIBS with neurofeedback may furthermore improve mood and anxiety symptoms in various disorders (Guerrero Moreno et al., 2021). These developments hold promise for more consistent NIBS effects in both research and clinical settings.

## 8.8 Concluding remarks

Visual perception and attention rely on communication within the vision-attention network. Within this network, higher-level frontoparietal areas send top-down signals to lower-level visual areas, to enhance visual perception at a certain (attended) location in space. The state of the brain may influence how signals propagate through this network. This fact may be exploited in an experimentally controlled manner, for instance by selectively adapting (i.e., fatiguing) specific top-down pathways to study endogenous attentional control (**Chapter 2**). Signal propagation can also be investigated and manipulated with TMS. When ignored, fluctuations in brain state can cause variability in the effects of TMS (**Chapter 3**). Multimodal TMS approaches are necessary to further investigate how TMS signals propagate through the brain as a function of the oscillatory and neurocognitive brain state (**Chapter 4**). Similarly, the effects of tACS are also often inconsistent and difficult to reproduce. It is therefore essential to target the correct oscillatory frequency, and calibrating tACS protocols to individual peak frequencies based on resting-state EEG data is a good way to achieve this (**Chapter 5**). Still, we may be able to develop better tACS protocols by stimulating a larger frequency range based on individual M/EEG measurements, rather than stimulating at a single peak frequency (**Chapter 6**). Finally, behavioral TMS experiments can be used to evaluate whether a certain brain region (such as the early visual cortex) is a part of the crucial pathway for processing a certain stimulus feature (such as the trustworthiness of faces) (**Chapter 7**).

Taken together, the work presented in this thesis shows that behavioral, TMS, and tACS effects often show large variability between and within individuals. Improved scientific practices may help us distinguish between real and spurious effects, for instance by performing more replication studies and by publishing both positive and negative findings. The variability in NIBS effects may be partially explained by individual differences in brain anatomy and functionality. Within-subject changes in the neurocognitive brain state and spontaneous fluctuations in the oscillatory brain state may furthermore contribute to NIBS variability. The consistency of NIBS effects may be improved by individualizing stimulation protocols based on neuroimaging data. Finally, this thesis outlined the possibilities and limitations of multimodal brain research.

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*Appendix A*

**Impact Paragraph**

*“Every great advance in science has issued from a new audacity of imagination”*

– John Dewey

The main goal of this doctoral thesis was to investigate how signals propagate within the vision-attention network, and how neuronal alpha oscillations play a role as a communication mechanism. After working for 4 years on this topic, the time has come for me to contemplate the potential impact of my, or rather our, efforts. Below, I share my personal views regarding the scientific, clinical, and educational impact of my (our) work.

The research reported in this thesis has been presented to different research groups and departments within the host university. It has furthermore been shared with the national and international cognitive neuroscience community through means of poster and oral presentations at several online and on-site conferences (see *“About the Author”* for a complete overview). In the General Introduction, I already emphasized that the methods of cognitive neuroscience are always evolving. Science in general does not only evolve in its ways of measuring and experimenting, but also in its ways of communicating. In the pursuit of my doctoral degree, it became more and more clear to me that scientists’ methods of knowledge dissemination are no longer fully focused on peer-reviewed publications and on-site conferences. Perhaps accelerated by the ongoing pandemic, scientists seem to be looking for more flexible ways of communicating their findings and establishing collaborations, such as online/hybrid meetings and conferences, sharing preprints, sharing data and analysis code, and making use of social media. These changes are in line with ongoing initiatives such as the movement towards open (*“FAIR”*) science, and the Dutch *“Recognition & Rewards”* program. I believe that this paradigm shift may be especially beneficial for early career researchers on fixed-term contracts that are trying to find a new academic position and/or obtain their own funding. Since the peer-review cycle can easily take one year for a single publication, there must be ways to evaluate progress and impact before the final product is published. Besides this, I also believe that we must find better ways to quantify the actual visibility and impact of our work, rather than clinging to the impact factor (IF) of the journal that it is published in. We already know that the IF provides limited information about individual articles (Bollen et al., 2009; Paulus et al., 2018), and that impact in different research fields cannot be easily compared (Radicchi et al., 2008). In any case, I hope to play my part in the

movement away from the “high IF journal”-centered mentality in academia, towards a more diverse and inclusive approach. In line with these developments, I (we) shared several preprints, datasets, and user-friendly analysis code. To gain more visibility, I also shared my (our) work on my personal academic website and on social media such as *Twitter*, *LinkedIn*, and *ResearchGate*. This has led to fruitful discussions with researchers from different countries.

As scientists, we can have many roles besides “just doing science”. For instance, we can be educators, mentors, and role models. I taught students from several master programs about the possibilities and limitations of non-invasive brain stimulation. I taught students from a local high school about brain imaging and stimulation methods, and about the implications of my (our) work. Multimodal brain research as described in this doctoral thesis requires advanced technical skills, and my hope is to inspire and encourage young females to dive into such technical topics. I told the “non-official” story behind our simultaneous TMS-EEG-fMRI set-up to PhD candidates at the *Ghent Doctoral Schools*. I furthermore shared my experiences during several phases of the research projects on *Twitter*. I also wrote a blog for *EDLAB* (the Maastricht University institute for education innovation), explaining how unforeseen circumstances in research can lead to novel insights (<https://edlab.nl/dealing-unforeseen-circumstances/>). Sharing this kind of background information can help others gain a deeper understanding of the challenges and accomplishments that happen behind the scenes before the end-result is published. Such information may be of special importance for early-career researchers, first-generation students/researchers, or researchers aiming to switch fields. By not only sharing the published manuscript, but by also taking the time to teach others about potential difficulties that may happen along the way, others may obtain a more realistic view on what constitutes “success” in academia.

If we take a closer look at the different projects presented in this doctoral thesis, what can we take away from them? The “attention adaptation” paradigm described in **Chapter 2** shows the theoretical potential of neuronal adaptation for studying cognitive processes and for targeting specific neuronal sub-systems within the human brain. I hope that this may inspire others to think outside the box and apply established paradigms to new contexts. In our case, across three experiments, results were statistically significant and expected, statistically significant and unexpected, and statistically non-significant. Clearly, behavioral

findings can differ strongly across studies, even if the experimental procedures are (nearly) identical. This chapter thus highlights the importance of replication studies in science, even if results are statistically strongly significant and in line with expectations.

TMS effects can also show considerable variability. **Chapter 3** proposed that the within- and between-subject variability in TMS effects may in part be explained by spontaneous fluctuations in the oscillatory brain state. It also compared two technical solutions for considering the oscillatory brain state during TMS. This information is relevant for fundamental and clinical applications of TMS, since it may help better predict and control the effects of TMS. Especially during TMS treatment, the goal is often to modulate specific functional brain pathways, so we should maximize our chances of targeting the desired pathway. Related to this, in **Chapter 4** we assessed how TMS signal propagation across the brain may depend on the oscillatory and/or the neurocognitive brain state during TMS. It shows the feasibility and theoretical utility of simultaneous TMS-EEG-fMRI in cognitive networks. It also provides concrete recommendations for future multimodal TMS studies, to increase the likelihood of visualizing brain-state-dependent TMS effects.

A central theme in this doctoral thesis is that NIBS protocols should be individually calibrated to enhance their consistency. With tACS, this often takes the form of individualizing the stimulation frequency based on the peak within a particular oscillatory frequency band. Typically, such a peak frequency is based on a single short resting-state M/EEG measurement. TACS is then often applied at that peak frequency during a different neurocognitive state (i.e., task performance) across different sessions. **Chapter 5** showed that individual peak alpha frequencies (“IAF”) are reliable both within and between sessions, and during resting state and task performance. It also showed that individualizing the stimulation frequency based on EEG was more accurate than using a standard frequency for everyone, and that rest-EEG data provided better results than task-EEG data. This provides empirical evidence for the commonly used approach of individualizing tACS frequencies based on rest-EEG data. We also found that a “Gaussian fit” procedure led to better (more reliable) IAF values compared to the traditional “maximum” method. To help other researchers implement this improved peak frequency detection technique, I created a user-friendly code that is shared along with the data on *DataverseNL*. In this code, I implemented an automatic peak rejection

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algorithm to help researchers determine objectively whether a peak is present in the power spectrum or not. This can be especially helpful in cases where many power spectra must be assessed regarding the presence or absence of an oscillatory peak. For comparison, the code then also calculates the peak frequency based on the traditional maximum method and the improved Gaussian method. This code can be of use to any researcher or clinician wanting to calibrate the rhythmic (tACS, TMS, or even sensory) stimulation frequency to an individual peak frequency within a defined oscillatory frequency band – or, more generally, to anyone interested in peak oscillatory frequencies.

**Chapter 6** goes one step further in terms of trying to increase the consistency of tACS effects. We developed and tested a broadband-alpha-tACS protocol that was based on individual resting-state EEG data. Though this study was only the first step, it shows that there is much more for us to explore in the domain of calibrating NIBS to individual oscillatory information. There are numerous brain-based disorders that show abnormal oscillatory activity, including Alzheimer’s disease, schizophrenia, and bipolar disorder (Başar et al., 2015). When it comes to clinical applications, tACS is an especially attractive method given its (relatively) low price and portability. We should therefore keep on pushing the boundaries towards more advanced and efficacious tACS protocols.

Finally, **Chapter 7** investigated whether processing of face trustworthiness relies on the early visual cortex (EVC) or not. We found a distinction between objective and subjective processing, in the sense that subjective processing was impaired by TMS to EVC, while objective processing was not. This teaches us that the processing of complex facial features can bypass EVC, similar to other evolutionarily relevant (but more basic) facial features such as emotions. This study also provides an example of how Bayesian statistics can help us draw conclusions regarding the absence of effects. Finally, it once again demonstrates the versatility of TMS as a research tool.

In sum, this doctoral thesis shows that behavioral, TMS, and tACS effects can show large variability, underlining the importance of replication studies and further methodological advancements. It encourages individual calibration of NIBS protocols for increasing their consistency, and outlines the promises and challenges of multimodal brain research.

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*Appendix B*

**General Summary**

Imagine yourself sitting in a crowded café in your favorite city. What do you see? Most likely there are several baristas preparing a variety of drinks. In one corner of the café, you may see students sitting with their laptops. In the other corner there may be a toddler with their caregiver, frantically playing with a pile of blocks. The café may feature a vast selection of colorful posters on the walls and flowers on the tables. But did you spot the emergency exit?

This everyday life situation illustrates the richness of our visual perception. Yet, our brain is unable to simultaneously process such an overflow of visual input in full detail. To solve this issue, our brain can focus on certain relevant stimuli and process them further, while ignoring the rest. This cognitive process is called “attention”. In the example described above, you could voluntarily shift your attention to different locations in the café until you find the relevant stimulus (i.e., the emergency exit).

How does the healthy human brain accomplish this? Visual perception and attention rely on information exchange between higher-level frontoparietal and lower-level visual brain areas. The main aims of this thesis were to further investigate how signals propagate through this so-called vision-attention network (*Part I*), to evaluate the role of neuronal alpha oscillations in visuospatial attention (*Part II*), and to better understand the relevance of the early visual cortex (EVC) for the processing of evolutionarily relevant visual stimuli (*Part III*). This thesis presents a multimodal approach to these aims, since it combines behavioral methodology, non-invasive brain stimulation (NIBS), and neuroimaging.

## Part I

The aim of **Chapter 2** was to develop a behavioral paradigm to specifically modulate top-down brain pathways involved in voluntary attention shifts to specific locations in space. Based on the concept of “neuronal adaptation”, we hypothesized that repeated attention shifts to a location should decrease attention task performance specifically at that (adapted) location. Across three experiments, we obtained one positive expected result, one positive unexpected result, and one negative result. These findings underline the importance of replication studies, even when results are as expected. We concluded that the “attention adaptation” paradigm could not (yet) be successfully developed, but that it may be worth pursuing this further. If it could be successfully developed, this paradigm may be used to answer unresolved

neuroscientific questions such as how attention moves through visual space. It might furthermore be combined with transcranial magnetic stimulation (TMS) to improve attention at specific (adapted) locations in space.

TMS is widely used in both research and clinical settings, but its effects tend to be inconsistent between and within individuals. **Chapter 3** presents an overview of recent literature regarding between- and within-subject variability in the effects of TMS. It demonstrates that spontaneous fluctuations in neuronal oscillations contribute to the variability of both immediate and aftereffects of TMS. This chapter highlights the benefits of multimodal TMS approaches and underlines the importance of individually calibrating TMS protocols to oscillatory markers. Finally, it explains how the latter can be achieved using simultaneous transcranial alternating current stimulation (tACS)-TMS, or “closed-loop” magneto-/electroencephalography (M/EEG)-based TMS.

The momentary oscillatory brain state influences how TMS signals propagate within the motor network. The neurocognitive state may also influence TMS signal propagation. It was unclear to what extent such mechanisms are at play in cognitive brain networks such as the vision-attention network. In **Chapter 4**, we therefore used simultaneous TMS-EEG-fMRI (functional magnetic resonance imaging) to assess how TMS signals spread from posterior parietal cortex to other brain areas, as a function of the oscillatory state (pre-TMS alpha power) or neurocognitive state (eyes open versus closed). We did not find brain state-dependent TMS-induced signal propagation. Instead, we found brain state-independent TMS-induced fMRI activations in sensory brain areas, which are most likely due to TMS side effects (e.g., somatosensory and auditory stimulation). Interestingly, fMRI responses to those TMS side effects seemed to be modulated by the neurocognitive state at the time of TMS. We provided concrete recommendations for future studies aiming to reveal “real” (but likely weak) brain-state-dependent TMS signal propagation in cognitive brain networks.

## Part II

Rhythmic stimulation methods such as tACS can be used to modulate neuronal oscillations to establish their causal involvement in cognition. However, results regarding the role of 7 – 13 Hertz alpha oscillations in visuospatial attention have

been inconsistent. When investigating neuronal oscillations, it is crucial to modulate the correct oscillatory frequency (e.g., the individual alpha frequency (IAF) during a neurocognitive state of interest). In **Chapter 5**, we therefore investigated how best to calibrate rhythmic stimulation protocols to individual oscillatory markers (such as the IAF). We measured short EEG segments from single electrodes in both hemispheres, within and between days, during two neurocognitive states (attention task performance versus eyes closed resting state). We then calculated IAF using two estimation methods. We found that 1) IAF was generally reliable, 2) individual calibration was superior to using a standard (10 Hertz) frequency, and 3) rest-EEG data along with a “Gaussian fit” approach led to the most consistent IAF estimates. These results validate the commonly used approach of determining IAF from a short resting state EEG measurement and then rhythmically stimulating the brain with that same frequency over time/days during cognitive task performance. It also suggests that a “Gaussian fit” estimation method might be superior compared to the traditional “maximum” method.

Though IAF-tACS is superior to standard 10 Hertz-tACS, its effects have been inconsistent. In **Chapter 6**, we investigated whether a more complex, biologically inspired tACS protocol might have more consistent effects. Individual EEG power spectra contain an alpha peak with more than just a single frequency. Targeting that entire peak frequency range might be more effective compared to stimulating at a single frequency. We developed a “broadband-alpha tACS” protocol by (IAF  $\pm$  2 Hertz) bandpass filtering the individual resting state EEG power spectrum. We also developed an “alpha-removed” (spectrally inverse) control tACS protocol. We found that, compared to sham-tACS, “broadband-alpha” tACS reduced the rightward attention bias and reduced attention benefits, “alpha-removed” tACS reduced the rightward attention bias, and IAF-tACS had no effects. Though not all findings were as expected, this first attempt at developing a more complex tACS protocol is promising and should be explored further in future studies.

### Part III

It was still unclear whether the EVC is causally involved in the processing of salient visual stimuli such as (un)trustworthy faces. Given their evolutionarily relevant character, these kinds of stimuli may need to be processed as quickly as possible

and might therefore bypass the EVC via other (faster) brain pathways. We investigated this in **Chapter 7** by employing a TMS masking paradigm. We presented rotated (un)trustworthy faces while applying TMS to EVC at 50, 100, or 150 msec after face stimulus onset, or not at all. For each face, participants judged the 1) objective (forced-choice) trustworthiness, 2) subjective visibility (rating) of trustworthiness, and 3) rotation (forced-choice). TMS to EVC disrupted rotation (control) task performance at 50 and 100 msec compared to no TMS, validating the neural efficacy of TMS in our subject sample. While TMS to EVC impaired the subjective visibility of trustworthiness at 50 and 100 msec compared to no TMS, objective trustworthiness performance was preserved. We concluded that objective trustworthiness judgments may not rely on EVC, and that the relevant information may thus travel via other (potentially sub-cortical) pathways in the brain. This chapter demonstrates that unimodal TMS studies can also be informative about processing pathways in the human brain.

## Conclusion

Taken together, this thesis demonstrated the potential of NIBS for unraveling brain network interactions, yet also showed that there is still much to be gained in terms of NIBS efficacy and reliability. Though NIBS and/or behavioral methodology may shed light on brain mechanisms even when used in isolation, there is a need to combine these methods with neuroimaging. Multimodal approaches can help us better understand and control for brain-state-dependent NIBS effects.



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*Appendix C*

**Algemene Samenvatting**

Stel je voor dat je in een overvol café zit in je favoriete stad. Wat zie je dan? Waarschijnlijk zijn er verschillende barista's bezig met het bereiden van verschillende drankjes. In de ene hoek van het café zie je misschien studenten zitten met hun laptop. In de andere hoek zit misschien een peuter met zijn verzorger, verwoed te spelen met een stapel blokken. In het café hangen kleurrijke posters aan de muur en staan er bloemen op de tafels. Maar heb je de nooduitgang al gezien?

Deze alledaagse situatie illustreert de levendigheid van onze visuele perceptie. Onze hersenen zijn echter niet in staat om tegelijkertijd zo'n overvloed aan visuele input tot in het kleinste detail te verwerken. Om dit probleem op te lossen, kunnen onze hersenen zich concentreren op bepaalde relevante stimuli en deze verder verwerken, terwijl ze de rest negeren. Dit cognitieve proces wordt "aandacht" genoemd. In het hierboven beschreven voorbeeld zou je vrijwillig je aandacht kunnen verplaatsen naar verschillende locaties in het café, totdat je de relevante stimulus (de nooduitgang) vindt.

Hoe doet het gezonde menselijke brein dit? Visuele waarneming en aandacht berusten op informatie-uitwisseling tussen frontopariëtale hersengebieden en visuele hersengebieden. De hoofddoelen van dit proefschrift waren om verder te onderzoeken hoe signalen zich verplaatsen door dit zogenaamde visie-aandacht-hersennetwerk (*Deel I*), om de rol van neuronale alfa oscillaties in visueel-ruimtelijke aandacht te evalueren (*Deel II*), en om de relevantie van de vroege visuele cortex ("EVC") voor de verwerking van evolutionair relevante visuele stimuli beter te begrijpen (*Deel III*). Dit proefschrift presenteert een multimodale benadering van deze doelstellingen, aangezien het gedragsmethodologie, niet-invasieve hersenstimulatie ("NIBS"), en "neuroimaging" combineert.

## Deel I

Het doel van **Hoofdstuk 2** was het ontwikkelen van een gedragsparadigma om "top-down" (feedback) hersenverbindingen te moduleren die betrokken zijn bij het vrijwillig verplaatsen van de aandacht naar specifieke locaties in de omgeving. Gebaseerd op het concept van "neuronale adaptatie", stelden we de hypothese dat herhaalde aandachtsverschuivingen naar een bepaalde locatie de gedragsprestatie

op die (“geadapteerde”) locatie zou moeten verslechteren. In drie experimenten kregen we één positief verwacht resultaat, één positief onverwacht resultaat, en één negatief resultaat. Deze bevindingen benadrukken het belang van replicatiestudies, zelfs wanneer de resultaten zijn zoals verwacht. Wij concludeerden dat het paradigma van “aandachtsadaptatie” (nog) niet met succes kon worden ontwikkeld, maar dat het wellicht de moeite waard is om dit verder te onderzoeken. Als dit paradigma met succes zou kunnen worden ontwikkeld, zou het kunnen worden gebruikt om onopgeloste neurowetenschappelijke vragen te beantwoorden. Bijvoorbeeld: hoe beweegt “aandacht” zich door ons gezichtsveld? Bovendien zou “aandachtsadaptatie” kunnen worden gecombineerd met transcraniële magnetische stimulatie (TMS) om de aandacht op specifieke (“geadapteerde”) locaties in het gezichtsveld te verbeteren.

TMS wordt veel gebruikt, zowel in onderzoek als in klinische settings, maar de effecten ervan zijn vaak inconsistent tussen individuen en binnen hetzelfde individu over de tijd. **Hoofdstuk 3** geeft een overzicht van recente literatuur met betrekking tot de variabiliteit in de effecten van TMS tussen en binnen proefpersonen. Het toont aan dat spontane fluctuaties in neuronale oscillaties bijdragen aan de variabiliteit van zowel de directe als de langdurige effecten van TMS. Dit hoofdstuk bespreekt de voordelen van multimodale TMS applicaties, en onderstreept het belang van het individueel aanpassen van TMS protocollen op basis van neuronale oscillaties. Tenslotte wordt er uitgelegd hoe dit laatste kan worden bereikt door gebruik te maken van simultane transcraniële wisselstroom stimulatie (“tACS”)-TMS, of van “closed-loop” magneto-/elektroencefalografie (M/EEG)-gebaseerde TMS.

Spontane fluctuaties in neuronale oscillaties beïnvloeden de wijze waarop TMS-signalen zich verspreiden in het motorische hersennetwerk. Ook de neurocognitieve toestand (d.w.z., waar iemand cognitief gezien mee bezig is) kan van invloed zijn op de verspreiding van TMS-signalen door het brein. Het was onduidelijk in hoeverre dergelijke mechanismen een rol spelen in cognitieve hersennetwerken zoals het visie-aandacht-netwerk. In **Hoofdstuk 4** gebruikten we daarom simultane TMS-EEG-fMRI (“functional magnetic resonance imaging”) om na te gaan hoe TMS signalen zich verspreiden van de pariëtale cortex naar andere hersengebieden. We bekeken of de verspreiding van TMS-signalen afhangt van neuronale oscillaties (d.w.z., de amplitude van alfa oscillaties) en/of de neurocognitieve toestand (d.w.z., ogen open of gesloten). We vonden hiervoor geen bewijs in onze data. In plaats daarvan vonden

we fMRI activiteiten in sensorische hersengebieden, die hoogstwaarschijnlijk te wijten zijn aan TMS-bijwerkingen (zoals somatosensorische en auditieve stimulatie). Het leek alsof de fMRI reacties op deze TMS-bijwerkingen gemoduleerd werden door de neurocognitieve hersentoestand tijdens de toediening van TMS. We gaven concrete aanbevelingen voor toekomstige studies die gericht zijn op het onthullen van “echte” (maar waarschijnlijk zwakke) hersenstaat-afhankelijke TMS-sigitaal verspreiding in cognitieve hersennetwerken.

## Deel II

Ritmische stimulatiemethoden zoals tACS kunnen gebruikt worden om neuronale oscillaties te moduleren om hun causale betrokkenheid bij cognitie vast te stellen. Echter, de resultaten betreffende de rol van 7-13 Hertz alfa oscillaties in visueel-ruimtelijke aandacht zijn inconsistent. Bij het onderzoeken van neuronale oscillaties is het van cruciaal belang om de juiste frequentie te moduleren (bijvoorbeeld: de individuele alfa frequentie (IAF) tijdens een bepaalde neurocognitieve toestand). In **Hoofdstuk 5** hebben we daarom onderzocht hoe ritmische stimulatieprotocollen het beste aangepast kunnen worden op basis van individuele neuronale oscillaties (zoals de IAF). We hebben korte EEG-metingen gedaan met één enkele elektrode in beide hersenhelften, binnen en tussen dagen, tijdens twee neurocognitieve hersenstaten (aandachtstaak en rust). Vervolgens berekenden we de IAF met behulp van twee schattingsmethoden. We vonden dat 1) IAF over het algemeen betrouwbaar was, 2) individuele aanpassing van stimulatieprotocollen op basis van EEG beter was dan het gebruik van een standaard (10 Hertz) frequentie, en 3) rust-EEG gegevens samen met een “Gaussian fit” schattingsmethode leidden tot de meest consistente IAF schattingen. Deze resultaten valideren de vaak gebruikte methode van het bepalen van de IAF op basis van een korte rust-EEG meting, en vervolgens het ritmisch stimuleren van de hersenen met diezelfde frequentie over tijd/dagen tijdens het uitvoeren van een cognitieve taak. Dit hoofdstuk suggereert ook dat een “Gaussian fit” schattingsmethode beter zou kunnen zijn dan de klassieke “maximum” schattingsmethode.

IAF-tACS is superieur aan standaard 10 Hertz-tACS, maar de effecten zijn nog steeds inconsistent. In **Hoofdstuk 6** hebben we onderzocht of een complexer,

biologisch geïnspireerd tACS-protocol consistentere effecten zou kunnen hebben. Individuele EEG “power spectra” bevatten een alfa piek met meer dan één enkele frequentie. Het stimuleren van die gehele piek zou effectiever kunnen zijn dan het stimuleren met één (piek)frequentie. We ontwikkelden een “breedband-alfa-tACS” protocol door het individuele EEG “power spectrum” te filteren (zodat alleen 7 – 13 Hertz alfa-activiteit overbleef). We ontwikkelden ook een “alfa-verwijderd” (tegenovergesteld) controle tACS protocol. We ontdekten dat “breedband-alfa” tACS de “attention bias” (aandachtsneiging) naar rechts verminderde en “attention benefits” (aandachtsvoordelen) verminderde. “Alfa-verwijderde” tACS leidde ook tot een verminderde “attention bias” naar rechts. IAF-tACS had geen gedragseffecten. Hoewel niet alle bevindingen waren zoals verwacht, is deze eerste poging tot het ontwikkelen van een complexer tACS-protocol veelbelovend en dient dit verder onderzocht te worden in toekomstige studies.

### Deel III

Het was onduidelijk of de vroege visuele cortex (“EVC”) causaal betrokken is bij de verwerking van belangrijke visuele stimuli zoals (on)betrouwbare gezichten. Gezien hun evolutionair relevante karakter is het mogelijk dat dit soort stimuli zo snel mogelijk verwerkt moeten worden en daarom de EVC omzeilen via andere (snellere) hersenverbindingen. We onderzochten dit in **Hoofdstuk 7** door gebruik te maken van TMS. We presenteerden geroteerde (on)betrouwbare gezichten terwijl we TMS toedienden aan de EVC. TMS werd op 50, 100, of 150 msec na aanvang van de gezichtsstimulus toegediend, of helemaal niet. Voor elk gezicht beoordeelden de deelnemers de 1) “objectieve” betrouwbaarheid (twee opties), 2) “subjectieve” zichtbaarheid van de betrouwbaarheid (op een schaal van één tot vier), en 3) rotatie (twee opties). TMS op 50 en 100 msec verminderde de gedragsprestatie op de rotatie (controle)taak, wat de werkzaamheid van TMS in onze proefpersonen valideert. TMS verstoorde de subjectieve zichtbaarheid van de betrouwbaarheid wanneer toegepast op 50 en 100 msec. De objectieve betrouwbaarheidsprestatie bleef intact na TMS. We concluderen dat objectieve betrouwbaarheidsverwerking niet afhankelijk is van de EVC, en dat de relevantie informatie zich dus via andere verbindingen in de hersenen kan verplaatsen. Dit hoofdstuk toont aan dat unimodale TMS studies ook informatie kunnen verstrekken over signaalverspreiding in het menselijk brein.

## Conclusie

Dit proefschrift heeft de potentie van NIBS voor het ontrafelen van hersennetwerken aangetoond, maar heeft ook laten zien dat er nog veel te winnen valt op het gebied van NIBS-effectiviteit en betrouwbaarheid. NIBS en/of gedragsmethodologie kunnen nuttig zijn voor het bestuderen van hersenmechanismen, maar de combinatie met “neuroimaging” kan van toegevoegde waarde zijn. Zulke multimodale benaderingen kunnen ons helpen om hersenstaat-afhankelijke NIBS effecten beter te begrijpen en te controleren.

The background of the page is a watercolor wash in various shades of blue, ranging from light sky blue to deep, dark navy blue. The wash is applied in a way that creates soft, organic, and somewhat irregular edges, giving it a textured, artistic appearance. The colors are layered, with darker tones appearing more concentrated in the upper right and lower right areas, while lighter tones are more prominent on the left and bottom edges.

*Appendix D*

**About the Author**

Shanice Janssens was born in Kerkrade, the Netherlands, on 5 December 1993. She obtained her high school diploma at Sophianum Gulpen in 2012. Given her keen interest in the human mind and brain, she pursued a bachelor's degree in psychology at the Faculty of Psychology and Neuroscience at Maastricht University. Thanks to the MaRBLLe (*Maastricht Research-Based Learning*) excellence program and her work as a student-assistant for Dr. Henna Toppenberg & Dr. Tom de Graaf, she gained her first experience with scientific research. After obtaining her Bachelor of Science in 2015 (*summa cum laude*), she was accepted to the Research Master in Cognitive and Clinical Neuroscience at Maastricht University. During her master studies, she applied for a Research Talent grant from the Dutch Research Council (*Nederlandse Organisatie voor Wetenschappelijk Onderzoek*), together with her supervisors Dr. Tom de Graaf and Prof. Dr. Alexander Sack. In 2017, the grant was awarded and Shanice obtained her Master of Science diploma (*cum laude*), allowing her to pursue a PhD.

During her PhD trajectory, Shanice investigated the vision-attention network in the healthy human brain. She now continues her work as a postdoctoral researcher in the Brain Stimulation and Cognition Lab at Maastricht University, led by Prof. Dr. Alexander Sack, in collaboration with Prof. Dr. Chris Baeken (Ghent University, Free University Brussels, & Eindhoven University of Technology) and Prof. Dr. Jacinta O'Shea (University of Oxford). The main goal of this project team is to use individualised non-invasive brain stimulation for investigating and modulating the brain network(s) involved in depression.

As a researcher, Shanice aims to be versatile, thorough, and independent yet cooperative. She is committed to increasing diversity and inclusivity within academia. With her own insights as a first-generation and female academic, she hopes to encourage others to pave their own paths – to simply *go with the flow*.

## Peer-reviewed publications

**Janssens, S.E.W.**, ten Oever, S., Sack, A.T., & de Graaf, T.A. (2022). “Broadband Alpha Transcranial Alternating Current Stimulation”: Exploring a new biologically calibrated brain stimulation protocol. *NeuroImage*, 253(June), 119109. <https://doi.org/10.1016/j.neuroimage.2022.119109>.

**Janssens, S.E.W.**, & Sack, A. T. (2021). Spontaneous fluctuations in oscillatory brain state cause differences in TMS effects within and between individuals. *Frontiers in Human Neuroscience*, 15, 745. <https://doi.org/10.3389/fnhum.2021.802244>.

**Janssens, S.E.W.**, Sack, A.T., ten Oever, S., & de Graaf, T.A. (2021). Calibrating rhythmic stimulation parameters to individual EEG markers: the consistency of individual alpha frequency in practical lab settings. *European Journal of Neuroscience*. <https://doi.org/10.1111/ejn.15418>.

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## Journal club articles

**Janssens, S.E.W.** (2022). The neural correlates of attention and awareness. *Nature Reviews Psychology*. <https://doi.org/10.1038/s44159-022-00049-9>. [Read-only open access version: <https://rdcu.be/cJOKf>].

## Book chapters

De Graaf, T.A., **Janssens, S.E.W.**, & Sack, A.T. (2021). Is non-invasive brain stimulation the low-hanging fruit? In: Schreiber, R. (eds) *Modern CNS Drug Discovery*. Springer, Cham. [https://doi.org/10.1007/978-3-030-62351-7\\_8](https://doi.org/10.1007/978-3-030-62351-7_8).

## Preprints

**Janssens, S.E.W.**, de Graaf, T.A., Duecker, F., Schuhmann, T., & Sack, A.T. (2022). Assessing TMS-evoked cognitive network responses depending on neurocognitive and oscillatory brain state: A simultaneous TMS-EEG-fMRI project. *BioRxiv*. <https://doi.org/10.1101/2022.04.07.487517>.

**Janssens, S.E.W.** (2021). Optimizing frontal-sensory alpha-band synchrony to improve attention: a commentary on Mishra et al. (2021). *OSF Preprints*. <https://osf.io/7gsca/>.

## Talks

**5 Apr 2022** – Haegens Lab : Brain Rhythms (Columbia University, NYC, USA & Radboud University, Nijmegen, the Netherlands). *Calibrating rhythmic stimulation parameters to individual oscillatory markers*.

**7 Mar 2022** – Women Researchers' Day (Maastricht, the Netherlands). *Non-invasive brain stimulation and neuroimaging in attention research*.

**13 Jan 2022** – Grotius College (high school, Heerlen, the Netherlands). *Brain imaging and stimulation methods*.

**15 Oct 2021** – Doctoral Schools Ghent University (Ghent, Belgium). *Simultaneous TMS-(EEG)-fMRI setup*.

**22 Sep 2021** – Brainbox Initiative Conference (online). *Calibrating non-invasive brain stimulation protocols to individual oscillatory markers*.

## Conference contributions

Member of the Diversity & Inclusion committee for the Dutch Society for Brain and Cognition (including the NVP conference in April 2022).

**Janssens, S.E.W.**, Sack, A.T., Duecker, F., Schuhmann, T., & de Graaf, T.A. (2020, May). Assessing brain-wide TMS-evoked responses depending on ocular and oscillatory state: a simultaneous TMS-EEG-fMRI project. CNS annual meeting, online. [Poster]

**Janssens, S.E.W.**, Sack, A.T., Jessen, S., & de Graaf, T.A. (2019, March). Can processing of face trustworthiness bypass early visual cortex? A TMS masking study. CNS annual meeting, San Francisco, USA. [Poster]

Ivanov, D., Kashyap, S., Haast, R.A.M., **Janssens, S.E.W.**, Huber, L., Poser, B.A., & Uludag, K. (2018, June). Human whole-brain sub-millimeter cerebral blood flow map using 7T ASL. Joint Annual Meeting ISMRM-ESMRMB. [Poster]

**Janssens, S.E.W.**, Sack, A.T., & de Graaf, T.A. (2017, June). In control of attention: teasing apart the brain's top-down mechanisms of attention allocation. Dutch Neuroscience Meeting, Lunteren, the Netherlands. [Poster]

## Data and analysis code

**Janssens, S.E.W.**, ten Oever, S., Sack, A.T., & de Graaf, T.A. (2022). "Broadband Alpha Transcranial Alternating Current Stimulation": Exploring a new biologically calibrated brain stimulation protocol. Dataset and experiment code, DataverseNL. <https://doi.org/10.34894/3LYMZF>.

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The background of the page is a vibrant blue watercolor wash. The color transitions from a deep, dark blue at the top to a lighter, almost white blue at the bottom, with various shades and textures in between, creating a soft, artistic effect. The text is centered in the upper half of the page.

*Appendix E*

**Acknowledgements**

*“If I have seen further, it is by standing on the shoulders of giants” – Isaac Newton*

## Promotion team

My sincere thanks to you, **Alex**, because none of this would have been possible without your support. I am especially grateful for the opportunity to apply for PhD funding together, and I feel so lucky that this allowed me to be a part of your research team. I also appreciate the fact that you are always open to my ideas and value my opinion. The past two years must not have been easy for you as a group leader, but you really helped me (and undoubtedly others) get through the pandemic with your honesty, humour, and involvement during the weekly lab meetings. I realize that none of this should be taken for granted, and I am very much looking forward to the years to come.

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## Brain Stimulation and Cognition Lab

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**Mevr. Puijk** (docent Frans), die altijd in mij geloofde en daardoor een grote invloed heeft gehad op mijn zelfvertrouwen.

## Private life

**Lars** – It is hard to find the right words. The greatness of the five years that we spent together cannot be captured in a single paragraph, or perhaps cannot be explained at all. You were there during many important moments of my life, and I will always treasure our memories. I am grateful for all the experiences we had together, in particular the amazing travels. Thanks also to Sylvia, Thomas, Jan, and the rest of your family, for always being so kind and welcoming.

Thanks to my cats for improving my quality of life by a factor of 1000. **Mona** the pretty girl: I miss you! **Sir James Clerk Maxwell**, I have so much love for you!

**Gesa & Felix** – Thank you for the board game nights, making sushi, celebrating New Year's Eve together, and the best ice cream I have ever eaten in my life!!!

**Marin & Bram, Gojko & Jasmina, Aline & Dominik, Martin & Thessely, João & Carolin** – thanks for the dinners, brunches, trips, weddings, parties, and all the good times we had. Thank you for making me feel included.

**Myrr** – Zo fijn om samen met jou te koken en om video's te kijken van mensen die heel goed (of totaal niet) kunnen zingen!

**Hugo** – Onze allereerste onderwijsgroep Sociaal Gedrag is alweer zo'n 10 jaar geleden. Ongelofelijk hè? Veel woorden hebben wij verder niet nodig.

**Leo & Antonio** – Thanks for the nice dinners, for making me laugh, and for the parties. I hope we get to spend many more moments in the sun together.

**Maria** – Thank you for the girls nights, parties, and good conversations. I am so glad that I met you!

**Chantal, Ghislaine, Miranda, & Tanja** – Mijn lieve vriendinnen uit Mechelen. Jullie zijn me heel dierbaar en ik ben trots dat we elkaar al zo lang kennen.

Grazie alla **famiglia Marrazzo** per essere così gentile e accogliente con me.

Aan mijn hele familie, bedankt dat jullie er zijn.

**Oma** – Ik had je graag mijn nieuwe tuin laten zien, en je had mijn promotie vast schitterend gevonden. Ik mis je, maar je bent er toch wel bij.

**Mama, papa, & Dean** – Ik woon natuurlijk al lang niet meer in Mechelen, maar het voelt toch altijd als thuiskomen bij jullie. Al weten jullie niet wat mijn werk nou precies inhoudt, en al begrijpen jullie mijn keuzes niet altijd, ik kan toch altijd op jullie terugvallen. Dat is pas echte rijkdom. Ik hou van jullie.

Finalmente, **Giuseppe**, chi avrebbe mai pensato che io e te fossimo così simili? Non riesco ancora a credere a quanto sono fortunata ad averti trovato. Grazie per la tua infinita fiducia in noi, tutto il cibo straordinario (in particolare le ottime pizze), il modo in cui mi fai (sor)ridere, grazie semplicemente per essere qui con me. Non vedo l'ora per il resto. ♡