# INVESTIGATING THE INTERPLAY OF THE HUMAN ATTENTIONAL AND VESTIBULAR SYSTEMS USING TRANSCRANIAL MAGNETIC STIMULATION

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**To Michi,**
without whom this thesis
would have never been possible

# SUMMARY

The aim of this doctoral thesis was to investigate the relationship between the processing of vestibular information, on the one hand, and higher cognitive functions such as visual (spatial) attention and perceptual decision making, on the other. In order to draw causal inference about the role of specific cortical regions in this interplay, two experimental studies were conducted which combined psychophysical task designs using verticality judgment tasks with transcranial magnetic stimulation (TMS).

The first study employed a simultaneous TMS-EEG approach to examine the role of the right intraparietal sulcus (IPS) within the dorsal parietal cortex in verticality judgments – a cortical area that has repeatedly been associated with both the visual attention and vestibular systems. Facilitatory effects of right IPS TMS on the bias of verticality perception were reported and mirrored by EEG results, which pointed to a normalization of individual perceptual biases reflected in a fronto-central ERP component following the stimulation. In contrast, no effects of left IPS TMS on either behavioural or electrophysiological measures were observed and right IPS TMS did not modulate performance in a control task that used the same set of stimuli (vertical Landmark task). These findings point to a causal role of the right IPS in the neuronal implementation of upright perception and strengthen the notion of vestibular-attentional coupling.

In the second study verticality judgments had to be made under different levels of perceptual demand to address the question of how perceptual decision making interacts with vestibular processing. Stimuli adapted from those used in the first study were presented in a visual search setting, which required perceptual and response switches, in a way that varied attentional demands. This task was combined with offline theta-burst TMS applied to the dorsal medial frontal cortex (dMFC). The dMFC has been found to crucially contribute to perceptual decision making and is connected to core parts of the vestibular cortical network. Analysis of distinct features of behavioural performance before as compared to following dMFC TMS revealed a specific involvement of the dMFC in establishing the precision and accuracy of verticality judgments, particularly under conditions of high perceptual load.

In summary, the results of the two studies support the idea of a functional link between the processing of vestibular information, (spatial) attention, and perceptual decision making, giving rise to higher vestibular cognition. Moreover, they suggest that on a cortical level this

interplay is achieved within a network of multimodal processing regions such as the parietal and frontal cortices.

# ABBREVIATIONS

| | |
|---|---|
| ADJ | Methods of adjustment |
| AIP | Anterior intraparietal area |
| CIP | Caudal intraparietal area |
| CCW | Counterclockwise |
| CW | Clockwise |
| dDdR | Different dimension different response |
| dDsR | Different dimension same response |
| dMFC | Dorsal medial frontal cortex |
| EEG | Electroencephalography |
| ERP | Event-related potential |
| FEF | Frontal eye fields |
| fMRI | Functional magnetic resonance imaging |
| GVS | Galvanic vestibular stimulation |
| hVIP | Human ventral intraparietal area |
| IFG | Inferior frontal gyrus |
| IPL | Inferior parietal lobule |
| IPS | Intraparietal sulcus |
| LIP | Lateral intraparietal area |
| MIP | Medial intraparietal area |
| MRI | Magnetic resonance imaging |
| MSOs | Multisensory orientation/integration centers |
| MST | Middle superior temporal area |
| MT | Middle temporal area |
| PET | Positron emission tomography |
| PIVC | Parietoinsular vestibular cortex |
| PPC | Posterior parietal cortex |
| preSMA | Pre-supplementary motor area |
| PSE | Point of subjective equality |
| sDdR | Same dimension different response |
| sDsR | Same dimension same response |
| SPL | Superior parietal lobule |
| STG | Superior temporal gyrus |
| SVV | Subjective visual vertical |
| tDCS | Transcranial direct current stimulation |
| TEP | TMS-evoked potential |
| TMS | Transcranial magnetic stimulation |
| TPJ | Temporo-parietal junction |
| VFC | Ventral frontal cortex |
| VIP | Ventral intraparietal area |
| VOR | Vestibular-ocular reflex |
| 2AFC | Two-alternative forced choice |

# TABLE OF CONTENTS

# 1 General introduction

## 1.1 The role of spatial attention and perceptual decision making in vestibular cognition

### a. Fundamentals of attention

Due to the limited processing capacity of the human visual system (Lennie, 2003) we are forced to select between simultaneously appearing stimuli. Therefore, there is a continuous competition for representation, analysis, and control between visual stimuli in our environment within our visual processing system. Due to this competition, ideally only those stimuli, which are currently relevant to our behavioural goals, will be processed. Accordingly, mechanisms that enable effective gating of relevant input, while discarding task-irrelevant information, are vital for our ability to successfully interact with our environment. This is achieved by a cognitive process termed visual attention (Awh et al., 2012; Beck & Kastner, 2009; Desimone & Duncan, 1995; Duncan, 1984; Posner & Petersen, 1990; Reynolds & Chelazzi, 2004). Visual attention biases the competition between relevant and irrelevant sensory input in a way that modulates neuronal activity in the related sensory brain areas. Specifically, when an (ideally task-relevant) stimulus is attended, increases in firing rates of neurons tuned to the properties of that stimulus are observed while the processing of irrelevant stimuli gets suppressed (Kastner & Ungerleider, 2000; Moore & Zirnsak, 2017; Reynolds et al., 1999; Reynolds & Chelazzi, 2004). As a consequence, the perceptual properties (e.g. stimulus contrast) of attended stimuli are enhanced and processing of those stimuli is facilitated (Carrasco, 2011; Carrasco et al., 2004). In this way visual attention can lead to improved behavioural performance (such as improved accuracy levels or faster reaction times) and altered subjective perception of the visual environment (Carrasco & Barbot, 2019). Visual attention can be further subdivided into different categories of how visual information is processed, depending on which aspect of a stimulus is relevant and thus attracts attention. Examples of taxonomies using such categories are bottom-up vs. top-down attention (selective attention, i.e. whether a stimulus is relevant due to its physical saliency or its relevance for internal goals), feature-based attention (i.e. whether a stimulus possesses relevant features such as a specific colour or shape), or spatial attention (i.e. whether a stimulus is located at a behaviourally relevant location).

Neurophysiological research has extensively studied the underlying brain mechanisms of visual attention using various methodologies, such as single-cell recordings in animals, human brain imaging and stimulation, and patient lesion studies. This work has revealed a widespread network involving thalamo-cortical and cortico-cortical connections (for comprehensive reviews see e.g. Desimone & Duncan, 1995; Itti & Koch, 2001; Moore & Zirnsak, 2017). However, as visual attention is not a unitary cognitive mechanism but comprises several sub-aspects as mentioned above, there seems to be no common neural substrate of visual attention per se but rather each attentional aspect relies on its own specific neural mechanisms (Moore & Zirnsak, 2017; Nobre, 2001). Spatial attention, which enables selective processing of stimuli at relevant locations (and which the present thesis will mainly focus on), is assumed to depend on coordinated activity of areas within a fronto-parietal network (Corbetta & Shulman, 2002, 2011; see Fig. 1). Within this network there are two interacting sub-networks which are related to distinct roles in spatial attention: first, a bilaterally organized dorsal fronto-parietal network involving the frontal eye fields (FEF), intraparietal sulcus (IPS) and superior parietal lobule (SPL) that directly controls shifts in spatial attention according to current top-down goals. Secondly, there is a right-lateralized ventral fronto-parietal sub-network comprising the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior temporal gyrus (STG) and ventral frontal cortex (VFC) that interferes with activity of the dorsal sub-network in case attention has to be reoriented to spatial locations containing highly salient or unexpected stimuli (in that way acting as a "circuit breaker"). This model, which was initially proposed based on brain imaging studies (Corbetta & Shulman, 2002), has also been supported by a number of patient studies which show that damage to the (particularly right) fronto-parietal network often causes an attentional impairment of the contralesional visual hemifield, a visuo-spatial disorder referred to as neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta & Shulman, 2011). Several studies have found links between neglect and processing of vestibular information (see section 1.1d for details) pointing to a putative role of the visual attention system in vestibular processing.

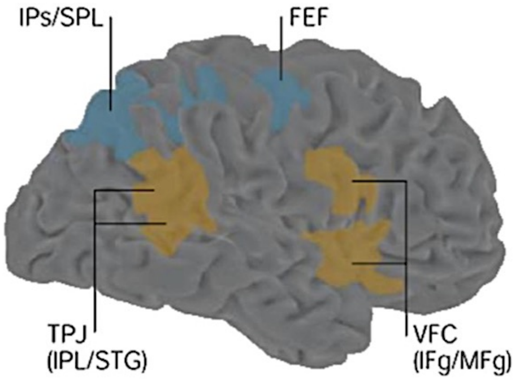

Figure 1: The functional-anatomical model of the human fronto-parietal attention network as proposed by Corbetta and Shulman (Corbetta & Shulman, 2002). The dorsal fronto-parietal network is depicted in blue. The ventral fronto-parietal network is shown in yellow.

### b. Fundamentals of perceptual decision making

Attention biases the weighting of the sensory information gathered from the different sensory systems according to its relevance. In order to reach a final percept of a stimulus and create an appropriate action, all the weighted information has to be combined and evaluated. This cognitive process is referred to as perceptual decision making. It involves the detection, discrimination, and categorization of sensory stimuli (Gold & Ding, 2013; Gold & Shadlen, 2007; Hanks & Summerfield, 2017; Heekeren et al., 2008). A large body of both animal and human research, in conjunction with various methods of computational modelling (Mulder et al., 2014) have proposed that sensorimotor areas of particular (posterior) parietal and dorsal prefrontal regions form a functional network crucial for perceptual decision making (Hanks & Summerfield, 2017; Heekeren et al., 2008; Mulder et al., 2014; Najafi & Churchland, 2018).

To study perceptual decision making, two-alternative forced choice (2AFC) tasks are commonly used. Such tasks require the participant to judge a specific property of a presented stimulus based on two possible alternatives, for example via a button press. By applying psychometric fitting to the collected data, the participant's responses can then be linked to the actual physical properties of the stimulus (Gold & Ding, 2013; Klein, 2001). In that way conclusions about distinct features of behavioural performance and perception and can be drawn (Angelaki, 2014; Gold & Ding, 2013; Hanks & Summerfield, 2017; Mulder et al., 2014). In detail, during psychometric fitting of data collected from 2AFC tasks, the proportion of trials in which a specific property of a stimulus is rated as belonging to one of two possible alternatives is plotted against each possible level of the presented stimulus property (Fig. 2). For example, if the size of a stimulus A compared to the size of a stimulus B has to be judged (alternatives: larger vs. smaller), a psychometric fit could depict the proportion of trials where stimulus A was perceived as larger than the comparison stimulus against all presented size difference levels (i.e. ranging from stimulus A being maximally larger than stimulus B to stimulus A being maximally smaller than stimulus B).

Earlier work on visual-vestibular interactions during perceptual discrimination tasks has shown that behavioural performance when analysed by means of psychometric fitting, as is done in the studies presented in this thesis, can be determined by two parameters (Angelaki, 2014; Baccini et al., 2014; Dyde et al., 2006; Paci et al., 2011). First, based on the 'sigma' or standard deviation of the fitted psychometric curve perceptual precision can be inferred. This parameter reflects the sensitivity or reliability of perceptual decisions (i.e. how variable responses are). In addition, perceptual bias can be computed, which represents the accuracy of one's perception in relation to the actual stimulus properties. This parameter is derived from the point of subjective equality (PSE) of the psychometric curve, i.e. the stimulus property level that corresponds to the 50% proportion of one alternative being chosen over the other (guessing point). However, while precision and bias can vary independently from one another, optimally, perceptual performance is both precise and unbiased at the same time. This can be illustrated with the example of the game darts: only players who throw the darts both on average based around the intended target (accuracy) and at the same time are precise in their throwing during the whole game (precision) will win the game.

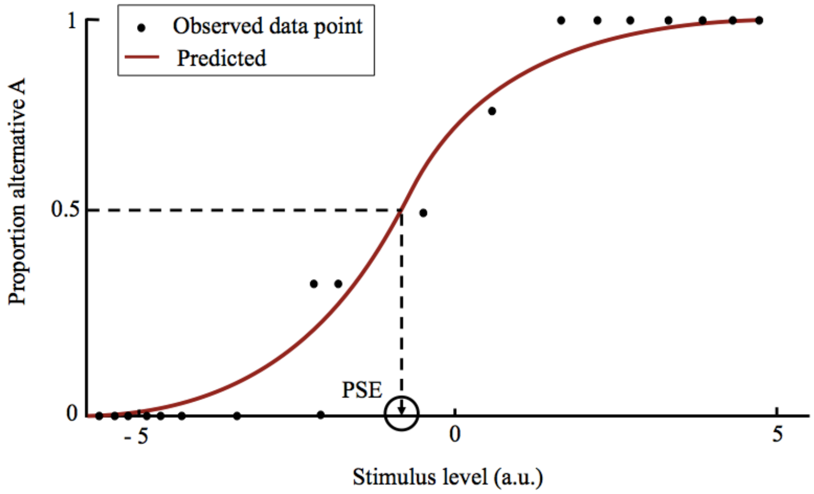

Figure 2: Psychometric fitting. The proportion of responses regarding one alternative (e.g. stimulus A being larger in size than stimulus B; "observed data points") is plotted as a function of the levels of the presented stimulus (e.g. the actual physical difference in size between stimulus A and B). The 50% point (i.e. point of subjective equality, PSE) obtained from the sigmoid fit to the data reflects the perceptual bias (Angelaki, 2014; Baccini et al., 2014; Dyde et al., 2006; Foxe et al., 2003). The standard deviation of the psychometric curve relates to the steepness of the slope of the sigmoid and provides a measure of the participant's discrimination threshold, thus reflecting response variability or precision. A smaller standard deviation corresponds to a steeper slope, indicating less variable / more reliable discrimination performance (Angelaki, 2014; Dyde et al., 2006).

### c. Vestibular cognition / higher vestibular functions

The vestibular system is fundamental for our ability to navigate and orient in the environment, establish and maintain balance and posture, and perceive self-motion (e.g. Dieterich & Brandt, 2018; Ertl & Boegle, 2019). In order to achieve those goals it not only processes sensory input arriving at the peripheral vestibular end organs in the inner ear (Goldberg et al., 2012) but is also heavily involved in, and reliant on, the subsequent multisensory integration of vestibular information with input arriving from other senses such as vision, audition, or proprioception (Brandt & Dieterich, 1999). Such integration is realized within a widespread thalamocortical network ranging from vestibular nuclei in the brainstem, thalamic nuclei, and cerebellar regions to a number of cortical areas (Brandt & Dieterich, 1999, 2017; Dieterich & Brandt, 2015; Lopez & Blanke, 2011; Lopez, Blanke, & Mast, 2012; Smith, Greenlee, DeAngelis, & Angelaki, 2017; zu Eulenburg, Caspers, Roski, & Eickhoff, 2012) which will be described in more detail in the following sections of this thesis. Thus, a constant interplay of peripheral and central processing steps is required for successful vestibular functioning.

Accordingly, in the past vestibular disorders were traditionally subdivided as peripheral or central based on their underlying anatomical pathologies (Brandt, Strupp, & Dieterich, 2014). However, this rigid classification system was not able to explain some vestibular dysfunctions sufficiently. As a result, in recent years the role of cognition and higher brain functions such as attention or spatial memory in vestibular processing has been increasingly recognized (Besnard, Lopez, Brandt, Denise, & Smith, 2016; Bigelow & Agrawal, 2015; Brandt et al., 2014; Dobbels et al., 2018; Frank, Sun, Forster, Tse, & Greenlee, 2016; Mast, Preuss, Hartmann, & Grabherr, 2014; Popp et al., 2017; Seemungal, 2014). This led to the proposal of an additional category of vestibular dysfunctions, termed “higher vestibular functioning” (Brandt & Dieterich, 2017; Brandt et al., 2014). Rather than classifying vestibular disorders based solely on their underlying anatomical deficits, the notion of “higher vestibular functioning” additionally takes functional aspects, such as accompanying cognitive symptoms and performance, into account. Higher vestibular disorders can arise from both peripheral or central vestibular lesions, affect cognitive performance, and are not limited to vestibular deficits alone but also involve other sensory modalities, i.e. are multisensory in nature (Brandt & Dieterich, 2017; Brandt et al., 2014). The term was chosen with analogy to the concept of higher visual disorders, which describes visual deficits that arise from dysfunctional cortical processing of visual information occurring after initial processing in the primary visual cortex (Ziehl & Kennard, 1996).

An example disorder, which has been classified as both a higher visual disorder as well as a higher vestibular disorder, is spatial hemi-neglect (Brandt et al., 2014; Karnath & Dieterich, 2006). Patients suffering from this disorder show an attentional impairment regarding the contralesional visual hemifield and consequently impaired processing of visual information within this hemifield due to lesions in areas of the fronto-dorsal attention network (Corbetta & Shulman, 2011). The observations of 1) high similarities in behavioural performance of neglect and vestibular patients (Karnath & Dieterich, 2006), 2) a close anatomical relation or even overlap of the multisensory vestibular cortex and the fronto-dorsal attention network (Corbetta & Shulman, 2002; Dieterich et al., 2003), and 3) interactions of vestibular processing and neglect symptoms (Karnath & Dieterich, 2006; Rubens, 1985) have led to the claim to not only classify neglect as a higher visual deficit but also as a higher vestibular disorder (Brandt & Dieterich, 2017; Brandt et al., 2014). This strongly supports the notion of a functional link between the (spatial) attentional and vestibular systems (Arshad, 2017).

### d. Link between (spatial) attention, perceptual decision making, and the vestibular system

Activity in sensory areas can be biased by attention in such a way that attention facilitates processing of relevant input while it suppresses distracting information (e.g. Carrasco, 2011). In addition, attention has been shown to interact with multisensory integration. More precisely, it is assumed that attention modulates multisensory integration under conditions of high competition between successive or concurrent inputs to different sensory modalities (Talsma et al., 2010). Both perceptual decision making (Najafi & Churchland, 2018) as well as vestibular processing (Brandt & Dieterich, 1999) rely on successful integration of sensory information from the different senses and therefore are likely to be influenced by attention.

Although early decision making research mainly focused on unisensory stimuli (Najafi & Churchland, 2018), ecologically valid perceptual decisions require multisensory information and integration. Attention enables the weighting and biasing of sensory information processing according to its relevance to the decision at hand (Summerfield & de Lange, 2014). For example, altered saliency levels and predictions of a stimulus depending on whether it is attended or not, have been found to be key aspects of perceptual decision making (Heekeren et al., 2008; Summerfield & de Lange, 2014). Given this functional link between attention and perceptual decision making it is not surprising that they also share common underlying neural substrates such as the dorsal parietal cortex and the frontal eye fields (Hanks & Summerfield, 2017; Summerfield & de Lange, 2014), regions which are also core parts of the human multisensory vestibular network (Dieterich & Brandt, 2015; Lopez & Blanke, 2011; Smith, Greenlee, DeAngelis, & Angelaki, 2017; zu Eulenburg et al., 2012).

Accordingly, a tight coupling of vestibular processing with attention (and perceptual decision making) is likely to exist and has been supported by both behavioural and neurophysiological research.

In particular behavioural work on the relation between neglect and vestibular functioning has suggested a close connection between the spatial attention and vestibular systems. Intriguing similarities in biased gaze patterns during neglect and after vestibular stimulation have been described (Karnath & Dieterich, 2006). Neglect patients often show pathological deviations of eyes and head in the horizontal plane, directed towards the ipsilesional (typically right) side (Fruhmann-Berger, Proß, Ilg, & Karnath, 2006; Fruhmann-Berger & Karnath, 2005; Karnath, Fetter, & Dichgans, 1996). Vestibular stimulation can cause biases in eye and head position that closely resemble those of neglect patients. In detail, following unilateral vestibular failure constant shifts in gaze patterns and head position towards the affected side, occurring both at rest and during active motor performance, have been described (Karnath & Dieterich, 2006). On the other hand vestibular stimulation by means of unilateral caloric irrigation (Karnath et al., 1996; Sturt & Punt, 2013; Vallar, Bottini, Rusconi, & Sterzi, 1993) or optokinetic stimulation (Pizzamiglio et al., 2004; Reinhart et al., 2016; Schaadt et al., 2016) has been found to reduce or even normalize the pathological gaze patterns of neglect patients by inducing contralesional (i.e. typically leftward) gaze shifts (for a review see Rosetti & Rode, 2002). In line with this, unilateral vestibular stimulation can be used to mimic the biased gaze and ocular exploration patterns of neglect patients in healthy participants (Karnath et al., 1996).

Supporting neurophysiological research reported closely related findings regarding the neural substrates of neglect / spatial attention and vestibular processing, mainly involving right-hemispheric parietal, temporo-parietal and frontal areas (Karnath & Dieterich, 2006). The response amplitude of parietal neurons is not only influenced by the spatial position of a stimulus with respect to the retina but also by a number of non-retinal factors, such as vestibular information or posture (Andersen, Essick, & Siegel, 1985; Pouget & Driver, 2000; Pouget & Sejnowski, 2001). Gain-modulation of neurons in monkey parietal area 7a by vestibular (rotational) stimulation has been observed (Snyder et al., 1998). In a more recent fMRI study it was found that in addition to vestibular input another factor that modulates human parietal field representations is attention (Sheremata & Silver, 2015). Specifically, increased visual field extents of both hemispheres occurred when participants covertly attended a moving stimulus. This is consistent with improved performance of neglect patients regarding processing of stimuli within the contralesional hemifield due to enhanced levels of attention, e.g. by means of phasic alerting (Fimm, Willmes, & Spijkers, 2006; Matthias et al., 2010). Such enhancement of alertness levels can, among others, be achieved by means of vestibular stimulation leading to improved performance on visuo-spatial tasks (e.g. Ferrè, Longo, Fiori, & Haggard, 2013; Fink et al., 2003; Lenggenhager, Lopez, & Blanke, 2007; Utz, Dimova, Oppenländer, & Kerkhoff, 2010), supporting the notion of a vestibular-attentional coupling.

The previously described observations of neuronal gain-modulation by non-retinal factors, such as vestibular input or attention, are in agreement with the finding that a large number of parietal cells are of a multisensory nature. That is, they are sensitive to stimuli of different sensory modalities, such as visual, tactile, auditory, or vestibular information (e.g. Pouget & Driver, 2000), and are involved in the integration these different inputs (Bremmer, Duhamel, Hamed, & Graf, 1997) as well as in sensorimotor integration (Sereno & Huang, 2014). Accordingly, in many cases neglect not only affects performance in one sensory modality but emerges crossmodally (Driver & Spence, 1998; Funk, Finke, Müller, Preger, & Kerkhoff, 2010; Kerkhoff, 2001; Làdavas, Pellegrino, Farnè, & Zeloni, 1998). This is possibly linked to polymodal interactions between different sensory inputs found at a neural level in the IPS (Duhamel et al., 1998) – a multimodal processing region within the parietal cortex, which contains neurons that are involved in the perception of axis orientation in three-dimensional space (Sakata et al., 1997) and which is an essential cortical structure for the processing of vestibular information (Göttlich et al., 2014; Grefkes & Fink, 2005; Helmchen et al., 2011) as is described in more detail in the next part of this thesis.

## 1.2 Parietal and frontal cortex contributions to vestibular processing

### a. The “human vestibular cortex”

Knowledge about the anatomy and neurophysiology of the human central vestibular system mainly stems from studies using different types of vestibular stimulation (Palla & Lenggenhager, 2014) in combination with brain imaging techniques (Ertl & Boegle, 2019) as well as from neurological data from lesion studies in vestibular patients (Dieterich et al., 2003; Fasold et al., 2002; Suzuki et al., 2001). After initial peripheral sensing and processing of vestibular (linear and rotational head acceleration) information in the vestibular organs located in the inner ears (i.e. the three semicircular canals and two otolith organs in each ear), the detected signals are forwarded to cortical structures via vestibular pathways passing through vestibular nuclei in the brainstem, the reticular formation, cerebellum, hypothalamus, and thalamus (Dieterich & Brandt, 2018; Hitier, Besnard, & Smith, 2014). On a cortical level, a widespread network responding to vestibular stimulation has been identified and has been suggested to form the human “vestibular cortex” (Guldin & Grüsser, 1998), which shows striking similarities to the vestibular cortical network identified in monkey (Brandt & Dieterich, 1999; Lopez & Blanke, 2011; see Fig. 3). One core of this network includes the posterior insula, retroinsular region and parietal operculum and consequently has been termed the parietoinsular vestibular cortex (PIVC) (e.g. Dieterich & Brandt, 2018). In addition, other hubs of this network involve regions of the somatosensory cortex, lateral and medial frontal cortex, TPJ, and the dorsal parietal cortex (for reviews see e.g. Dieterich & Brandt, 2015; Frank & Greenlee, 2018; Lopez, Blanke, & Mast, 2012; Lopez & Blanke, 2011; Smith, Greenlee, DeAngelis, & Angelaki, 2017; zu Eulenburg, Caspers, Roski, & Eickhoff, 2012). Although the human “vestibular cortex” receives and processes afferent vestibular information bilaterally, it is assumed to be particularly lateralized to the non-dominant hemisphere (i.e. right handers show predominant activations of right-hemispheric vestibular regions while for left handers the left hemisphere is more strongly activated; Dieterich et al., 2003; Lopez et al., 2012; zu Eulenburg et al., 2012). Moreover, the human vestibular cortex is highly multisensory as most of the vestibular information which arrives at the cortical level becomes integrated with signals from other sensory domains (e.g. visual or somatosensory information), or has already undergone such multisensory integration in earlier processing steps, such as in the brainstem (Dieterich & Brandt, 2015; Guldin & Grüsser, 1998; Lopez & Blanke, 2011). In line with this, dysfunctional multisensory interaction and integration can cause clinical vestibular symptoms such as vertigo and dizziness (Dieterich & Brandt, 2008).

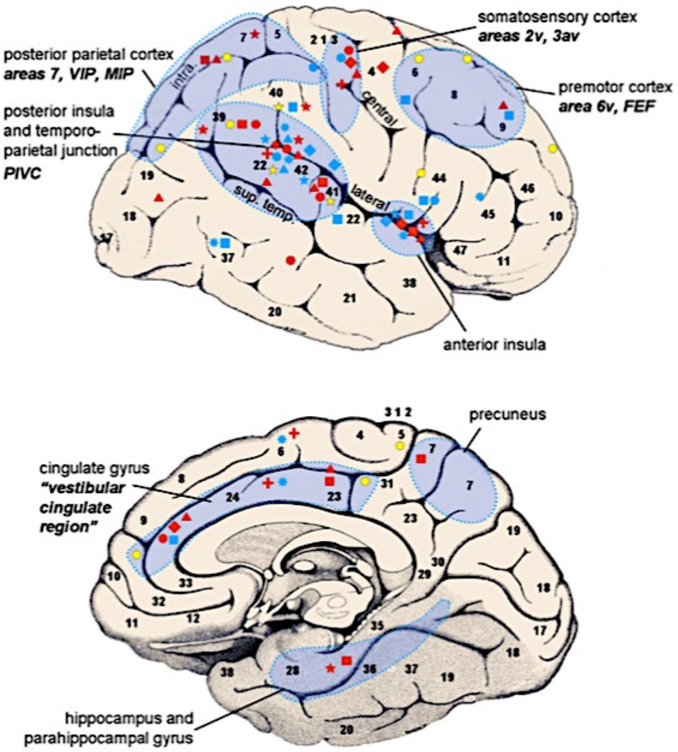

Figure 3: Schematic representation of the human vestibular cortex (adapted from Lopez & Blanke, 2011). Areas were revealed by neuroimaging work during vestibular stimulation (red symbols: caloric stimulation, blue symbols: galvanic stimulation, yellow symbols: short auditory stimulation). The numbers on the cortex refer to the cytoarchitectonic areas defined by Brodmann.

The aim of the present thesis is to investigate the interplay of the attentional, decision making and vestibular systems. As mentioned earlier, spatial attention is thought to be realized within a cortical network involving (right lateralized) parietal and frontal regions (Corbetta & Shulman, 2011) and perceptual decision making has also been associated with activations in these areas (Hanks & Summerfield, 2017; Summerfield & de Lange, 2014). In accordance with that, in order to establish a potential link between (spatial) attention, perceptual decision making, and the vestibular system, the following sections focus on parietal and frontal contributions to vestibular processing.

### b. Involvement of the parietal cortex in vestibular processing

Concerning the human parietal cortex functional imaging work using fMRI and PET protocols in combination with vestibular stimulation (Dieterich & Brandt, 2008; Lopez & Blanke, 2011) has reported vestibular related activations of the angular and supramarginal gyrus within the inferior parietal lobule (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bottini et al., 1994; Dieterich et al., 2003; Frank & Greenlee, 2014; Schlindwein et al., 2008; Stephan et al., 2005; Suzuki et al., 2001), the precuneus (Suzuki et al., 2001), the lateral superior parietal lobule (Vitte et al., 1996), and the IPS (Fasold et al., 2002; Suzuki et al., 2001). Corresponding to that (Lopez & Blanke, 2011), microstimulation and tracer studies in monkeys reported activations of area 7 (putative homologue to human inferior parietal lobe; Faugier-Grimaud & Ventre, 1989) and areas located at the fundus of the IPS (Bremmer, Klam, Duhamel, Ben Hamed, & Graf, 2002; Bremmer, Schlack, Duhamel, Graf, & Fink, 2001; Klam & Graf, 2003; Schlack, 2005; Schlack, Hoffmann, & Bremmer, 2002) in association with processing of vestibular information.

The IPS is located on the lateral surface of the parietal lobe and separates the parietal lobe into the superior parietal lobule (SPL) and the inferior parietal lobule (IPL). Electrophysiological and anatomical work in non-human primates has shown that the IPS contains a row of subregions, which are functionally distinct and highly interconnected with each other in a modular fashion (Grefkes & Fink, 2005). According to their topographical arrangement in the macaque IPS these subregions have been termed anterior intraparietal area (AIP), ventral intraparietal area (VIP), medial intraparietal area (MIP), lateral intraparietal area (LIP), and caudal intraparietal area (area CIP). Together they are crucially involved in the perceptual-motor coordination of eye and hand movements (Culham & Kanwisher, 2001; Grefkes & Fink, 2005). Moreover, the IPS has been linked to spatial information processing, visual attention, and plays an important role in the multisensory integration necessary for guiding and controlling action in space (Greenberg et al., 2012; Grefkes & Fink, 2005; Lauritzen et al., 2009; Silver & Kastner, 2009). In macaques a functional dissociation within the IPS has been described: whereas its anterior parts are linked to processing of sensorimotor information, posterior regions are rather concerned with visual information (Grefkes & Fink, 2005; Guipponi et al., 2013). Still, none of the subregions of the macaque IPS seem to respond to only one sensory modality, which highlights the importance of the IPS in multisensory processing (Grefkes & Fink, 2005) such as required during visual-vestibular interactions (Smith et al., 2017). With particular relevance for the present thesis, area VIP in the fundus of the IPS has been described as a key hub of the vestibular processing network (Lopez & Blanke, 2011). This area is closely connected to several visual areas (particularly middle temporal area (MT) and middle superior temporal area (MST)), as well as to motor, somatosensory, and auditory regions (Baizer et al., 1991; Lewis, 2000; Maunsell & van Essen, 1983). In addition, it receives vestibular information, responds to moving stimuli of different sensory modalities, and is consequently highly involved in the perception of self-motion and object motion (Bremmer et al., 2002; Colby et al., 1993; Schlack, 2005). Furthermore, it has been suggested that vestibular signals are processed flexibly in area VIP depending on perception and attentional demands (Chen et al., 2018). Functional imaging work in humans has found an area, which constitutes the human homologue of monkey area VIP (hVIP; Bremmer et al., 2001.; Guipponi et al., 2013; Konen & Kastner, 2008; Sereno & Huang, 2006). Similar to the monkey area, hVIP is located within in the fundus of the IPS, mostly anterior to the angular gyrus (Sereno & Huang, 2014). A vestibular role of area hVIP has further been described by recent non-invasive brain stimulation studies, which reported effects on multisensory processing (Konen & Haggard, 2014) as well as on postural sway (Kaulmann et al., 2017) following hVIP stimulation.

Evidence from human patient studies supports the involvement of the IPS, or parietal cortex more generally, in vestibular perception. Lesions to parietal structures have been found to be accompanied by vestibular dysfunctions and vice versa (Dieterich & Brandt, 2015). fMRI studies suggest that acute vestibular failure correlates with activity and glucose metabolism in the inferior and superior parietal lobules and the precuneus (Becker-Bense et al., 2014; Bense et al., 2004). Likewise, damage to the inferior parietal lobule has been linked to rotational vertigo (Nicita et al., 2010; Schneider et al., 2006; Urasaki, & Yokota, 2006). Electrical stimulation of the IPS applied to awake patients during brain surgery has been shown to cause various vestibular sensations such as feelings of full body rotation in space, falling sensations, perceived self-motion through space (both of the whole body or single body parts), or illusions of motion of objects which are actually fixed in space (Blanke, Perrig, et al., 2000). Similarly, there are reports that invasive stimulation of the precuneus (Kahane et al., 2003) and the posterior parietal cortex (Blanke, Perrig, et al., 2000; Kahane et al., 2003) elicits various vestibular illusions in epileptic patients, including sensations of body tilt and sway, rotation, dizziness, falling or even flying, and distortions of verticality perception (Kremmyda et al., 2019).

An increasing body of non-invasive brain stimulation studies (Ahmad et al., 2014; Ertl & Boegle, 2019) also points to a causal involvement of the parietal cortex in processing vestibular information. Several studies reported modulations of specific properties of the caloric-induced vestibular-ocular reflex (VOR) due to transcranial direct current stimulation (tDCS) over parietal cortical areas (Ahmad et al., 2014; Arshad et al., 2014, 2019; Kyriakareli, Cousins, Pettorossi, & Bronstein, 2013). In addition, parietal tDCS was found to alter thresholds of rotational self-motion perception (Kyriakareli et al., 2013) and to induce changes in tonic seated posture in stroke patients (Babyar et al., 2016). Distortions of distinct aspects of vestibular guided navigation, such as perceived changes of angular position in space (Seemungal, Rizzo, Gresty, Rothwell, & Bronstein, 2008a) or more general displacement perception (Seemungal, Rizzo, Gresty, Rothwell, & Bronstein, 2008b), have been observed following transcranial magnetic stimulation (TMS) applied over the posterior parietal cortex. A series of studies have suggested a causal role of the parietal cortex in verticality perception (Kheradmand & Winnick, 2017). Stimulation of different parietal areas such as the supramarginal gyrus (Kheradmand, Lasker, & Zee, 2015; Otero-Millan, Winnick, & Kheradmand, 2018), the temporo-parietal junction (Fiori et al., 2015; Santos et al., 2018; Santos-Pontelli et al., 2016), or the right superior parietal lobule (Lester & Dassonville, 2014) by means of tDCS or TMS has been found to lead to modulations of what is perceived as upright. Supporting the notion of a lateralization of the human vestibular cortex (Dieterich et al., 2003; Lopez et al., 2012; Schlindwein et al., 2008) the majority of these non-invasive brain stimulation studies reported stronger or exclusive stimulation effects when the stimulation was applied to right parietal structures in right-handers as compared to left-hemispheric or bilateral parietal stimulation (for a review see Kheradmand & Winnick, 2017).

### c. Involvement of the frontal cortex in vestibular processing

In addition to parietal areas, regions within the frontal cortex have also been proposed to belong to the human vestibular cortex (e.g. Dieterich & Brandt, 2015; Lopez et al., 2012; Lopez & Blanke, 2011). However, in contrast to the large amount of research regarding parietal contributions to vestibular perception in the human, studies concerning vestibular-related involvements of other cortical regions such as the frontal cortex are rather sparse. Brain imaging data in humans showed activations of frontal cortex areas including the inferior frontal gyrus (IFG) and operculum (Fasold et al., 2002; Frank & Greenlee, 2014; Lobel et al., 1998; Miyamoto et al., 2007), superior and middle frontal gyri (possibly representing oculomotor-related activation of the human frontal eye fields due to vestibular input; Bense et al., 2001; Blanke, Spinelli, et al., 2000; Fasold et al., 2002; Lopez & Blanke, 2011; Miyamoto et al., 2007; Paus, 1996; Petit, Clark, Ingeholm, & Haxby, 1997; Stephan et al., 2005), primary motor cortex (Bense et al., 2001), and premotor cortex (Emri et al., 2003; Lobel et al., 1998; Miyamoto et al., 2007) due to vestibular stimulation. Regarding frontal activations in animals, the primary motor cortex, premotor cortex and dorsomedial frontal cortex (dMFC) seem to be predominant in receiving and processing vestibular input (Ebata et al., 2004; Fukushima et al., 2010; Fukushima, Sato, Fukushima, Shinmei, & Kaneko, 2000; Lopez et al., 2012; Lopez & Blanke, 2011; Sugiuchi, Izawa, Ebata, & Shinoda, 2005). In monkeys these areas are crucial for (oculo-) motor functioning. Thus, activations found there might not only represent processing of vestibular information but in addition are likely to reflect oculomotor activations related to vestibular perception (e.g. the generation and suppression of the vestibulo-ocular reflex; Ebata et al., 2004; Fukushima et al., 2000, 2010; Lopez & Blanke, 2011).

The dMFC is located on the dorsal brain surface anterior to the motor cortex. It lies anterior to the precentral sulcus and is surrounded by the superior frontal sulcus and cingulate cortex (Tehovnik et al., 2000). Behaviorally, the dMFC has been linked to various oculomotor functions such as the integration of oculomotor and skeletomotor behavior and visuo-motor learning (Tehovnik et al., 2000). Accordingly, a high connectivity between the dMFC and other visual, motor, and oculomotor centers has been observed in monkeys and humans. Moreover, in humans this region is associated with higher-level cognitive and social functions such as social judgments, “theory of mind”, and perceptual decision making (Ferrari et al., 2016; Keuken et al., 2014; Sallet et al., 2013). In a human fMRI study four areas within the dMFC were identified, including the supplementary motor area (SMA), presupplementary motor area (preSMA), prefrontal areas, and frontal polar areas (Sallet et al., 2013). Functionally, similar functional coupling patterns of these four areas with the frontal, medial prefrontal, and dorsal prefrontal regions to those observed in the macaque were reported. In addition, the preSMA within the dMFC is thought to be an essential part of a task general network for perceptual decisions in which it is specifically involved in setting response thresholds (Keuken et al., 2014). Recent imaging work has shown that the preSMA is modulated by task difficulty and exhibits close connections to the striatum, dorsolateral prefrontal cortex, IPS, IFG, and the insula (Keuken et al., 2014; Neubert et al., 2010; Swann et al., 2012; Weigard et al., 2019). As mentioned earlier the IPS, IFG, and insula are key hubs of the human vestibular network (e.g. Baier et al., 2012; Dieterich & Brandt, 2019; Lopez & Blanke, 2011; Smith et al., 2017; zu Eulenburg et al., 2012). The functional connectivity of these areas with the dMFC speaks in favor of a role of the dMFC in processing vestibular information.

Indeed, in line with the above described correlational brain imaging work in humans, neurological data in epilepsy patients (Hewett & Bartolomei, 2013) also revealed frontal contributions to vestibular perception. Links between epileptic seizures in frontal regions and sensations of rotational vertigo have been found (Hochman, 1983; Joseph & Chand, 1993; Kluge, Beyenburg, Fernandez, & Elger, 2000; Lopez, Heydrich, Seeck, & Blanke, 2010), which in turn have been associated with out-of-body and disembodiment illusions (Lopez et al., 2010). Similarly, electric stimulation of the frontal cortex can cause feelings of vertigo and dizziness (Kim, Sunwoo, & Lee, 2016) and lead to further vestibular perceptions such as body sway and motion (Kahane et al., 2003). Lesions involving the inferior frontal gyrus (and in particular the inferior operculum) seem to be related to disturbed verticality perception

(Konzelmann, 2013) and visual orientation discrimination (Kim, Morrow, Passafiume, & Boller, 1984).

In summary, there is a broad indication that the parietal as well as the frontal cortex (despite the literature situation being far more limited regarding the latter) critically contribute to vestibular processing. This is also supported by work showing strong functional connectivity between parietal and frontal areas and the PIVC, the core of the human "vestibular cortex" (Frank & Greenlee, 2018; Wirth, Frank, Greenlee, & Beer, 2018). In particular, due to their functional connectivity profiles with other vestibular key regions areas hVIP and the dMFC are likely to play a role in vestibular processing. Moreover, these areas are not only part of the human cortical vestibular system but also form a functional network for spatial attention and decision making (Corbetta & Shulman, 2002, 2011; Hanks & Summerfield, 2017) and are of a highly multisensory nature (Brandt, Strupp, & Dieterich, 2014; Dieterich & Brandt, 2015, 2018). Therefore, it seems plausible that manipulation of activity within these areas, for example by means of non-invasive brain stimulation, could modulate vestibular-related perception. The studies of the present thesis aimed to shed more light on this question. To that end, effects of parietal (hVIP) and frontal (dMFC) brain stimulation on a fundamental vestibular-related perceptual process - verticality perception - were examined. Studying verticality perception seems to be particularly suited for investigating the interplay of the vestibular and attentional systems as it has been shown to be related to both of these, which will be described more closely in the following section.

### 1.3 The subjective visual vertical (SVV)

A standard test within the clinical routine of vestibular patients is the examination of their verticality perception. It is assumed that precise and stable perception of verticality is dependent on incoming multisensory signals from the visual, somatosensory, postural motor, and vestibular systems (Baier & Dieterich, 2014; Utz et al., 2011). In order to reach a final percept of what is upright these signals need to be integrated into an internal model (Barra et al., 2010; Bonan et al., 2015; see Fig. 4). Verticality perception can be behaviorally analyzed in terms of the subjective visual vertical (SVV), which provides a measurement of the deviation of the subjectively perceived vertical axis from the true physical vertical within the roll plane (Van Nechel et al., 2000). The SVV task typically requires participants to align a visually presented line until they perceive it as being upright or, in case of a 2AFC task version, to judge the tilt direction of a flashed line or Gabor patch (clockwise vs. counterclockwise tilt). Healthy participants can usually perform the SVV task effortlessly with an accuracy of < 2 - 2.5 degree (Brandt, Dieterich, & Danek, 1994; Lopez, Lacour, Ahmadi, Magnan, & Borel, 2007), whereas patients suffering from injury to the either peripheral or central nervous structures can show severe pathological tilts in this task (Brandt et al., 1994; Brandt & Dieterich, 1994; Yelnik et al., 2002). These deviations in SVV can be due to impairments regarding initial verticality perception stages, during which the different sensory inputs are processed separately, as well as from the ensuing multimodal comparison and integration steps of those inputs (Van Nechel et al., 2000).

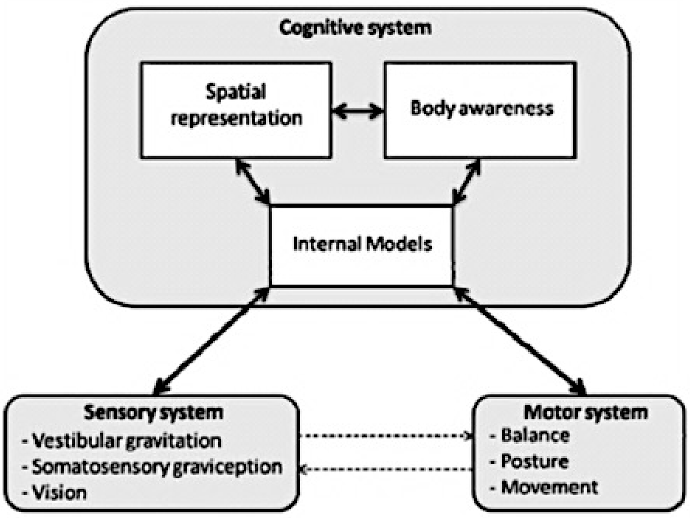

Figure 4: Model of verticality representation (from Barra et al., 2012). The final verticality/SVV percept is determined by bottom-up sensory and motor information and the influence of top-down processes from cognitive systems.

Human imaging and lesion studies suggest that there is no key brain region for the required integration of the different sensory input sources (Baier, Suchan, Karnath, & Dieterich, 2012).

Rather, several central multisensory brain areas such as the posterolateral thalamus (Barra et al., 2010; Brandt & Dieterich, 1994), posterior insula (Brandt et al., 1994), temporal gyrus (Rousseaux et al., 2015), and right parietal cortex (Baier et al., 2012; Darling, Pizzimenti, & Rizzo, 2003) seem to contribute to this process and have been suggested to form a large network responsible for verticality perception with dominant contributions coming from vestibular structures (Baier & Dieterich, 2014; Van Nechel et al., 2000). Accordingly, brain injury to a number of subcortical and cortical areas including a range of (predominantly right-hemispheric) parietal regions can lead to pronounced tilts of the SVV. These tilts can remain unrecognized by the affected patients (Kerkhoff & Zoelch, 1998) despite the fact that they severely impair balance and gait ability and correlate with subjective vestibular disability (Bonan et al., 2007; Pérennou et al., 2008). Furthermore, they are associated with distinct postural disorders such as lateropulsion and pusher syndrome (for a review see Pérennou et al., 2014). Notably, the precise location of the lesion is important for determining both the direction of the tilt as well as its degree (Brandt & Dieterich, 1994). Specifically, it has been shown that lesions involving structures of the right hemisphere cause more severe tilts of the SVV as opposed to left-hemispheric lesions, pointing to a dominance of the right hemisphere in verticality perception (Baier et al., 2012; Baier & Dieterich, 2014) comparable to the earlier described right hemispheric dominance regarding vestibular processing in general as well as in spatial attention.

Several studies (e.g. Bonan, Leman, Legargasson, Guichard, & Yelnik, 2006; Kerkhoff & Zoelch, 1998; Utz et al., 2011) have suggested a close relationship between verticality perception and visuo-spatial attentional performance. Stroke patients suffering from neglect demonstrate a more severe tilt of the SVV than stroke patients without neglect symptoms (Bonan et al., 2006; Saj, Honoré, Bernati, Coello, & Rousseaux, 2005). Likewise, postural disorders due to impaired verticality perception have been associated with neglect (Honoré et al., 2009). Verticality perception depends not only on bottom-up influences and low-level interactions between visuo-spatial and vestibular processes (see Fig. 4; Barra et al., 2012; Clément et al., 2009) but also on the creation of an internal model of one's environment, which in turn relies on directions given from both ego- and allocentric reference frames (Barra et al., 2010). Parietal neurons have been found to be crucial for the formation of those reference frames (Barra et al., 2010; Borel, Lopez, Péruch, & Lacour, 2008; Pouget &

Sejnowski, 2001) as they are involved in the remapping and spatial transformation of coordinates coming from different sensory modalities (Sereno & Huang, 2014). In accordance with this, lesions studies in neglect patients suggest that the integration of egocentric and allocentric coordinate information is achieved within a parieto-temporal-occipital network including the IPS (Chechlacz et al., 2010). Similarly, in a study on the influences of top-down cognitive factors on verticality perception it was found that parietal neurons along the IPS are critical for becoming aware of the position of one's own body in space and, in turn, for successful SVV estimates (Barra et al., 2012).

Again, as a further link between spatial attention and verticality perception, neglect can occur within different reference frames depending on the exact site and size of the brain lesion (Chechlacz et al., 2010; Doricchi & Galati, 2000; Driver & Pouget, 2000; Olson, 2003) and also the SVV can be distorted with respect to different modalities such as the visual, haptic, and postural domain (Pérennou et al., 2014). Furthermore, such distortions were found to be associated with each other and dependent on neglect severity (Kerkhoff, 1999; Perennou et al., 2008). This might be attributed to the multisensory quality of neurons of core parts of the human cortical vestibular network, which process vestibular information arriving from the peripheral vestibular organs and at the same time respond to somatosensory, optokinetic, and/or visual information (Baier & Dieterich, 2014; Karnath & Dieterich, 2006). As already mentioned above, successful verticality perception (like spatial attention and perceptual decision making) relies on the successful integration of information coming from different sensory modalities, which consequently might also be achieved by such a "multisensory vestibular cortex" (Baier & Dieterich, 2014; Darling et al., 2003), including dorsal parietal regions such as the IPS (Karnath & Dieterich, 2006) or the ventral intraparietal area (VIP) in the fundus of the IPS (Bremmer et al., 2002; Chen et al., 2011).

Considering all these similarities and links between spatial attention and verticality perception, it is feasible that spatial attention interacts with the integration of vestibular inputs with information from other sensory domains required for perceptual decision of what is upright, such as vision. This question was addressed in the two studies presented in this thesis by means of 2AFC paradigms using SVV stimuli. In addition, in order to be able to not only draw correlative conclusions about the relation between spatial attention, perceptual decision making and vestibular processing, but to further investigate the causal role of specific parietal and frontal regions in vestibular perception, these SVV paradigms were combined with a neuroscientific research tool that allows establishing causal brain-behavior relationships: transcranial magnetic stimulation (TMS).

## 1.4 Fundamentals of TMS-EEG

### a. TMS

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique. In the 1870s it was reported that current applied to the open brain led to action potentials in the human cortex (Fritsch & Hitzig, 1870). A century later, it became possible to evoke contractions of arm and hand muscles by means of brain stimulation through the intact scull, without the participant reporting any pain (Barker et al., 1985). This was achieved by TMS. Since then, TMS has become an increasingly popular neuroscientific method for manipulating cortical activity in humans (Hallett, 2007; Pascual-Leone, 2000; Walsh & Cowey, 2000). Magnetic stimulation is based on the principle of electromagnetic induction (see Fig. 5). During discharge a transient magnetic field is created around the TMS coil, which is positioned on the head. The magnetic field is proportional to the current intensity and induces an electrical field perpendicular to it for about 100-200µs. When the magnetic field within the coil builds up and decays again, an electric current is induced, which is used for stimulating cortical areas located beneath the coil through the intact scalp (Ruohonen & Ilmoniemi, 2002). Depending on the orientation of the electrical field with respect to the neuronal membrane, its intensity and its duration, the pulse either depolarizes or hyperpolarizes the stimulated cortical neurons (Siebner & Ziemann, 2007). Nerve cells located at superficial cortical layers are more amenable to this type of stimulation than cells from lower structures as the strength of the magnetic field decays quadratically with increasing distance to the coil (Ridding & Rothwell, 2007). Generally, the depth range of a standard TMS coil is about 1-6 cm at maximum intensity (Hess et al., 1987). Despite the produced magnetic fields being very focal in contrast to other, more direct brain stimulation techniques (e.g. microstimulation), TMS allows the stimulation of networks of neurons but not of single cells alone. Moreover, varying orientation, position or material of the coil have been shown to have significant effects on the spatial resolution of TMS and thus, need to be carefully taken into consideration when designing TMS experiments (Stokes et al., 2005).

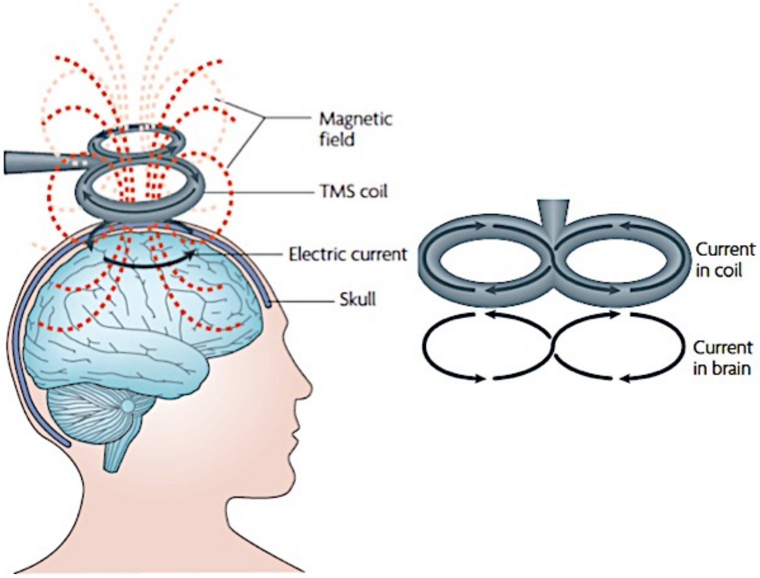

Figure 5: Physics of TMS (adopted from Ridding & Rothwell, 2007).

Neuroscientific research can benefit greatly from TMS as it helps to overcome a limitation of many of today's neuroscientific research techniques (e.g. fMRI, EEG, PET), which is that those methods are only able to make inferences about the correlation between the activity of a certain brain area and a cognitive function. By contrast, TMS can be used to establish causal brain-behavior relationships as it selectively activates or deactivates neurons of the stimulated brain area. This possibility to induce temporary activity changes within roughly delimited brain regions in participants by means of TMS allows the study of the causal role of specific brain regions in different cognitive processes and behavior. By investigating the effects of stimulation of a particular brain region on certain aspects of behavior (e.g. reaction times or accuracy) sensory and higher brain functions can be mapped. For instance, TMS has been used to identify functional specialization of brain areas with respect to distinct attentional functions (Walsh & Cowey, 2000) and to examine attentional competition between hemispheres or within specific brain areas (Dambeck et al., 2006; Walsh et al., 1998). In addition, there is growing interest in the clinical use of TMS for the treatment of different neurological and psychiatric patient groups, as well as for the diagnostics of movement disorders and central motor pathways (Ziemann, 2017).

TMS has been used to study both verticality perception as well as perceptual decision making. It has been shown that offline theta-burst stimulation to specific parts of the parietal cortex, such as the supramarginal gyrus (Kheradmand et al., 2015), superior parietal lobule (Lester & Dassonville, 2014), or the temporo-parietal junction (TPJ; Fiori et al., 2015) can induce significant transient deviations of SVV biases in healthy participants. Likewise, shifts in verticality perception biases following transcranial direct current stimulation of the TPJ have been reported (Santos et al., 2018; Santos-Pontelli et al., 2016). However, such shifts could only be reported under conditions where the participants' SVV was already biased due to e.g. tilted head positions (Kheradmand et al., 2015) or rod-and-frame effects (Lester & Dassonville, 2014) or when SVV tasks were used that required participants to verbally instruct an examiner to align a test line to the perceived vertical (Fiori et al., 2015; Santos et al., 2018; Santos-Pontelli et al., 2016). In the latter case it cannot be ruled out that the respective stimulation effects did not only emerge from modulated perceptual processes related to verticality perception but potentially also from altered processing at other stages. Moreover, all mentioned earlier studies used offline stimulation protocols. In contrast, in study 1 of this thesis, SVV performance was measured during ongoing brain stimulation in order to investigate immediate effects on brain activity and the relationship to behavior. Moreover, this study was the first to combine brain stimulation with concurrent brain imaging (using EEG) during a SVV task, which allowed to not only assess behavioral consequences of the stimulation, but in addition to examine associated effects on brain activity patterns.

With respect to perceptual decision making, non-invasive brain stimulation work has mainly focused on stimulation of the frontal cortex. In a recent TMS study it has been shown that stimulation of the preSMA within the dMFC modulated decision thresholds (Berkay et al., 2018). These findings were in line with earlier work that in addition reported an accuracy bias associated with increased decision thresholds due to preSMA inhibition induced by means of TMS (Tosun et al., 2017). Thus, TMS can be used to modulate perceptual decision making performance. Moreover, these studies point to a role of the dMFC in response selection during perceptual decision making. A row of earlier brain stimulation work has indicated that the dMFC might, however, not only be involved in response selection in general. Rather it seems that it selectively plays a role in conditions where not only response conflicts occur but where at the same time perceptual selection demands are high (Becker et al., 2014; Duque et al., 2013; Taylor et al., 2007). Using a visuo-motor task in combination with TMS stimulation of the dMFC and primary motor cortex (M1) it has been reported that dMFC stimulation affected M1 activity and in turn response switching. Again, this could however only be found when perceptual demands were high (Duque et al., 2013), suggesting that the dMFC is particularly involved in perceptual decision making when perceptual processing is difficult. In accordance with that, effects of dMFC TMS on motor cortex activity under conditions where action reprogramming was required have been described (Mars et al., 2009; Neubert et al., 2010). To what extent the dMFC contributes to perceptual decision making in a visual-vestibular context (such as during verticality judgments) has, however, not been investigated so far. Study 2 of this thesis aimed at shedding more light on this question by applying dMFC TMS during a SVV task of varying levels of perceptual demand.

Although TMS offers important advantages over other neuroscientific methods it also has limitations. While TMS can be used to draw conclusions about even subtle changes in behavior caused by altered cortical activity following the stimulation, the temporal patterns of the induced alterations of cognitive processes cannot be inferred from it. Moreover, potential spreads of activity modulation from the targeted stimulation areas to other brain regions cannot be studied using TMS alone (Sack & Linden, 2003). In order to overcome these drawbacks TMS has to be combined with other neuroimaging methods such as PET or fMRI (Bestmann et al., 2004; Fox et al., 1997; Paus et al., 1997; Sack & Linden, 2003) or, particularly if the temporal dynamics of the stimulation effects are of interest, with electroencephalography (EEG) (Bestmann & Feredoes, 2013; Miniussi & Thut, 2010; Taylor, 2018; Taylor & Thut, 2012; Taylor, Walsh, & Eimer, 2008).

### b. EEG

Cognitive processing is determined by several subcomponents within the processing stream. In order to disentangle those components, neuroscientific methods providing high temporal resolution are required. Recording electrical activity of the cerebral cortex by means of electroencephalography (EEG) offers this ability. By placing multiple electrodes along the scalp surface cortical activity related to neurophysiologically separate processing stages (ranging from early sensory processing to the motor output) can be measured on a millisecond scale (Luck, 2005). The EEG recording reflects electrical signals which are generated by simultaneous postsynaptic activity of firing neurons (Peterson et al., 1995). By averaging across voltage deflections of these signals locked to specific time points or events (such as the presentation of a stimulus), so called event-related potentials (ERPs) can be derived. By this means, a number of ERP components have been linked to different sensory, cognitive and motor processes. Apart from the time-locked ERPs another way to associate cognitive processes with brain activity patterns using EEG is to analyze oscillations of the EEG signal. Similar to ERPs, in the past almost every cognitive process has been related to either an event-related EEG oscillation or oscillation at rest (Herrmann et al., 2016). Comparing different properties of ERPs or oscillations (e.g. amplitude, latency or topography across the scalp) across different tasks, populations, or time points allows investigation of the neurophysiological mechanisms related to the processing of particular stimuli with a high temporal resolution. This has contributed greatly to a better understanding of the (particularly temporal) link between brain activity patterns and various behavioral functions. However, although several source localization techniques have been developed over the years, the exact intracranial source of a scalp-recorded EEG signal cannot be determined solely based on EEG data. Moreover, in contrast to TMS, EEG data are not suitable for deriving causal structure-function relationships but can only provide correlative information. Combining EEG measurements with TMS can thus offer substantial advantages for investigating causal involvements of brain regions in behavior and cognition, which will be discussed in the following section of this thesis.

### c. TMS-EEG

As described earlier, TMS offers the advantage to infer causality between brain structure and behavior. However, it does not allow the identification of cortical responses to the stimulation and cannot show potential activation spread from the stimulated area to other brain regions, especially if those are not accessible for TMS (e.g. if they are located too deeply within the brain). By comparison, EEG offers insights into temporal dynamics of different stages of processing which are, however, only of a correlational nature. By combining TMS with concurrent EEG recordings of brain activity the limitations of both of these two methods can be overcome and valuable causal information about the timing of the interaction of activity in different cortical areas can be gained. The integration of the temporally and focally precise TMS stimulation with the high temporal resolution of EEG reveals information about both the activation sequence of cortical regions and their causal involvement in behavior. Recent technical developments have made the (online) combination of TMS-EEG possible by offering TMS compatible EEG electrodes. Beyond that, combined TMS-EEG presents the challenge of artefacts in the EEG, observed shortly following the pulses. These result from the electromagnetic discharges from the TMS coil and are several fold larger than the actual EEG potentials (Ilmoniemi et al., 1997). Recent technical and scientific developments have offered several hard- and software solutions to overcome this problem, such as adapted EEG amplifiers or offline artifact removal methods (Daskalakis et al., 2012; Hill et al., 2016).

Due to this methodological progress TMS-EEG can be used to study several neuroscientific questions: modulations of the electrophysiological response of a cortical area following the stimulation (so called TMS-evoked potentials, TEPs), alterations of ongoing rhythmic brain activity (oscillations) due to the stimulation and causal consequences for behavior, and TMS induced modulation of functional cortical networks. Thus, TMS-EEG provides the opportunity to causally assess functional dynamics of the neurophysiological state of the cortex and the associated effects on behavior. TMS-EEG has been quiet intensively used for studying visual attention (Taylor & Thut, 2012). However, although there is growing interest in investigating vestibular processing using TMS or other non-invasive brain stimulation techniques there is, so far, hardly any work that combines brain stimulation with imaging methods, let alone EEG (Ertl & Boegle, 2019). One exception is the first study presented in the present thesis (chapter 2.1) which applied a TMS-EEG paradigm in order to study the causal role of the IPS within the dorsal parietal cortex in verticality judgments, on both behavioral and neurophysiological levels.

## 1.5 Aims of the present thesis

This thesis comprises two experimental studies that aim to investigate the interplay between the vestibular, (spatial) attention, and perceptual decision making systems. To that end, distinct features of verticality perception assessed by means of 2AFC SVV paradigms were examined.

The first study (chapter 2.1) was concerned with the role of the right IPS in verticality judgments. As described earlier this area has been related to spatial attention, vestibular processing, and multisensory integration and is therefore likely to play an essential role in verticality perception. Although earlier work has reported detrimental effects of TMS stimulation on SVV performance in healthy participants (Fiori et al., 2015; Kheradmand et al., 2015; Otero-Millan et al., 2018), modulation of IPS activity by means of online TMS as applied in this study was not previously found to result in increased SVV biases. By contrast here a facilitatory effect of the stimulation was expected as 1) in lesion studies examining patients with pathological SVV deviations the IPS does not usually show up, 2) the mentioned previous studies stimulated areas located much more ventrally, and 3) parietal TMS has been shown to reduce the inhibition of other sensory and cognitive processes which normally occur due to parietal activity, in this way leading to so-called "paradoxical facilitation" of behavioural performance (Corbetta & Shulman, 2011; Duecker & Sack, 2015; Hilgetag, Théoret, & Pascual-Leone, 2001). In addition, in order to draw conclusions about the timing of potential TMS effects on behavioural performance and to study electrophysiological modulations of cortical activity following the stimulation, concurrent EEG was applied.

In the second study (chapter 2.2) highly similar SVV stimuli were used to establish a possible link between vestibular processing and perceptual decision making. EEG analysis of the first study revealed effects over midline frontal electrodes related to individual SVV biases and demonstrated the importance of taking resting baseline SVV biases into account when examining TMS effects on verticality perception. In line with that, the second study employed an offline theta-burst protocol to the dorsal medial frontal cortex (dMFC), a cortical area that has been associated with perceptual decision making in general and uncertainty of perceptual decisions in particular (Berkay et al., 2018; Tosun et al., 2017). Moreover, the dMFC is closely connected to core vestibular areas (Baier et al., 2012; Keuken et al., 2014; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Swann et al., 2012; Weigard, Beltz, Reddy, & Wilson, 2019) and has been associated with postural ability (Schöberl et al., 2017) and vestibular information processing (Fasold et al., 2002). The same SVV task as in the first study was used to classify participants based on their resting SVV bias. In addition, in order to vary perceptual and attentional demands, SVV judgments had to be made in a visual search setting that encompassed different levels of perceptual and response demands.

# 2 Projects

The following chapter contains two original studies: One peer-reviewed, published study (chapter 2.1) and one manuscript submitted for publication (chapter 2.2).

## 2.1 Project 1: Egocentric processing in the roll plane and dorsal parietal cortex: A TMS-ERP study of the subjective visual vertical.

This study has been published as Willacker, L., Dowsett, J., Dieterich, M., & Taylor, P.C.J. (2019). Egocentric processing in the roll plane and dorsal parietal cortex: A TMS-ERP study of the subjective visual vertical. *Neuropsychologia, 127,* 113-122.

Author contributions:

Lina Willacker and Paul C.J. Taylor conceived the experiment. Lina Willacker and James Dowsett programmed the experiment. Lina Willacker collected the data and analyzed the data with help of James Dowsett. Lina Willacker wrote the paper, which was commented and revised by Paul C.J. Taylor and Marianne Dieterich. Lina Willacker is the only first author of this paper.

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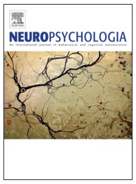

# Egocentric processing in the roll plane and dorsal parietal cortex: A TMS-ERP study of the subjective visual vertical

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ABSTRACT

The intraparietal sulcus within the dorsal right posterior parietal cortex is associated with spatial orientation and attention in relation to egocentric reference frames, such as left or right hemifield. It remains unclear whether it plays a causal role in the human in the roll plane (i.e. when visual stimuli are tilted clockwise or anticlockwise) which this is an important aspect of egocentric visual processing with clinical relevance in vestibular disorders. The subjective visual vertical (SVV) task measures the deviation between an individual's subjective vertical perception and the veridical vertical, involves the integration of visual, and vestibular information, and relies on a distributed network of multisensory regions that shows right lateralization and inter-areal inhibition. This study used combined TMS-EEG to investigate the role of the human dorsal parietal cortex in verticality perception using the SVV task in darkness. Participants were sorted according to their baseline bias at this task i.e. those with either a slight counterclockwise versus clockwise bias when judging a line to be truly vertical. Right parietal TMS facilitated verticality perception, reducing the difference between groups. ERPs suggested that the behavioral TMS effect occurred through normalizing individual SVV biases, evident frontally and late in the trial, and which was abolished after right parietal TMS. Effects were site and task specific, shown with a homologous left hemisphere control, and a landmark task performed on the same stimuli. These results support a right lateralization of visual-vestibular cognition and a distinct representation of the roll plane for egocentric processing in dorsal parietal cortex.

## 1. Introduction

Posterior parietal cortex has been associated with the co-ordination between different sensorimotor representations. Transforming one reference frame into another allows, for example, relating visual information to that from other systems. Verticality perception (e.g. discriminating the orientation of a line tilted off-vertical, a common psychophysical task) relies on afferent information coming from visual, somatosensory, and vestibular systems (Brandt and Dieterich, 2017; Utz et al., 2011), which need to be integrated into an internal model (Barra et al., 2010; Bonan et al., 2015). Behaviorally, verticality perception can be assessed by means of the subjective visual vertical (SVV) task, a measurement of the deviation of the perceived vertical axis from the physical vertical within the roll plane (Van Nechel et al., 2001). In the SVV task the participant is asked to relate or align the orientation of an external visual cue with their perception of what is upright. This task engages the vestibular system, and indeed the SVV is used as a clinical tool to measure disturbances within the vestibular system (e.g. Dieterich and Brandt, 1993) as shown from converging evidence (reviewed in e.g. Dieterich and Brandt, 2015) ranging from patient lesion (Baier et al., 2012a,b) to computational modelling studies (Glasauer et al., 2018). The nature of any causal involvement of human dorsal parietal areas in SVV however remains unclear, but would be in agreement with the finding that a large number of parietal neurons are sensitive to stimuli from different sensory modalities (e.g. Pouget and Driver, 2000) and are involved in integrating them (Bremmer et al., 1997).

Interactions between different sensory signals are found at a neural level in the intraparietal sulcus (IPS, Duhamel et al., 1998) – an essential cortical structure for the processing of vestibular information (Göttlich et al., 2014; Grefkes and Fink, 2005; Karnath and Dieterich, 2006) comprising neurons which are involved in the perception of axis

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orientation in three-dimensional space (Sakata et al., 1997) and including the macaque ventral intraparietal area (VIP) in the IPS fundus (Bremmer et al., 2002; Chen et al., 2011; Laurens et al., 2017). TMS of medial parietal regions at alpha-frequency (10 Hz) can bias processing in different modalities and it has been postulated that this frequency may be important for VIP contributions to multimodal processing (Heed et al., 2015). Studies that have targeted a human analogue of VIP with TMS have found effects indicative of multisensory processing (Konen and Haggard, 2014) and on postural sway, suggesting a vestibular role (Kaulmann et al., 2017).

Interference to parietal cortex has been modelled in terms of disinhibition, whereby the parietal cortex normally inhibits or competes with other processes. If parietal disinhibition is reduced by stimulation or lesions, this leads to so-called "paradoxical facilitation" (Corbetta and Shulman, 2011; Duecker and Sack, 2015; Hilgetag et al., 2001; Kinsbourne, 1977). Reciprocal inhibition between sensory systems, in particular between visual and vestibular systems, may be key to understanding not only vestibular function but also dysfunction (Brandt et al., 2012; Dieterich and Brandt, 2015) such as the enhanced visual activation after vestibular failure (Dieterich et al., 2007), or the deactivations in vestibular cortex during visually induced self-motion perception (Brandt et al., 1998), attenuating the sensory consequences of action within a predictive coding framework (Klingner et al., 2016). The current study attempts to combine the parietal and visual-vestibular inhibition accounts, to investigate the role of dorsal parietal cortex in verticality judgments. To this end, a combined TMS-EEG SVV paradigm is used to investigate the causal contribution of the human dorsal parietal cortex in verticality perception. We report evidence for egocentric roll-plane specific processing from a right-lateralised network that normally finds balance between visual and vestibular systems (Brandt and Dieterich, 2017). It was hypothesised here that disrupting visual processing through parietal TMS would lead to facilitation of vestibular processing, improving performance at the SVV task (through paradoxical facilitation). Whereas normally participants would be expected to show inaccuracies (biases) at this task at baseline, these biases would be reduced by TMS. A control task was used to test whether any effects were specific to processing in the roll plane, a control site (left hemisphere stimulation) to rule out for non-specific effects of TMS, and online ERP was used to measure whether the effects of TMS included aspects of processing that were normally modulated in cognition without stimulation. By contrast, previous studies have found TMS to increase the SVV tilt away from the stimulated side by disrupting much more ventral areas, which show up in lesion analysis in patients with abnormal SVV (Baier et al., 2012; Barra et al., 2010; Brandt and Dieterich, 2017; Perennou et al., 2014). IPS does not usually show up in these lesion analyses despite being associated with the processes involving egocentric spatial cognition, visual-vestibular processing and spatial attention (e.g. Duhamel et al., 1998; Konen and Haggard, 2014; Laurens et al., 2017). Accordingly, IPS TMS then here was not expected to lead to abnormal SVV tilt in one direction, but rather to facilitate performance when visual information had to be processed in the egocentric roll plane.

## 2. Materials and methods

### 2.1. Participants

32 healthy right-handed (Oldfield, 1971; Salmaso and Longoni, 1985) participants (16 males, mean age: 27.4 ± 0.9 years) took part in the study. This sample size was chosen to facilitate reliability of the grand averages after splitting the participants into two groups according to SVV bias (see below). All participants had normal or corrected-to-normal vision. Participants had no history of vestibular symptoms, nor of any neurological disorders, and all baseline SVV measurements (see below) were within the normal range ($-2^\circ$ to $+2^\circ$). Written informed consent according to established safety guidelines for TMS research (Rossi et al., 2009; Wassermann, 1998) was obtained from all participants and the study was approved by the ethics committee of the medical faculty of the Ludwig Maximilian University of Munich. Participants received either 10€ per hour or course credits for participation.

### 2.2. TMS

TMS was delivered using a MagPro ×100 machine (Magventure, Denmark) with a figure-of-eight coil (MCF-B70, outer winding diameter: 97 mm). In the TMS blocks repetitive trains of 6 pulses were applied on every trial starting at visual stimulus offset, with a frequency of 10 Hz and an intensity of 110% of the individual active motor threshold (mean intensity: 48% ± 1% of maximal stimulator output). The TMS coil was held by the experimenter with the handle pointing backwards. The target sites were defined anatomically based on individual structural 3T MRI scans as the point on the intraparietal sulcus nearest the dorsal tip of the suprmarginal gyrus. This region is comparable to the most dorsal (and TMS-accessible) part of a large visual-vestibular region shown in recent fMRI and DTI studies to extend from there into the intraparietal sulcus where it includes a suggested potential human homologue of monkey VIP (Frank et al., 2016; Smith et al., 2017). TMS sites were marked on each participant's structural MRI scan using infrared stereotactic registration (Brainsight, Rogue Research, Canada), and converted into MNI space (mean MNI (x,y,z) coordinates of right parietal sites: 45, −40, 56; the homologous left hemispheric control site: 41, −48, 55; Fig. 1A). Note that inter-individual variability in the position of the suparmarginal gyrus in standard (MNI) space on an average reference brain leads to some spread within the cluster of TMS sites: the variability here corresponds well with reported previously in the literature for gyral features (e.g. Mayka et al., 2006). In addition, the target areas were marked on the EEG cap and foam "bridges" (height: 10.5 mm) were glued around them to prevent the TMS coil from touching the EEG electrodes.

### 2.3. Procedure

Stimuli were presented on a 55.8 cm LCD PC screen (1680 × 1050 pixel resolution) with a refresh rate of 60 Hz. Participants viewed the display from a distance of 50 cm with their chin resting on a chin rest and their eye level aligned with the center of the screen. The edges of the screen were covered by a black paper circular cut-out of 28 cm diameter, and all testing was conducted in an extremely darkened room, to eliminate visual environmental cues about verticality. At the beginning of each trial a white central fixation dot appeared for 1000 ms on black background (Fig. 1C). Participants were instructed to fixate this dot throughout the whole trial. Following that, the target stimulus (a white line) was presented in addition to the fixation dot for 100 ms. During the Subjective Visual Vertical (SVV) blocks the task was to indicate whether the flashed line was tilted in a counterclockwise (CCW) or clockwise direction (CW) relative to true vertical. During the Landmark blocks participants had to decide whether the fixation dot was located within the upper or lower half of the line. Participants were instructed to respond as quickly and accurately as possible via button presses with a custom-built response box using their right hand. An index finger response was required if the line was perceived as being tilted counterclockwise or if the dot was in the upper half of the line, while a middle finger press indicated a clockwise tilt or that the dot was in the lower half. After offset of the visual line stimulus, the central fixation dot remained on the screen for 1000 ms and, during TMS blocks, six TMS pulses were delivered at 10 Hz starting immediately at visual stimulus offset i.e. 100 ms after visual stimulus onset. At the end of each trial the fixation dot disappeared and the screen stayed blank for a random interval of 2000–3000 ms. In total, participants performed six 5-min blocks of 60 trials (three SVV blocks and three Landmark blocks, each with one of the three TMS conditions (no TMS, left or

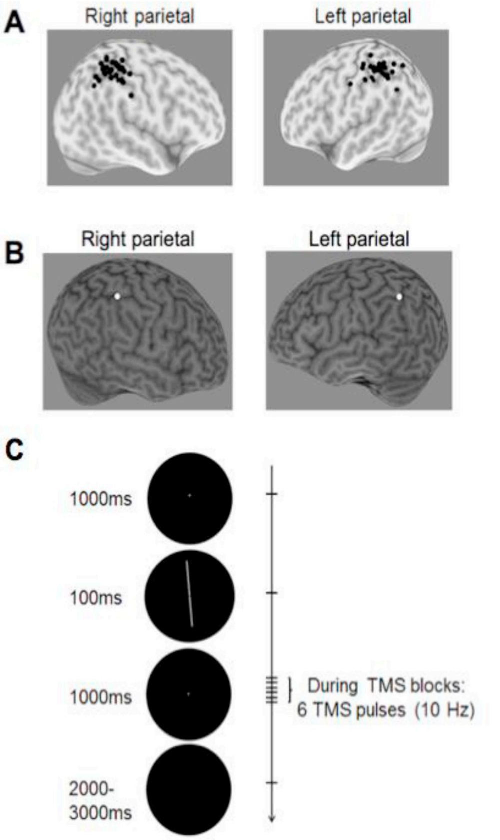

**Fig. 1.** A: Location of the right parietal and left parietal TMS sites for all 32 participants, overlaid on a 3D reconstruction of the template 152-MNI brain (peeling depth: 14 mm). B: Location of the right parietal and left parietal TMS sites for an example participant. C: Trial sequence. The target stimulus (a white line) was flashed (100 ms) on top of the fixation dot. The line was either tilted CW or CCW and was shifted either upwards or downwards from the screen center. After line offset participants received TMS either over their right or left parietal cortices. During SVV blocks participants judged the tilt direction of the line (left or right tilt), during Landmark blocks they indicated the position of the fixation dot within the line (in upper or lower half of the line).

right) with block order counterbalanced between participants). Resting EEG was measured during 2 min central fixation blocks performed at the start, middle and end of the whole experiment (part of a separate ongoing study gathering participants' resting EEG).

### 2.4. Stimuli

Stimuli consisted of a straight, white line presented on a black background. The central fixation point (diameter 0.6°) became black when the line was flashed on top of it (so that the dot was still visible). Lines were 23.2° of visual angle long and 1.2° wide. To prevent the jagged edges which normally occur when near-vertical lines are presented on a conventional computer monitor, the edge of the lines were blurred. Dot position remained central and line length remained constant. Critically, both line orientation and vertical position were varied across all trials. The orientation of the line within the roll plane could deviate ± 2° from the vertical, in steps of 0.17°, omitting true vertical (0°) trials as has been done previously (Lopez et al., 2011) to prevent additional confounds where exactly vertical stimuli can evoke higher neural responses than tilted stimuli. In addition to the tilt angle of the line, the ratio between the length of the upper and lower part of the line was varied across all trials over a range of a ratio between 0.8 and 1.1 (i.e. maximal length upper part = 10.4° visual angle and length lower part = 13.1° visual angle or vice versa; step size: 0.14°). Again, the top and bottom parts of the line were never of equal length, as with the orientation manipulation. For each participant a set of 60 randomly combined tilt angle-bisection ratio lines was generated. The same set of lines was presented on each block but in a random order. Each block contained 60 trials (30 CW and 30 CCW tilts combined with 30 upward and 30 downward bisections).

### 2.5. EEG

EEG was recorded continuously with a BrainAmp DC amplifier (Brain Products, Munich, Germany) from 64 passive Ag-AgCl electrodes, with all online filters deactivated (no notch filter) and a sampling rate of 1000 Hz and impedance maintained ≤ 10 kΩ. Electrodes were placed according to the 10-10 system, with a left earlobe active reference and ground right behind FPz. hEOG used electrodes either side of the right eye, vEOG was derived from an electrode below the right eye and FP2.

### 2.6. Data analysis

#### 2.6.1. Behavior

Psychometric fitting of the observed data was used to assess individual SVV and Landmark performance (Angelaki, 2014; Baccini et al., 2014; Dyde et al., 2006; Foxe et al., 2003; Lopez et al., 2011). The point of subjective equality (PSE, reflecting a participant's individual SVV and Landmark bias) and the steepness of the slope of the sigmoid (i.e. standard deviation of the curve, providing a measure of the participant's discrimination threshold, thus reflecting response variability or uncertainty) were derived. To allow for negative values in the measurements (i.e. CCW and downward biases), absolute (i.e. unsigned) differences of biases between pairs of TMS conditions were computed (i.e. absolute difference right TMS minus no TMS, absolute difference left TMS minus no TMS, and absolute difference right TMS minus left TMS; Fiori et al., 2015; Funabashi et al., 2012; Gnanasegaram et al., 2016). Trials containing reaction times less than 200 ms or exceeding 2000 ms were excluded from analysis.

#### 2.6.2. EEG

Offline, data were re-referenced to the average of the left and right earlobes. As TMS pulses create artefacts in the EEG signal, the signal recorded during the TMS blocks within time bins of 50 ms after the pulses was replaced by a “straight line” between the preceding and following data point in the time windows 100-150 ms, 200-250 ms, 300-350 ms, 400-450 ms, 500-550 ms, and 600-650 ms after line onset. A high-pass filter (low cutoff: 0.01 Hz), followed by a notch filter (50 Hz), and a low-pass filter (high cutoff: 40 Hz) were applied for all blocks. All analyses were performed in Matlab using customized scripts and the EEGLAB Toolbox (Delorme and Makeig, 2004). For ERP analyses the data was segmented into 600 ms segments, ranging from 200 ms before to 400 ms after line onset. The signal was baseline corrected to the 200 ms before stimulus onset. Trials were excluded from analysis if the vEOG or hEOG channel signal exceeded 160 µV, or if a channel's signal range (i.e. maximum-minimum of the signal) exceeded 200 µV during the segment (Sawaki et al., 2015). If fewer than 30 artifact free trials per block were obtained for any electrode, it was removed completely from all analysis in order to ensure a sufficiently high signal-to-noise ratio of the ERP averages. Twelve channels were accordingly excluded (F3, FCz, FC1, FC4, C1, C2, C3, CP1, CP2, CP3, CP4, & P2). Note that our conservative TMS artifact removal procedure ensures clean data by ignoring the signal for 50 ms time windows after each pulse.

#### 2.6.3. Statistics

The level of significance was set to $p \leq 0.05$. When necessary for non-normally distributed data, non-parametric tests were used. In case of violation of sphericity, degrees of freedom in the ANOVAs were adjusted by Greenhouse-Geisser corrections. Unless otherwise stated, results are presented as mean ± standard error.

## 3. Results

### 3.1. Behavior

#### 3.1.1. Subjective visual vertical

Participants performed the SVV task accurately (85.0%). At the group level, mean SVV tilt (the tilt of a line judged to be vertical) was almost perfectly unbiased (0.1 ± 0.1°) with a range of individual values (−1.0°–1.3°) falling within normal limits (approx. ~2°, Brandt et al., 1994; Lopez et al., 2007). No direction-dependent effects of TMS were found i.e. neither TMS condition biased the group mean SVV tilt either towards a more clockwise or more counterclockwise direction ($p = 0.8$: right TMS: 0.2° ± 0.1°, left TMS: 0.1° ± 0.1°). To test for any direction-independent improvement of performance after TMS, such that biased performance at baseline was corrected and became more aligned with the true vertical, effects of TMS are scored as absolute (i.e. unsigned) differences relative to no TMS within each participant (Funabashi et al., 2012; Gnanasegaram et al., 2016). Improvements of SVV bias occurred after TMS to either area (Fig. 2A, absolute difference right TMS - no TMS: mean = 0.52° ± 0.1°, absolute difference left TMS - no TMS: mean = 0.35° ± 0.1°). Importantly, right TMS improved individual SVV bias to a greater extent than left TMS, meaning this effect is site-specific and not confounded by the general sensation of receiving TMS, demonstrable statistically as the significant difference between the two absolute differences from baseline ($t(31) = 2.6$, $p < 0.05$, Cohen's $d = 0.61$; Fig. 2A) as well as the significant difference from 0 of the absolute difference between right TMS and left TMS ($t(31) = 6.0$, $p < 0.01$, Cohen's $d = 1.1$).

The participants were sorted into those with a resting clockwise or counterclockwise bias (18 versus 14 respectively). We then tested whether these two groups were still statistically different after TMS or whether the TMS had acted to homogenize the group. The significant interaction between SVV subgroup and TMS condition ($F(1.6,48.8) = 3.8$, $p = 0.04$, eta2 = 0.11; Fig. 2B), indicated that the extent to which the participants could be grouped varied with TMS condition. To specify how this varied with condition, we first found that the two subgroups differed in their SVV biases at baseline i.e. without TMS ($t(30) = -7.8$, $p < 0.01$). That was to be expected given that we had grouped the participants according to their SVV bias, but demonstrated that the difference was statistically significant. The two groups were still dissociable with left TMS ($t(30) = -3.1$, $p = 0.01$). Critically, with right TMS the two subgroups' SVV biases were no longer different ($t(30) = -1.6$, $p = 0.12$). This shows a normalizing effect specifically of right TMS on verticality perception. The threshold or certainty in SVV judgments was influenced by neither right TMS nor left TMS as compared to baseline (Friedman's test: $p = 0.14$). Furthermore, there was no interaction between SVV subgroup x TMS condition for SVV thresholds ($F(1.2,36.2) = 1.1$, $p = 0.32$).

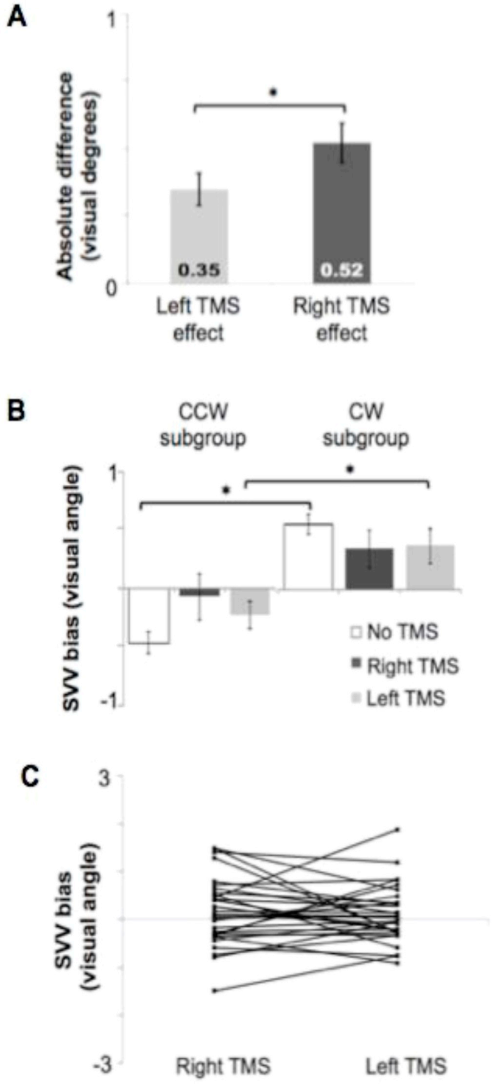

**Fig. 2.** A: Absolute group differences between the two TMS conditions and baseline (no TMS). B: SVV biases during the 3 TMS conditions depending on SVV subgroup (counterclockwise CCW vs. clockwise CW baseline SVV bias). C: Individual SVV biases during the right and left TMS condition for each participant.

#### 3.1.2. Vertical landmark control task

Accuracy at the Landmark task was comparable to the SVV (Landmark: 83.2%, SVV: 85.0%, Wilcoxon signed rank test: $p = 0.70$). The group mean did not show any detectable upward or downward bias (0.0° ± 0.1°, range = −0.8°–0.4°; $p = 0.71$), and this did not change with TMS (right TMS: 0.0° ± 0.0°, left TMS: 0.0° ± 0.0°; $p = 0.40$). Right TMS did not have any effect similar to that above indicating that the role of this target site is specific to the SVV task: there was no difference in performance during right TMS compared to left TMS (absolute difference no TMS-right TMS vs. absolute difference no TMS-left TMS: Wilcoxon signed-rank test: $p = 0.22$).

By contrast, for the Landmark task a baseline bias dependent effect of left TMS rather than right TMS was observed ($F(1.7,49.9) = 9.5$, $p < 0.01$, eta$^2 = 0.24$; Fig. 3A). When separating participants into participants with an upward bias ($n = 15$) versus a downward bias ($n = 17$) the two subgroups differed in their biases during no TMS ($t(30) = 7.0$, $p < 0.01$) and also during right TMS ($t(30) = 3.5$, $p < 0.01$), but not during left TMS ($t(30) = 1.3$, $p = 0.19$). As for the SVV task this again suggested a normalizing TMS effect, in this case, however, regarding the left as opposed to the right hemisphere. Note

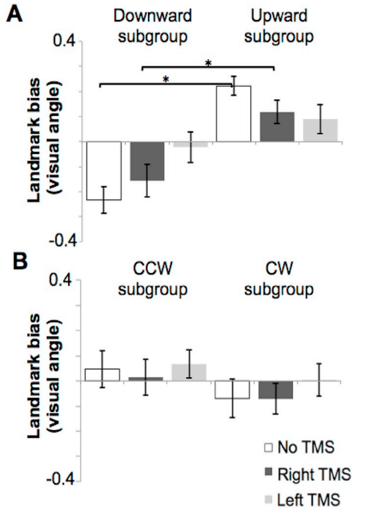

**Fig. 3.** A: Average Landmark biases during the 3 TMS conditions depending on Landmark subgroup (downward vs. upward baseline Landmark bias). B: Average Landmark biases during the 3 TMS conditions depending on Landmark subgroup (counterclockwise CCW vs. clockwise CW baseline SVV bias).

that evidence for this unexpected effect is weaker than the association between the right hemisphere and SVV in that the initial effect on absolute differences (above) was lacking. Importantly, and independently of any potential role of the left hemisphere in vertical landmark judgements, this shows that the causal role of the right parietal site in verticality judgments is task-specific.

To ensure that the effect of right TMS on SVV bias described earlier was not a result of participants in either one of the two SVV subgroups (clockwise vs. counterclockwise bias) being more strongly influenced by right TMS on visuo-spatial tasks in general, a subsequent analysis examined the relation between TMS effect and SVV subgroup in the Landmark task. No such interaction between SVV subgroup x TMS condition was found (F(1.5,44.9) = 0.2, p = 0.77; Fig. 3B). This confirmed that the normalizing effect of right TMS was specifically linked to the SVV task, whereas a significant interaction would have pointed towards a more global effect of right TMS on visual processing independent of task. An ANOVA included performance for both tasks and TMS stimulations sites together, and although it did not show effects of tasks, TMS condition nor the interaction between the two (all p's > 0.05), the three way interaction was evident, supporting a task- and group- and site-specific effect (F(2,60) = 3.6, $p < 0.05$, eta$^2$ = 0.11). Neither right nor left TMS affected Landmark thresholds as compared to baseline (Friedman's test: p = 0.14).

### 3.2. Reaction times

Reaction times in the baseline (no TMS) SVV condition (665 ms ± 31) were significantly faster than those in the baseline Landmark condition (738 ms ± 30; t(31) = −4.2, $p < 0.01$, Cohen's d = 0.43). In contrast to the described bias results, reaction time analysis did not reveal a hemisphere and task specific TMS effect on SVV performance. In detail, TMS speeded reaction times in both tasks (F(1.6,50.0) = 9.4, $p < 0.01$, eta$^2$ = 0.23), however, there was no difference in reaction times between the respective right TMS and left TMS conditions within each task (SVV: right TMS: 593.01 ± 29.64 ms, left TMS: 612.18 ms ± 31.62 ms, t (31) = −1.2, p = 0.23; Landmark: right TMS: 653.78 ms ± 31.11 ms, left TMS: 670.96 ms ± 34.73 ms, t(31) = , p = 0.51) with no interaction between TMS condition and task (F(2,62) = 0.2, p = 0.84).

### 3.3. ERP results

#### 3.3.1. SVV

In order to identify potential candidates for an ERP correlate of baseline SVV bias a difference wave was formed comparing participants with a clockwise minus counterclockwise baseline SVV bias. We adopted a strategy suggested recently in the ERP community (Luck and Gaspelin, 2017) to address the inherent statistical problems (e.g. multiple comparison correction) of testing for differences between conditions in rich datasets with many time points and electrodes. The logic is to perform two orthogonal analyses on different datasets. The first step examined only noTMS data and explored at which electrodes and time-bins the difference between subgroups is the largest. The second step focuses on those electrodes and time-bins but this time only tests the TMS data. The key test is whether subgroups still differ after TMS within this time and area of interest.

The difference wave butterfly plot comprised 4 peaks or troughs. The largest waveform difference between the two baseline SVV subgroups was found around electrode FC2 at time bin 280 - 300 ms post-stimulus (i.e. after line onset; Fig. 4A). Participants with a CCW baseline SVV bias displayed significantly higher FC2 amplitudes than participants with a CW bias in this particular time bin (3.5 μV ± 1.5 μV vs. −0.6 μV ± 1.2 μV; t(30) = 2.1, p = 0.04, Cohen's d = 0.76).

For completeness another analysis checked whether participants with a CW or CCW bias differed significantly in the ERP amplitude at the other peaks or troughs in the difference wave: PO7 was tested at 100-130 ms, CPz at 175–200 ms and Oz at 250–270 ms, but none of these showed group differences (all p's ≥ 0.05).

The effects of TMS on brain activity mirrored those on behavior: consistent with the behavioral SVV results, TMS affected participants' FC2 amplitudes differently depending on whether they showed a CW or CCW baseline SVV bias (F(2,2) = 3.00, p = 0.06, eta$^2$ = 0.90; Fig. 5). FC2 amplitude between the two SVV subgroups differed during no TMS (t(30) = 2.1, p = 0.04, Cohen's d = 0.76), marginally during left TMS (t(30) = 1.9, p = 0.07, Cohen's d = 0.67), but showed no difference in FC2 amplitude during right TMS (t(20.45) = 0.1, p = 0.90), which again pointed towards a normalizing effect of right TMS for the SVV task.

#### 3.3.2. Vertical landmark control task

This frontocentral signal which correlated with baseline SVV tilt, and was affected by TMS in the same way as behavior, did not show any such relation during the Landmark task. There was no difference in FC2 amplitude between participants with an upward vs. downward bias during the Landmark task either without TMS or in either TMS condition (F(2,2) = 6.1, $p < 0.01$, eta$^2$ = 0.17; t-tests: all p's > 0.19; Fig. 6B). The task and hemisphere specificity of the TMS effect on behavior was further supported by the finding that FC2 amplitudes during the baseline Landmark block were independent of SVV baseline subgroup (F(2,2) = 2.5, p = 0.09; Fig. 6A). FC2 amplitudes were in general significantly more positive for the SVV than compared to the Landmark task (F(1,31) = 18.6, $p < 0.01$, eta$^2$ = 0.38; no TMS: t(31) = 3.6, $p < 0.01$, Cohen's d = 0.44; right TMS: t(31) = 2.4, p = 0.02, Cohen's d = 0.31; left TMS: t(31) = 2.2, p = 0.03, Cohen's d = 0.22). Neither a significant main effect of TMS condition (F(2,62) = 1.9, p = 0.17) nor an interaction between TMS condition and task was observed (F (2,62) = 0.6, p = 0.54). Taken together these results emphasized that the normalizing effect of right TMS on verticality perception was also reflected at an electrophysiological level within 300 ms after stimulus onset over frontocentral cortex, and that this was strikingly similar in pattern to the behavioral effect.

## 4. Discussion

This study tested whether right dorsal parietal cortex plays a causal role in the neuronal implementation of verticality judgments, with the

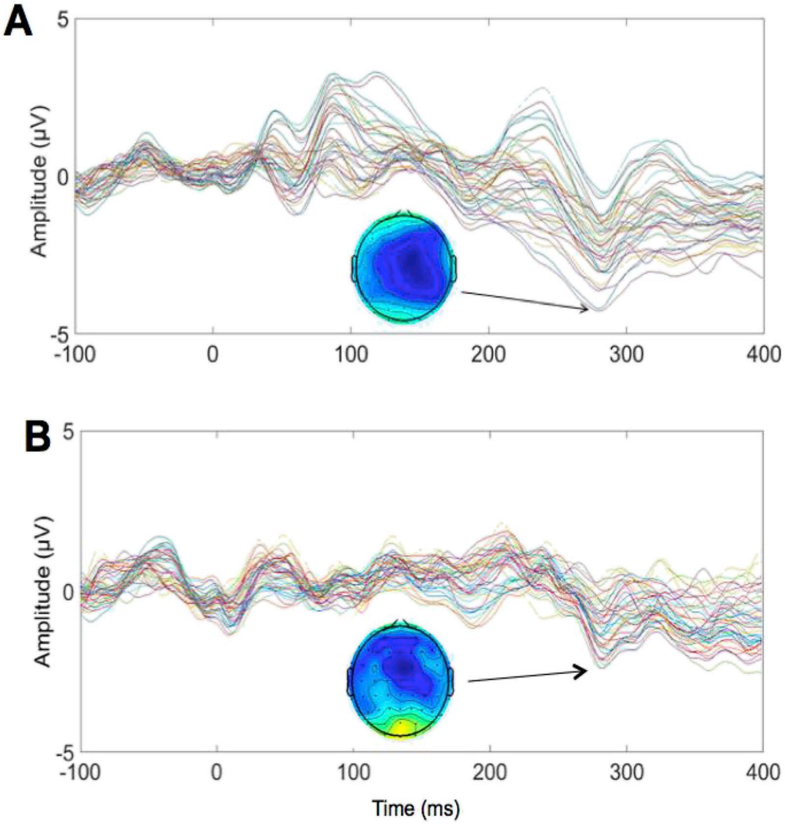

**Fig. 4.** A: ERP difference waves comparing participants with a clockwise minus counterclockwise baseline SVV bias in their ERP amplitudes for all recording electrodes and the corresponding topoplot at time point 280 ms after stimulus onset obtained during the baseline (no TMS) SVV measurements. B: ERP difference waves comparing participants with a clockwise minus counterclockwise baseline SVV bias in their ERP amplitudes for all recording electrodes and the corresponding topoplot at time point 280 ms after stimulus onset obtained during the baseline (no TMS) Landmark measurements.

SVV task, compared to a Landmark task, using a common set of stimuli for both tasks. The results show that participants displayed an inherent clockwise or counterclockwise SVV bias, as well as a vertical pseudoneglect during baseline. In line with the hypothesis, right parietal TMS reduced the normal SVV bias, improving performance, such that participants with a resting counterclockwise (CCW) or clockwise (CW) bias were shifted towards the veridical vertical. In contrast, no such normalizing effect of right parietal stimulation on Landmark biases was observed.

Right parietal stimulation did not increase relative, but rather absolute, SVV biases and thus, did not mimic pathology of the primary vestibular system. Rather our results suggest that as part of a larger vestibular network (Brandt and Dieterich, 2017) the right parietal cortex is involved in visual cognition in a vestibular context. Specifically, this area may be necessary in situations when visual-vestibular interactions are task-relevant, by guiding perception in a vestibular-relevant reference frame, the roll plane: successful verticality perception relies on the integration of visual, vestibular, and somatosensory signals and has been linked to spatial attention (Karnath and Dieterich, 2006). Likewise, the right IPS has repeatedly been associated with multisensory integration (particularly of visual-vestibular signals) and attention (Baier et al., 2012a,b; Darling et al., 2003) and has been proposed as a possible interface between spatial orientation and spatial attention (Agosta et al., 2014; Kerkhoff and Zoelch, 1998). Right parietal TMS might change the weighting of the different sensory inputs within the integration process by decreasing the relative weight of the more uncertain information source and at the same time increasing the weighting of more certain information. Thus, when interfering with activity over the right parietal cortex, endogenous information sources (i.e. vestibular information coming from the otoliths) which are used for a representation of one's environment were boosted while exogenous (visual information) sources might have been downgraded within the multisensory integration process (Dieterich and Brandt, 2015; Brandt et al., 2012; Klingner et al., 2016). To what extent the effect of TMS on SVV bias depends on the individual relative dependency on the different sensory signals and their weighting within in the integration process should be addressed in future studies. Additionally, the source of the interindividual variability in resting perceptual bias in itself could be explored, for example by measuring interindividual differences in the extent of particular cortical areas (e.g. Schwarzkopf et al., 2010), or the structural and functional connectivity between them (e.g. Barch et al., 2013). In general, our results emphasise the importance of taking inter-individual variability in individual resting perceptual biases into account when studying verticality judgments in healthy subjects, particularly in combination with brain stimulation interventions (Thomas et al., 2017; Varnava et al., 2013).

The electrophysiological effects of TMS were consistent with the behavioral pattern. Right TMS had a homogenizing effect on the late

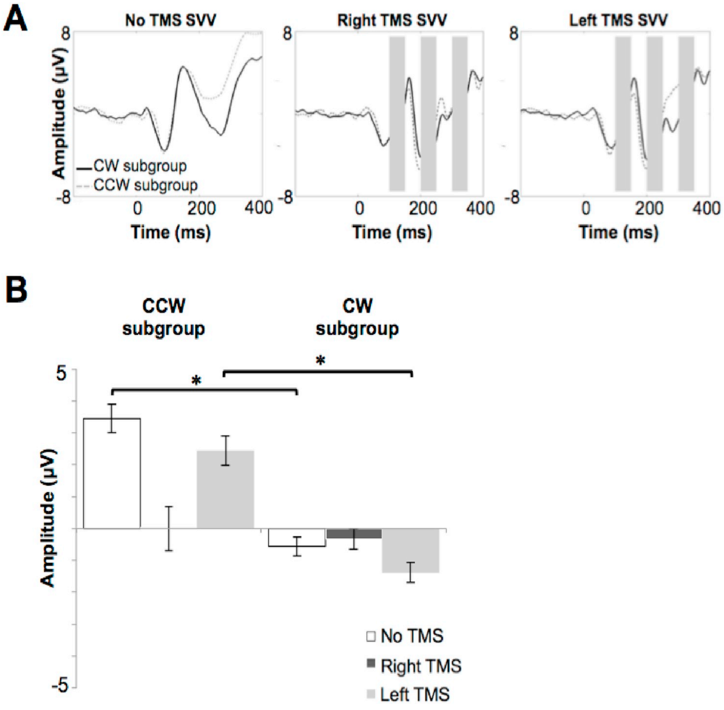

**Fig. 5.** A: Mean frontocentral (electrode FC2) ERP time series during the 3 SVV TMS conditions for each SVV subgroup (counterclockwise CCW vs. clockwise CW baseline SVV bias). Grey bars indicate interpolation times of the TMS pulses. B: Mean frontocentral (electrode FC2) ERP amplitudes during the 3 SVV TMS conditions depending on SVV subgroup (counterclockwise CCW vs. clockwise CW baseline SVV bias).

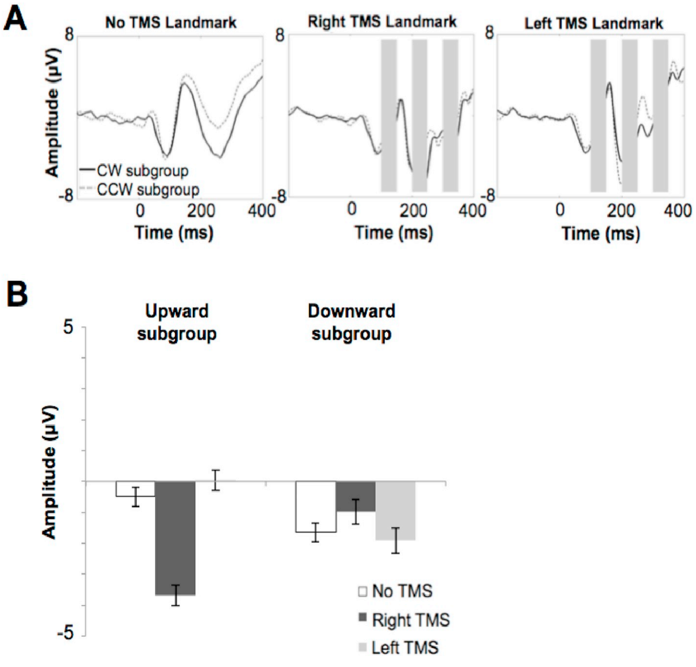

**Fig. 6.** A: Mean frontocentral (electrode FC2) ERP time series during the 3 Landmark TMS conditions for each SVV subgroup (counterclockwise CCW vs. clockwise CW baseline SVV bias). Grey bars indicate interpolation times of the TMS pulses. B: Mean frontocentral (electrode FC2) ERP amplitudes during the 3 SVV TMS conditions depending on Landmark subgroup (upward vs. downward baseline Landmark bias).

frontocentral ERP component related to verticality judgment, while this same component was not altered by TMS regarding the Landmark task. Thus, right parietal TMS did not only homogenize behavioral SVV biases but also their related neuronal correlate in the ERP. This suggests that the effect of TMS did not solely consist of completely artificial effects produced by functionally irrelevant changes in brain activity (Krakauer et al., 2017) but is an example of the use of ERP with TMS to show that the effects at least included those modulated during normal cognition (Taylor, 2018). The no TMS trials in this study were used to split the participants into the two subgroups, and the left TMS trials were in the design as a control condition. Comparing and contrasting right TMS with left TMS allows controlling for the non-specific artefacts of TMS such as the sound and tactile sensation of receiving stimulation. The sole comparison between TMS and no TMS conditions was avoided here because non-specific artefacts are not present in the noTMS condition and so such differences could be attributable to these non-neural confounds. The immediate spatial resolution of EEG does not favour strong inferences regarding spatial localisation, but future work may explore the localisation of this effect with other analysis techniques or methods and whether it reflects operation of a fronto-parietal network. Parietal TMS can lead to frontal activations as measured with fMRI in spatial cognition tasks (Hill et al., 2017; Leitão et al., 2017; Sack, 2009). Importantly, the right parietal TMS effect on SVV judgments was not attributable to the sound or feel of TMS in general or a speed-accuracy trade off. Furthermore, the reported double dissociation of the TMS effect between the SVV and Landmark task confirms that our results do not reflect a general spatial attentional effect in all axes (including up-down), but are specifically associated with spatial biases in the roll plane. The control analyses also excluded the possibility that the SVV-specific right TMS effect was confounded by the way of grouping participants into two SVV subgroups (e.g. with participants in one of the two subgroups showing greater learning effects during the experiment, or being more susceptible to TMS in general, etc.) as no SVV subgroup dependent TMS effects on Landmark biases were reported. We also found some evidence that left parietal TMS (the control site) affected performance at the vertical landmark task (the control task), although we emphasise that this is was not statistically as strong as the main effect of right TMS on the SVV, and left parietal TMS effects at visuospatial tasks are less common as a rule (Rushworth and Taylor, 2006). However some exceptions to this are that left parietal TMS affects discrimination of the local, less salient stimulus in tasks requiring ignoring a global form (Mevorach et al., 2005, 2009) and this is specific to 10 Hz TMS as used here (Romei et al., 2012). Furthermore left PPC TMS may be a good example of network TMS effects: left PPC TMS compensates for right parietal damage (e.g. Agosta et al., 2014), and furthermore left IPS TMS was found to affect the EEG microstate topography only during a visuo-spatial and not a semantic task (Croce et al., 2018). Left parietal repetitive TMS affects functional connectivity across the dorsal attentional network (Battelli et al., 2017). Future work will be necessary to disentangle which key aspects of the task or network underlie this effect.

The right IPS has been suggested to be one of the main integrators of visuo-spatial orientation and attention (Agosta et al., 2014; Kerkhoff and Zoelch, 1998) and a core region for the integration of ego- and allocentric information (Chechlacz et al., 2010; Galati et al., 2000), a prerequisite for an optimal perception of verticality and orientation in space (Barra et al., 2010; Karnath et al., 1996). Right hemispheric lesions cause more severe tilts of the SVV than left-hemispheric lesions, pointing to a dominance of the right hemisphere in verticality perception (Brandt and Dieterich, 2017), similar to what has been described regarding visuo-spatial attention. In line with that, several studies suggested a close relationship between visuo-spatial performance and verticality perception (Bonan et al., 2006; Kerkhoff and Zoelch, 1998), indicating a potential interplay between visual cognition and vestibular processing, as suggested from other brain stimulation studies looking at this or nearby regions (Arshad, 2017). The vestibular input for navigation – tracking head position during motion – may be critical to the intimate relationship between attention and navigation as two aspects of spatial exploration (Nau et al., 2018) and for parietal involvement during navigation tasks (e.g. Nitz, 2012; Whitlock, 2017).

IPS is only one part of a highly distributed system (Grieves and Jeffery, 2017). Patients suffering from injury to the peripheral or central nervous structures can show pathological tilts in the SVV task (Brandt and Dieterich, 1994; Brandt et al., 1994; Dieterich and Brandt, 1993; Glasauer et al., 2018; Yelnik et al., 2002), which can arise from initial perceptual stages, during which the different sensory inputs are processed separately, as well as from the subsequent integration steps of the different input signals (Van Nechel et al., 2001). Based on findings from various imaging and lesion studies there seems to be no single key region for the required integration process (Brandt and Dieterich, 2017). Rather, several subcortical and cortical regions including the right parietal cortex (Baier et al., 2012a,b; Darling et al., 2003) are involved in this process and form a large network responsible for verticality perception (Brandt and Dieterich, 2017; Van Nechel et al., 2001). Other nodes, areas and time-windows have been evident in studies that used other methods, tasks. In particular, not separating out participants according to bias can reveal other parts of the network, for example a late ERP component associated with verticality judgments localized to bilateral temporo-occipital and parieto-occipital areas (Lopez et al., 2011). One other important part of the network that has been stimulated with TMS or tDCS to affect the SVV (and other tasks testing aspects of vestibular function) is a part of parietal cortex much more ventral to the one stimulated here (Arshad, 2017; Kheradmand et al., 2015; Leitão et al., 2017; Santos-Pontelli et al., 2016; Seemungal et al., 2008). TMS of those more ventral regions increased SVV errors (Fiori et al., 2015) and if the head is tilted the SVV errors are shifted in the opposite direction of head tilt (Kheradmand et al., 2015; Otero-Millan et al., 2018). Whereas those studies interpreted a role for more ventral areas as generating an internal reference (Kheradmand and Winnick, 2017), this more dorsal area can be framed as playing a role in the relative weighting of sensory inputs (see above). Here by contrast a much more dorsal parietal site was targeted on the basis of recent imaging results suggesting a potential human homologue of VIP within the IPS (Billington and Smith, 2015; Frank et al., 2016; Smith et al., 2017). Future work with other methods can examine whether in the human there is further functional subdivision with greater depth into the IPS as might be expected from the macaque (Bremmer et al., 2002; Chen et al., 2011; Laurens et al., 2017), but which is difficult to address with TMS. Some recent imaging results show larger areas here that may span both more superficial and deeper parts of the sulcus (Frank et al., 2016; Smith et al., 2017). TMS has been instrumental in revealing that different parts of the parietal lobe play different roles in spatial cognition (Rushworth and Taylor, 2006; Sack, 2009).

The observed normalizing effect of right dorsal parietal TMS on SVV biases in healthy controls suggests a potential relevance of non-invasive brain simulation for clinical research as it might serve as a tool for not only exploring (through transiently resetting) slight biases in verticality perception as observed in our participants but also in pathological SVV biases such as found in patients suffering from vestibular disorders or neglect. Apart from this issue future work should concern the role of hemispheric lateralization and handedness on the reported results. In conclusion the present study points to an essential role of the right dorsal parietal cortex in establishing the perception of visual vertical.

## Declaration of interest

None.

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## CRediT authorship contribution statement

**Lina Willacker:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **James Dowsett:** Methodology, Software, Writing - review & editing. **Marianne Dieterich:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition. **Paul C.J. Taylor:** Conceptualization, Methodology, Formal analysis, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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## 2.2 Project 2: Reducing variability of perceptual decision making with offline theta-burst TMS of dorsal medial frontal cortex.

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Author contributions:

Lina Willacker and Paul C.J. Taylor conceived the experiment. Lina Willacker programmed the experiment. Lina Willacker collected the data with help of Marco Roccato and Beril Nisa Can. Lina Willacker analyzed the data and wrote the paper, which was commented and revised by Paul C.J. Taylor and Marianne Dieterich. Lina Willacker is the only first author of this paper.

# Reducing variability of perceptual decision making with offline theta-burst TMS of dorsal medial frontal cortex.

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# Abstract

Background: Recent evidence suggests that the dorsal medial frontal cortex (dMFC) may make an important contribution to perceptual decision-making, and not only to motor control.

Objective/Hypothesis: By fitting psychometric functions to behavioural data after TMS we tested whether the dMFC is critical specifically for the precision and or bias of perceptual judgements. Additionally we aimed to disentangle potential roles of the dMFC in dealing with perceptual versus response switching.

Methods: A subjective visual vertical task (SVV) was used in which participants weight visual (and other, e.g., vestibular) information to establish whether a line is oriented vertically. To ensure a high perceptual demand (putatively necessary to demonstrate a dMFC involvement) SVV lines were presented inside pop-out targets within a visual search array. Distinct features of perceptual performance were analysed before as compared to following theta-burst TMS stimulation of the dMFC, a control site, or no stimulation, in three groups, each of 20 healthy participants.

Results: dMFC stimulation improved the precision of verticality judgments. Moreover, dMFC stimulation increased reaction times, selectively when both perceptual and response switches had occurred.

Conclusion: These findings point to a causal role of the dMFC in establishing the precision and accuracy of perceptual decision making, demonstrably dissociable from an additional role in motor control in situations of high perceptual load.

Keywords: dMFC; verticality perception; TMS; perceptual decision-making

## Introduction

In studies of perceptual decision-making, two independent features can be disentangled, by fitting a psychometric function to behavioural data from two-alternative forced choice (2AFC) paradigms [1]: bias (i.e. how biased perception of a stimulus is in relation to its actual properties) and precision (i.e. how reliable or variable perception of a stimulus is, also sometimes referred to as simply "threshold" or "sensitivity"). Although normally associated with lateral intraparietal cortex (LIP) or frontal eye fields (FEF), it is important to explore other areas [2], and dorsal medial prefrontal cortex in particular, including the presupplementary motor area (preSMA), has been linked [3]. In transcranial magnetic stimulation (TMS) studies, preSMA stimulation has modulated decision thresholds [4,5], in line with increased decision thresholds after preSMA inhibition [6]. Other work has elaborated the clear evidence for dMFC's motor role [7–10]. Yet it remains unclear whether the human dMFC plays a causal role in controlling the precision of perceptual decision-making. Moreover, appropriate explanations about the behavioural consequences of TMS on neural activity by means of computational modelling of recorded data are needed [11].

The function of the dMFC in response control has conventionally been studied with exclusively visual stimuli. The integration of visual and vestibular information has attracted particular attention in terms of examining bias and precision [1,12–14]. Although a key visual-vestibular hub lies around inferior parieto-insular cortex [15–18], the network also encompasses medial frontal areas [16,19]. There are close connections between dMFC and core vestibular areas (e.g. inferior frontal gyrus and insula [8,20–24]). dMFC activity has been linked to the amount of body sway in patients with vestibular problems [25] and midline frontal effects were reported in a recent parietal TMS-EEG verticality perception study [26]. The dMFC is then a candidate for perceptual decision making during verticality judgments.

The present study employed a visual search paradigm combining verticality perception (SVV) with perceptual switches and response switches. The first hypothesis was that TMS of the dMFC would interfere with the precision of verticality judgements. Given that previous work demonstrated a dMFC TMS effect on response selection on trials with high perceptual load [9,10,27,28], verticality judgments were made in a visual search setting. An additional non-search SVV condition was included to establish participants' resting bias. Additionally, in the search blocks, target defining and response defining features were orthogonal: this allowed testing the second hypothesis that dMFC TMS would specifically affect performance (in this case reaction times) in the more attentionally demanding situation, when the target-defining dimension would switch from one trial to the next.

## Material and methods

### *Participants*

60 right-handed participants [29,30] took part (mean age: 25.5 ± 3.4 years, 37 females). Participants were divided into three groups of 20. A first group received dMFC TMS (mean age: 25.5 ± 2.3 years, range: 22 – 30 years, 14 females). To control for general alerting effects of TMS, and practice effects, a control TMS group underwent TMS stimulation over the vertex (mean age: 24.5 ± 2.0 years, range: 21 – 29 years, 8 females) and a further group did not receive any TMS (mean age: 26.7 ± 4.8 years, range: 23 – 41 years, 15 females). There was no overlap between participants in the three groups except one case between the dMFC and control TMS group and two cases between the control TMS and no TMS group. Note that although full cross-over designs help exclude population-based biases, they also are more sensitive to training effects over sessions or unblinding of the participants. All participants had normal or corrected-to-normal vision, and no history of any neurological disorders. Written informed consent according to established safety guidelines for TMS research [31] was obtained from all participants and the study was approved by the local ethics committee. Participants received monetary compensation.

### *TMS*

The two TMS groups received stimulation after the first half (i.e. after five out of ten blocks; “pre-session”; Fig. 1) of the experiment using a MagPro X100 (Magventure, Denmark) with a figure-of-eight coil (MCF-B70, outer winding diameter: 97 mm). TMS used the standard theta-burst TMS protocol used widely [49,52]: TMS lasted 47 seconds (200 bursts, each comprising three pulses at 50Hz, repeated every 200 ms (5Hz), 600 pulses in total) at 80%

active motor threshold (mean intensity: 27 % ± 6 % of maximal stimulator output; no intensity difference between the two groups: t(38) = 1.22, p = 0.23; dMFC group: 28 ± 1 %, control TMS group: 26 ± 1 %) to either the dMFC or the vertex. dMFC was defined as one and a half electrode positions anterior to electrode Cz according to the 10-20 International System [7,9]. A vertex control site, used in previous dMFC TMS studies [6,54] was chosen, because it is both near the active site and also over the midline, so that the two stimulation sites were well-matched for stimulation sensation – participants rate TMS over these regions similarly as low on scales of annoyance [32]. At the end of the experiment, coil positioning was confirmed for five participants in each TMS group using neuronavigation (Brainsight, Rogue Research, Canada, mean dMFC MNI (x,y,z) coordinates: -1, 36, 60; mean vertex MNI coordinates: -3, -12, 81). Despite variability of the stimulation sites in the y-axis within each TMS group the two groups did not overlap (Fig. 1). This target localisation method was based on previous dMFC TMS experiments [7,9,10]. One advantage of targeting midline areas is that the two hemispheres abut, meaning lower variability in the MNI x-axis than for other areas. Note the z co-ordinate of a TMS site does not imply the extent of stimulation depth. The TMS coil was held with the handle pointing backwards. Coil orientation was selected based on previous studies [7,9,10]. Note that with midline targets, holding the coil in any other way than parallel to the midline would lead to differential medial-lateral directions of induced current. During stimulation participants rested.

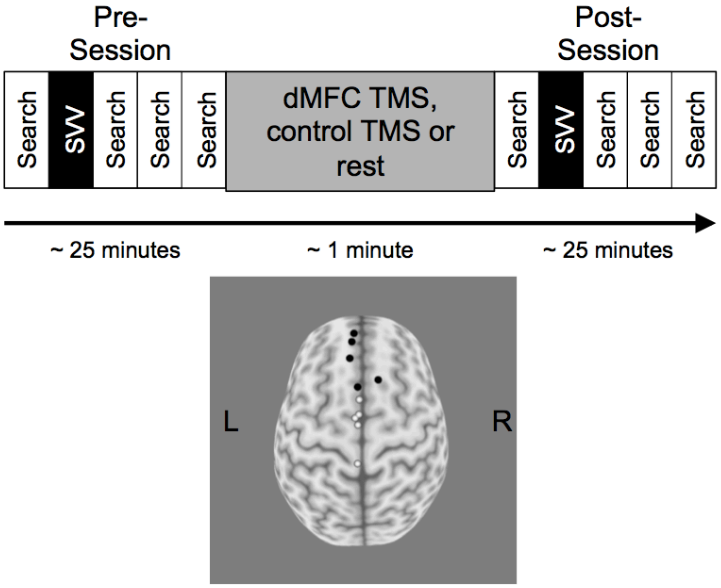

Figure 1: Upper panel: experimental procedure. During the pre-session and post-session two task blocks were performed (SVV and visual search; block order counterbalanced). Between sessions participants received either dMFC TMS, control site (vertex) TMS or rested. Lower panel: location of the dMFC (black dots) and vertex (white dots) TMS sites for 5 participants from each group.

*Procedure*

Stimuli were presented on a 55.8 cm LCD monitor (1680 x 1050 pixel resolution, refresh rate of 60 Hz). Viewing distance from the screen was fixed to 50 cm using a chin rest and participants' eye level was aligned with the screen centre. In order to avoid any environmental cues for verticality, the experiment was conducted in an extremely darkened room and the monitor edges were covered by a black paper 28 cm diameter circular cut-out [26]. Trials began with a white fixation dot (Fig. 2). After 1000 ms the target display appeared, showing either a single white line for 100 ms (Subjective Visual Vertical (SVV) blocks) or a visual search array for 200 ms (search blocks). The search array consisted of 8 white lines out of which 7 distractor lines were either placed inside white circles or red squares while the target line was always positioned inside a red circle. During the SVV condition participants had to indicate whether the flashed line was tilted in a counterclockwise (CCW) or clockwise direction (CW) relative to true vertical. In the search condition the task was to judge the tilt direction of the target line. Next a blank screen was shown for 2000 - 3000 ms. Responses were given as quickly and accurately as possible with a button box. Participants pressed the left button with their right index finger for CCW tilts and the right button with their right middle finger for CW tilts.

Before the session, 24 practice trials of each condition were performed. For TMS groups participants' motor thresholds were obtained after the practice block. Participants then performed the first five experimental blocks ("pre-session"; one SVV block of 60 trials and four search blocks of 50 trials each; block order counterbalanced between participants). Afterwards, either theta-burst TMS was applied, or participants were rested for one minute. For the no TMS group, potential influencing factors were equated with those of the TMS groups, such as time taken between the first and second part of the experimental blocks and the lightning of the room. After the TMS stimulation or break, respectively, the second half of the experimental blocks was performed ("post-session"; one SVV block of 60 trials and four search blocks of 50 trials each; same block order as for the pre-session).

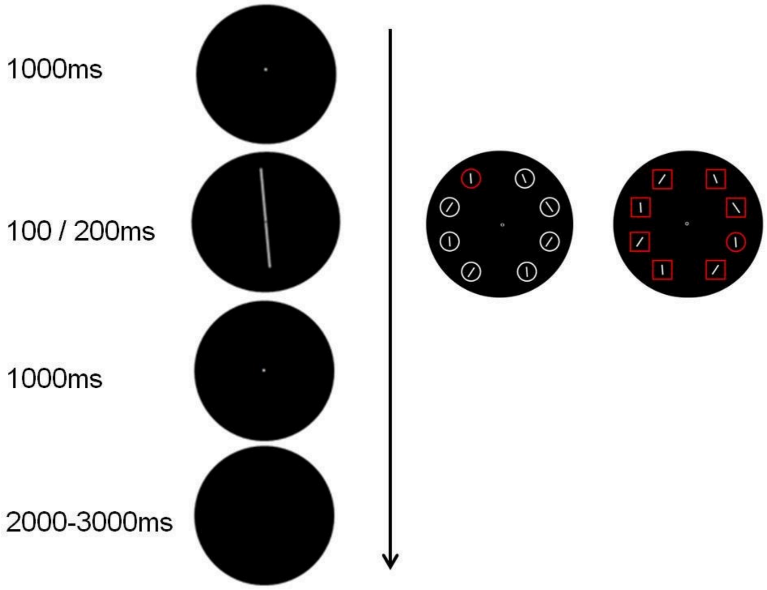

Figure 2: Left: Schematic trial sequence SVV task. Right: Search task.

*Stimuli*

Stimuli were presented using Psychtoolbox [33]. In the SVV condition the target stimulus was a straight white line (23.2° of visual angle long, 1.2° wide) shown on black background and on top of the central fixation point (diameter 0.6°), which became black when the line was flashed. Tilt deviated up to ±2° from true vertical, in steps of 0.17°. No true vertical (0°) trials were included.

For the search condition, stimuli consisted of 8 white, straight lines (3.0° long and 0.2° wide) drawn within the either circles (diameter: 3.4° visual angle) or squares (side length: 3.4° visual angle), at eight equidistant locations around fixation (distance from the centre: 12° visual angle). To adjust for the smaller stimuli compared to the SVV condition, a larger tilt range of ±4° from true vertical, in steps of 0.33°, was used, and truly vertical lines were included. Tilt angles of the 8 lines were different. The target stimulus always appeared within a red circle, with equal likelihood at any one of 8 possible locations, and could be different from the other seven distractor stimuli in one of two dimensions: either shape or colour. For shape pop-out trials, the red circular target was presented among lines within red, square distractors. For colour pop-outs, the red circular target was presented among lines within white, circular distractors. Search trials were classified relative to the preceding trial: same dimension (sD): the dimension of the distracting stimuli on the current trial matched the preceding trial; different dimension (dD): the dimension of the distracting stimuli on the current trial switched (i.e. either from shape to colour or from colour to shape); same response (sR): participants responded with the same button press; different response (dR): the participant's response switched (either from CCW to CW tilt judgment or vice versa). These conditions were then combined into four trial types: sDsR, sDdR, dDsR, and dDdR (Fig. 3). For each of these types 100 trials were performed in a randomized order across blocks.

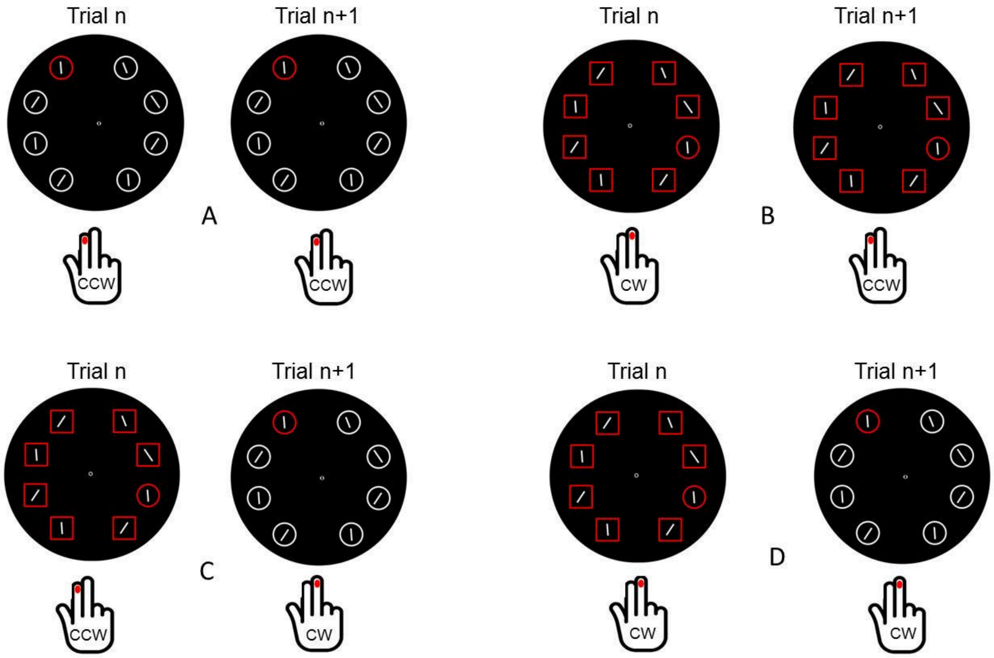

Figure 3: Schematic of the four switch trial types of the search task: A: same dimension, same response (sDsR), B: same dimension, different response (sDdR), C: different dimension, different response (dDdR), D: different dimension, same response (dDsR).

### *Data analysis*

Psychometric fitting of the observed data was used to derive individual SVV performance [1,12,34–36]. The point of subjective equality (PSE, reflecting the individual SVV bias) and the steepness of the slope of the sigmoid (i.e. standard deviation of the curve, which gives a measure of the participant's discrimination threshold, in that way reflecting response variability or precision) were computed for both tasks. Please note we use the term bias and not "accuracy" to reflect the PSE to make it more easily distinguishable from other analyses: In addition, the impact of dMFC TMS on performance in the two different tasks was investigated in terms of reaction times, accuracy, and perceptual versus response switching, analysed using ANOVA and post-hoc t-tests, with alpha set to 0.05 and effects sizes supplied when present.

# Results

## *TMS effects on precision*

Precision in the post-session differed from the pre-session according to both TMS and task (interaction Session (pre/post) x experimental group (dMFC, control, no TMS) x task (SVV, search): F(2,57) = 6.57, $p < 0.01$, $eta^2 = 0.19$). TMS effects were specific to the search task (interaction Session x experimental group for search task: F(2,57) = 4.38, p = 0.02, $eta^2 = 0.13$; Fig. 4; for SVV task: F(2,57) = 1.75, p = 0.18). This pattern was driven by dMFC TMS decreasing the variability of responses compared to the pre TMS session (i.e. improved precision of SVV judgments; t(19) = 3.97, $p < 0.01$, Cohen's d = -0.83) with no such effects following control TMS (t(19) = 1.49, p = 0.15) or no TMS (t(19) = -0.83, p = 0.42). This could not be explained by any baseline (pre TMS / break) differences between the three groups (F(2,59) = 1.68, p = 0.20). Moreover, the dMFC TMS effect was specific to the search task and did not occur in the SVV task (F(2,57) = 0.23, p = 0.79).

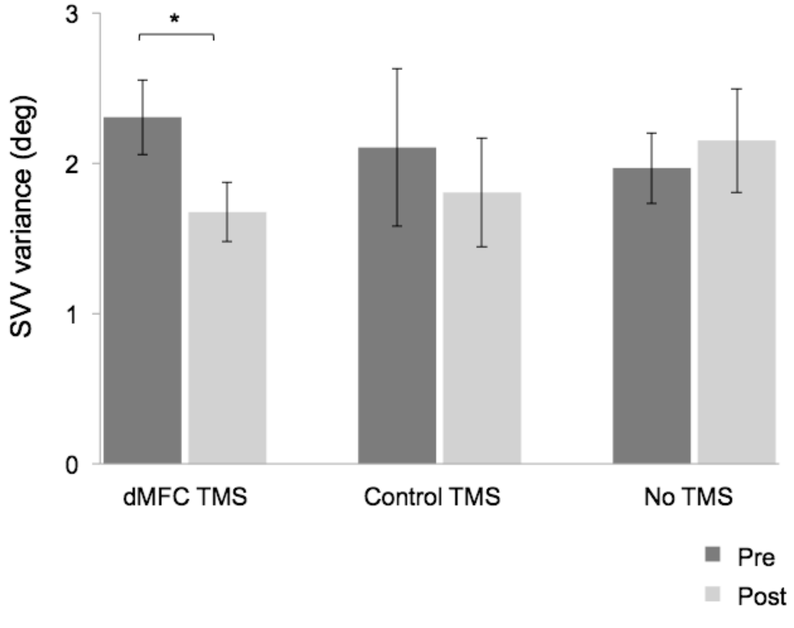

Figure 4: Variability of SVV responses in the search task before TMS / break (pre) vs. after TMS / break (post) for the three experimental groups showing that dMFC TMS reduced variability (i.e. increased precision).

### *TMS effects on bias*

No changes regarding SVV bias were observed in either of the two tasks or for any of the three experimental groups (all p's > 0.44). This was also true when participants were split on the basis of their performance in SVV blocks into those with a resting clockwise or counterclockwise bias (ANOVAs testing Session (pre/post) x experimental group (dMFC; control, no TMS) x SVV baseline bias subgroup (CW/CCW) all p's > 0.57).

### *TMS effects on accuracy*

An increase in accuracy (i.e. percent correct responses) during the search task specific to the dMFC TMS group was found. This was statistically evident as the interaction present in the search but not SVV blocks (Session x experimental group for search task: F(2,57) = 3.72, p = 0.03, $eta^2$ = 0.12; Session x experimental group for SVV task: F(2,57) = 0.20, p = 0.82; improvement of dMFC TMS group compared to preTMS during search task: t(19) = -3.82, p < 0.01, Cohen's d = 0.83; Fig. 5). In contrast, accuracies for the control TMS group (t(19) = -1.62, p = 0.12) and no TMS group (t(19) = -0.64, p = 0.53) did not differ between post- and pre- sessions. Again, there were no differences in baseline accuracy levels between the three groups here (F(2,59) = 1.68, p = 0.20) nor in the SVV task (F(2,57) = 0.20, p = 0.82). Accuracy was significantly higher in the SVV task as compared to the search task both in the pre-session (t(59) = 6.69, p < 0.01, Cohen's d = -0.85) and the post-session (t(59) = 3.42, p < 0.01, Cohen's d = -0.40).

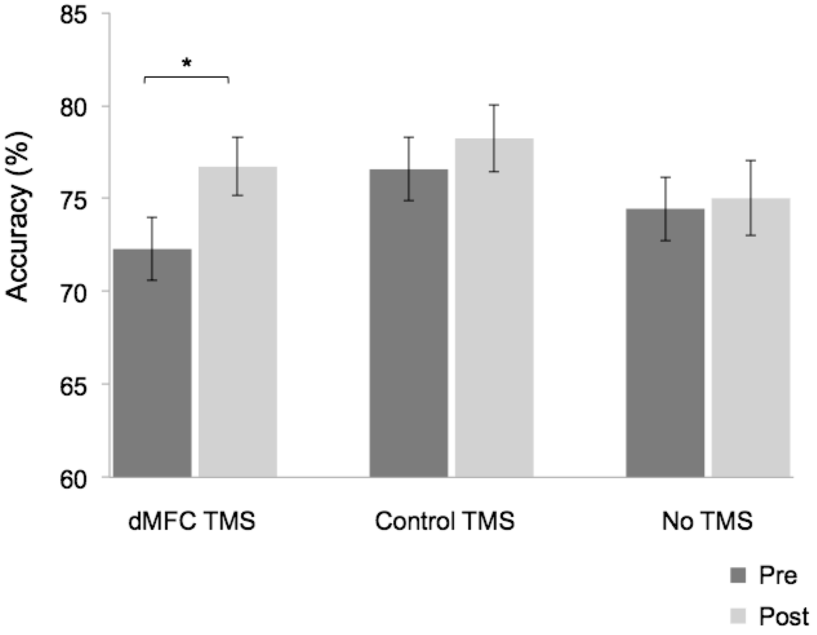

Figure 5: Accuracy (% correct responses) in the search task before TMS / break (pre) vs. after TMS / break (post) for the three experimental groups showing that dMFC TMS increased precision accuracy in the search task.

### *TMS effects on perceptual versus response switching: reaction times*

Reaction times were faster after TMS or a break, as compared to baseline, regardless of experimental group or task (F(2,57) = 1.20, p = 0.31). To assess to what extent this speeding of reaction times was dependent on the type of information switch from one trial to the next, TMS effects on reaction times in the four different switch conditions of the search task (sDsR, sDdR, dDsR, & dDdR) were analysed. A significant interaction between Session (pre/post) x dimension switch (sD vs. dD) x response switch (sR vs. dR) x experimental group (dMFC TMS, control TMS, no TMS) (F(2,57) = 3.54, p = 0.04, $eta^2 = 0.11$) as well as interactions between response switch x Session (F(1,57) = 5.46, p = 0.02, $eta^2 = 0.09$) and response switch x experimental group (F(2,57) = 3.63, p = 0.03, $eta^2 = 0.11$) indicated differential effects of TMS on both types of switch conditions for the three groups. dMFC TMS seemed to stop the speeding effect of reaction times as compared to baseline when both perceptual and response-relevant features switched (within dMFC TMS group: Session x dimension switch x response switch: F(1,19) = 7.56, p = 0.01, $eta^2 = 0.29$; dDdR condition: t(19) = 0.10, p = 0.92; Fig. 6).

In addition there was a significant Session x response switch interaction (F(1,19) = 6.58, p = 0.02, eta$^2$ = 0.26) exclusively for the dMFC group (other two groups: p's > 0.58). In the experimental design the control TMS and no TMS group were considered as a baseline, meaning these results could either be interpreted as dMFC TMS slowing trials where both types of information switch, or preventing practice effects. As before, the dMFC TMS effect could not be attributed to baseline reaction times differences between the three groups (independent t-tests: all p's > 0.13).

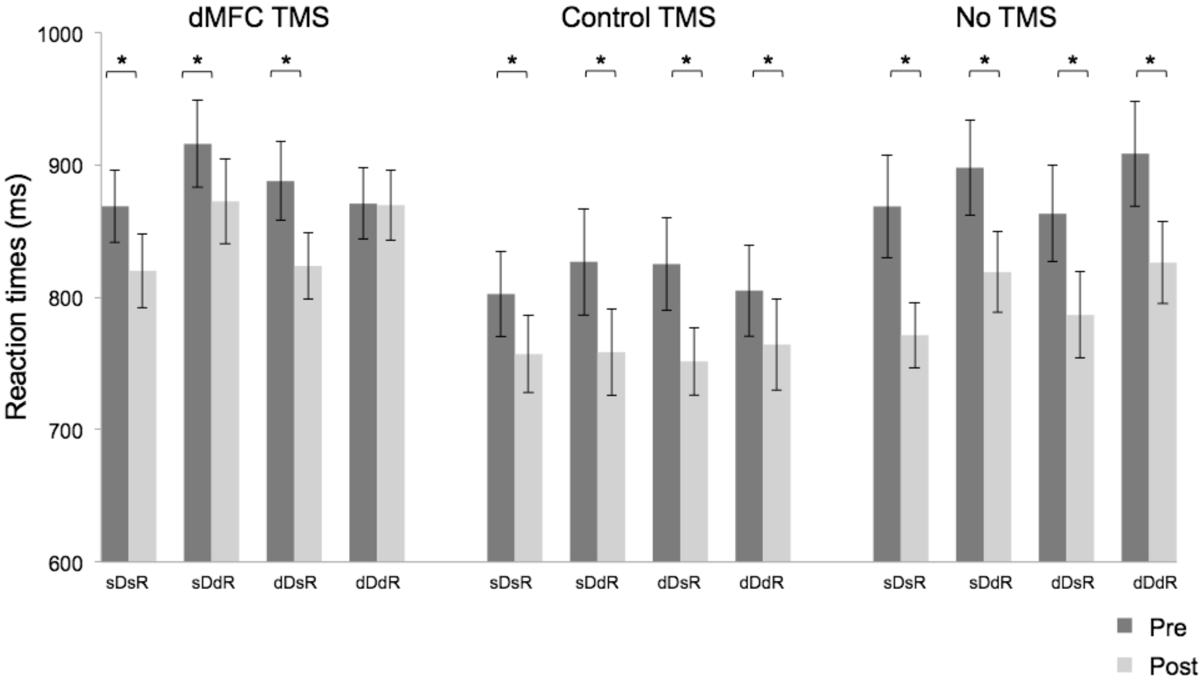

Figure 6: Reaction times in the search task before TMS / break (pre) vs. after TMS / break (post) for the four different switch conditions of the search task for the three experimental groups.

*TMS effects perceptual versus response switching: accuracy*

Accuracy was also calculated in terms of percent correct and not psychometric fitting (due to the subdivision of data into 8 different trial types per block). This revealed a general response switch cost (main effects of response switch, sR vs. dR; F(1,57) = 33.83, p < 0.01, eta$^2$ = 0.37) as well as sensitivity to the combination of response and dimension switch type over time

(Session x dimension switch x response switch: $F(1,57) = 6.30$, $p = 0.02$, $eta^2 = 0.10$). Critically, interactions involving experimental group (dMFC TMS, control TMS, no TMS) (Session x experimental group: $F(2,57) = 11.46$, $p < 0.01$, $eta^2 = 0.29$; Session x response switch x experimental group: $F(2,57) = 10.25$, $p < 0.01$, $eta^2 = 0.27$) suggested that accuracy was affected by TMS. Note that no 4-way interaction (TMS x dimension switch x response switch x experimental group: $F(2,57) = 0.04$, $p = 0.96$) nor any other main effects or interactions were observed. dMFC TMS improved accuracy on both the response switch trial types. Firstly it improved accuracy on dDdR trials as compared to baseline ($t(19) = -2.18$, $p = 0.04$, Cohen's $d = 0.45$; Fig. 7). Given that this accuracy increase was accompanied by slowed reaction times (see above, Fig. 6), this points to a potential speed-accuracy trade off (SAT) effect due to dMFC stimulation, consistent with previous studies. However, dMFC TMS also improved accuracy for the other type of response switch trials, on which no reaction time slowing was observed (sDdR trials, $t(19) = -4.67$, $p < 0.01$, Cohen's $d = 1.13$). This suggests that dMFC TMS was both affecting the SAT and also increasing response switch costs. Additionally, in the no TMS group there was a significant decrease instead of increase in accuracy after the break on dDdR trials ($t(19) = 2.69$, $p = 0.01$, Cohen's $d = -0.74$). Alternatively this may reflect an effect from vertex TMS e.g. due to spread.

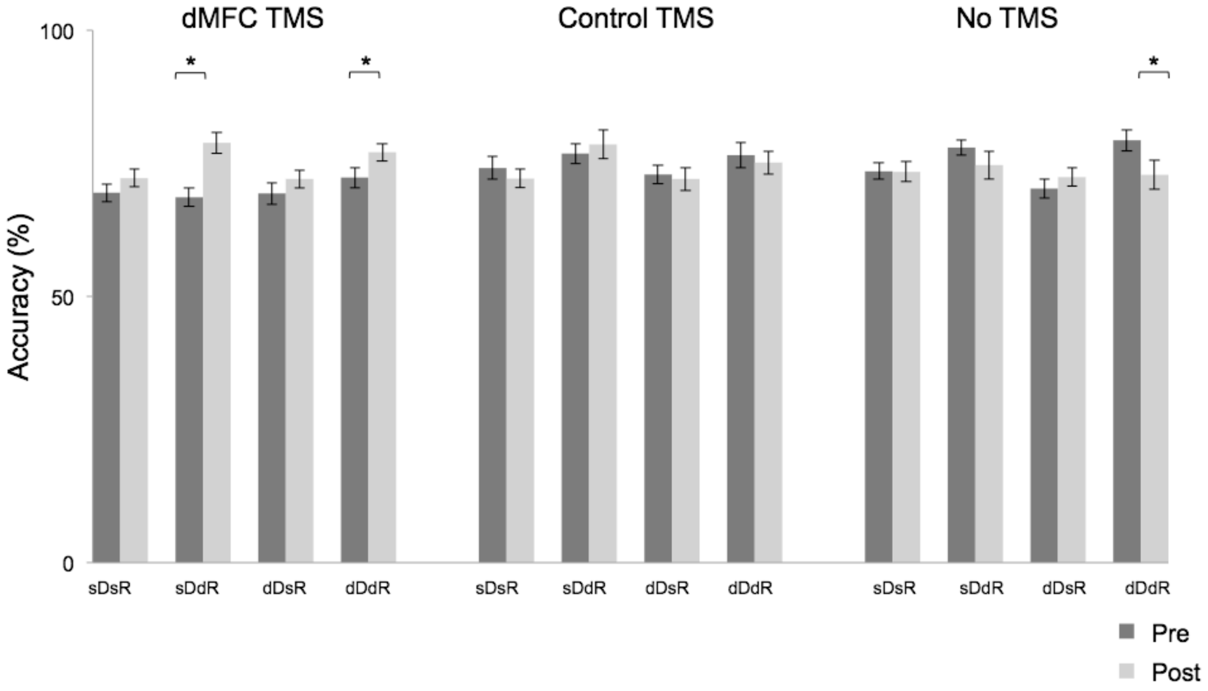

Figure 7: Accuracy (% correct responses) in the search task before TMS / break (pre) vs. after TMS / break (post) for the four different switch conditions of the search task for the three experimental groups.

### *TMS effects on switch conditions of the SVV task*

Investigating RT response switch costs in the SVV task, (as with search above) omnibus ANOVA including Session (pre/post) x response switch (sR vs. dR) x experimental group did not show an interaction (F(2,57) = 0.68, p = 0.51). However, if anything there was a trend in the opposite direction from in the search task, significant with post-hoc t-tests although not supported by intermediate ANOVAs. dMFC TMS seemed to induce a speeding rather than a slowing of dR reaction times (t(19) = 5.15, p < 0.01, Cohen's d = -1.12). Regarding accuracy there were no interactions between Session x response switch x experimental group nor between Session x response switch nor between response switch x experimental group (all p's > 0.11).

# Discussion

## *dMFC in the precision of perceptual decision making and the subjective visual vertical*

Dorsal medial frontal cortex (dMFC) activity correlates with trial-to-trial variations in response caution [37] and the dMFC has been proposed to be a part of a brain network for sensory evidence integration [38,39]. dMFC TMS can increase or decrease perceptual decision thresholds [4,6]. Here our task design allowed extending this previous work to investigate precision versus bias of perceptual decision-making. Proficient observers are both precise and unbiased. Higher precision reflects more reliable discrimination by the observer. Precision is a measure of variance in responses corresponding to the steepness of the fitted sigmoid, calculated as the 'sigma' of the cumulative Gaussian fit of the psychometric function [1]. "Bias" in this sense is the bias of the percept compared to the true stimulus value. dMFC TMS did not affect bias. A simple SVV task (without search) was used primarily to classify participants according to their resting baseline bias and to check for bias-specific effects during search: online parietal TMS has affected bias depending on participants' resting bias [26]. However, while the dMFC is involved in establishing the precision of verticality judgments, particularly under situations of high perceptual load (such as during a search task setting), we did not find evidence that it plays a crucial role in the bias of verticality perception.

dMFC lies outside the conventional network related to vestibular processing and the SVV [15–18], yet it is a main hub in a network that is responsible for perceptual decision making in which it exerts top-down control to other nodes such as the intraparietal sulcus (IPS) or insula [24,40], areas which form the human core vestibular region [15–17]. Moreover, dorsal medial frontal cortex may contribute to the processing of vestibular information [16,19]. A functionally relevant interaction between the right IPS and dMFC during verticality judgments should not be ruled out. Rather, future work should address the involvement of the fronto-dorsal spatial attention network with its cortical core regions located in the posterior parietal and frontal cortices [41,42] more closely. This may help illuminate a proposed broader relationship between the classical attentional and vestibular networks giving rise to higher vestibular cognition [43–45].

### *dMFC in response control when perceptual demands are high*

dMFC is activated in visual search in the attentionally demanding situation where switches in the target-defining dimension are accompanied by response switches [27]. dMFC TMS affects action reprogramming only when the stimulus discrimination is hard and not easy [28]. The dMFC may be particularly critical for response selection if perceptual attentional demands are high [46]. This was generally the case here during the search task, but also in particular during the "dDdR" trials where response selection had to be made under conditions of difficult perceptual selection. The slowing of reaction times on dDdR trials with dMFC TMS was superimposed on top of an overall TMS-related speeding. In addition, the observed speeding of reaction times could reflect global practice effects in the search task as the same pattern of faster responses over time was also observed even for the no stimulation control group. This speeding was found on almost all conditions, with the single exception of the dDdR trials. Reaction times on these trials involving both perceptual (dimension) and response switches did no longer differ from baseline after dMFC TMS whereas reaction times in all other search task conditions (and importantly dDdR reaction times for the two control groups) were faster. Given that this only occurred under situations where both response and perception (dimension) switched (i.e. trials with high perceptual load), and only with dMFC TMS, this dDdR effect cannot be attributed to general non-site specific distraction from the TMS, but rather is evidence of dMFC TMS slowing reaction times on this condition.

dMFC has been linked to the speed-accuracy trade off that occurs when both higher accuracy and slowed reaction times reflect more time spent on selecting relevant from irrelevant information [5,24,40,47,48]. This was also partly evident in the current study where dMFC TMS both lengthened reaction times and increased accuracy on these dDdR trials. Note that a speed-accuracy trade-off cannot fully explain all the effects during the dimension/response switch analysis because dMFC TMS affected accuracy on response switches independently of whether the dimension switched, whereas the reaction time effect was more selective.

*Limitations and Outlook*

Future work could directly compare several areas with different tasks and protocols. Previous heterogeneous effects of dMFC TMS on decision threshold may be attributed to task difficulty [4–6,40,49]. The first continuous theta burst TMS study produced inhibitory effects, with excitation after intermittent bursts [50]. There may however be no direct 1:1 mapping between continuous/intermittent and inhibitory/facilitatory theta burst TMS: modelling suggests that continuous protocols elicit inhibitory and facilitatory effects simultaneously with different time-courses [51]. Accordingly there is now high variability evident in the literature [53]. Here, continuous theta burst facilitated performance. TMS effects may be highly task-specific: future work dMFC TMS studies should use tasks that do not require orientation judgements. By using two sites and two different tasks, one with multiple switch types, we were able to dissociate between multiple hypotheses regarding dMFC function – this did necessarily increase the number of statistical tests performed. Future studies with simpler designs - only examining one task, site, or switch type - may allow replicating the core findings here with fewer tests and with multiple comparison correction. Additionally no effects on bias were found here with offline theta TMS as were found previously with an online 10 Hz TMS protocol [26] and this could be addressed directly by comparing both areas with both protocols.

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# 3 General Discussion

The aim of this thesis was to investigate the interplay of the attentional, decision making, and vestibular systems. The following sections will briefly summarize the two conducted experimental studies and discuss implications of their findings for the understanding of vestibular-attentional interactions, methodological considerations when studying human higher vestibular processing, and future clinical and scientific work.

## 3.1 Summary of findings

The first study presented in this thesis (Willacker et al., 2019; chapter 2.1) aimed to examine the role of the right intraparietal sulcus (IPS) in verticality perception. Spatial orientation and navigation are dependent upon our ability to form a stable and precise perception of verticality, which in turn is posited to rely on a distributed network of multisensory regions. The right posterior parietal cortex, especially the right IPS, has been consistently associated with spatial orientation and attention. A combined EEG-TMS paradigm was applied to investigate the role of the human parietal cortex in both verticality perception (subjective visual vertical SVV task) and spatial attention (Landmark task) in healthy participants. Results indicated that repetitive right IPS TMS facilitated verticality perception by normalizing individual SVV biases, which was also reflected on an electrophysiological level over a frontocentral site. No such hemisphere-specific results were found for the Landmark task. Thus, this study points to a hemisphere-specific role of the ventral IPS region in verticality perception and spatial attention, and provides a promising new direction for furthering our understanding about the neural implementation of spatial orientation in healthy and clinical populations. In addition, it supports the ideas of right lateralization and disinhibition for healthy visual-vestibular processing.

In the second study (chapter 2.2) the role of the human dorsal medial frontal cortex (dMFC) in verticality judgments during different levels of attentional load was investigated. Increasingly, TMS is being shown to improve performance in cognitive tasks. Such effects are normally only described in terms of relatively crude measurements such as reaction time or accuracy. This study used psychometric fitting to demonstrate that TMS can reduce variability – i.e. increase "precision". This effect was shown for a specific brain structure-function relationship that is of particular interest: although the human dMFC has been linked to perceptual decision making, the nature of any causal involvement of this area in the precision and bias of perceptual judgments remained unclear prior to this study. Evidence for a causal involvement of the dMFC in establishing the precision and accuracy of perceptual decision making for verticality perception was reported, particularly in situations of high perceptual load.

## 3.2 Conclusions about the relationship between the attentional and higher vestibular systems

The combined results from both conducted studies support the idea of a functional interplay between the vestibular, spatial attentional, and perceptual decision making systems. In addition, they emphasize that distinct behavioural features such as bias, precision, or accuracy contribute to overall verticality perception and can be modulated independently.

Study 1 of this thesis (chapter 2.1) showed that the right IPS is involved in the establishment of the bias of verticality perception. However, no effects related to the threshold/precision of SVV judgments were observed. In contrast, the contribution of the dorsal medial frontal cortex (dMFC) to verticality judgments seems to follow the almost opposite pattern: study 2 (chapter 2.2) did not find any evidence for a crucial function of this cortical area regarding SVV biases. Instead, the dMFC seems to play a role in the precision/uncertainty and accuracy of SVV estimates. This applied, however, only for situations where SVV judgments had to be made under conditions of high perceptual load (when the SVV was tested in a visual search surrounding) but not in a more standard SVV setting, as used in study 1 where no concurrent distracting visual information was presented next to the SVV line stimulus. This functional dissociation suggests a potential functional interaction between the right dorsal parietal cortex and the medial frontal cortex with respect to verticality perception or higher vestibular processing more generally. Optimal visual-vestibular perceptual performance is determined by both a small bias and high precision (Angelaki, 2014). While right lateralized parietal structures seem to contribute mainly to the perceptual bias, the frontal cortex is concerned with the uncertainty and reliability of vestibular related perception when perceptual and visual attentional demands are high. This is in agreement with earlier non-invasive brain stimulation work on parietal contributions to verticality perception which showed shifts in SVV biases due to interference with activity in parietal regions (Fiori, Candidi, Acciarino, David, & Aglioti, 2015; Kheradmand, Lasker, & Zee, 2015; Kheradmand & Winnick, 2017; Lester & Dassonville, 2014). In accordance with results from study 1, these previous studies did not report any modulations of perceptual precision related to the stimulation. Moreover, while parietal areas show up in lesion studies in patients that demonstrate pathological tilts of the SVV, reports on (medial) frontal lesions associated with disturbed verticality perception are scarce (Baier & Dieterich, 2014; Baier, Suchan, Karnath, & Dieterich, 2012; Brandt & Dieterich, 1994; Brandt, Dieterich, & Danek, 1994; Dieterich & Brandt, 2018; Konzelmann, 2013). Given the findings of the two presented studies, this could be explained by the fact that only the bias (tilt) of patients' SVV is typically investigated in clinical routine, while the precision of their verticality estimates is not taken into account. In addition, clinical SVV assessments do not include conditions of higher perceptual demand (such as in study 2). The medial frontal cortex, however, seems to be relevant for the precision of verticality judgments, particularly when perceptual load is increased. Therefore, the medial frontal cortex might have not been described as a typical lesion site associated with impaired verticality perception in vestibular or neurological patients despite it having a relevant role in establishing the distinct features of verticality judgments. To further substantiate the functional dissociation and interplay of the dorsal parietal and medial frontal cortices in visual-vestibular processing, future studies should compare the effects of reversed stimulation of the two regions during the two paradigms (i.e. dMFC stimulation applied to a SVV-Landmark task as used in study 1 and IPS TMS during SVV judgments in a visual search setting). To test for direction effects of the proposed parietal-frontal correspondence combined stimulation paradigms are needed. Further, such paradigms would help to shed more light on the temporal sequence of parietal-frontal interactions during processing of visual-vestibular information.

In general, the results of the two studies presented in this thesis strongly agree with the literature on higher vestibular functioning (Brandt & Dieterich, 2017; Brandt, Strupp, & Dieterich, 2014) and vestibular cognition (Besnard et al., 2016; Bigelow & Agrawal, 2015; Hitier et al., 2014; Seemungal, 2014; Smith, 2017). Such literature argues that vestibular processing is not solely reliant on the functioning of peripheral and core central vestibular structures but is also affected by, and interacts with, higher cognitive processes such as attention. By modulating activity within cortical regions proposed to be main hubs of the human fronto-dorsal spatial attention network (Corbetta & Shulman, 2002, 2011), and by varying perceptual demands during a visual-vestibular task, this thesis was able to demonstrate such interactions giving rise to higher vestibular functioning. Further, the regions stimulated in the present studies are considered to be highly multimodal (i.e. they respond to, and integrate, various sensory information, such as that required for optimal verticality perception; Baier, Suchan, Karnath, & Dieterich, 2012; Baier, Thomke, et al., 2012; Darling, Pizzimenti, & Rizzo, 2003). Therefore, the present results complement the existing literature which suggests that the human "vestibular cortex" is multisensory in nature, with performance and perception being dependent upon constant interactions between different multisensory regions (Brandt & Dieterich, 2017). As such, the reported TMS effects on verticality perception should be considered as network effects concerning multiple parts of the human vestibular and attentional networks rather than effects limited to the stimulated regions themselves. Functionally the parietal cortex and dMFC are not strictly separable from other parts of the vestibular network as they are highly interconnected, both inter- and intra-hemispherically (Brandt & Dieterich, 1999; Dieterich & Brandt, 2018; Lopez & Blanke, 2011; Lopez et al., 2012; zu Eulenburg et al., 2012). This is also underpinned by the EEG findings from study 1, which showed fronto-central effects following IPS stimulation, thus, revealing parietal-frontal activation linked to visual-vestibular processing.

The findings of the two studies in this thesis highlight the importance of multisensory integration for vestibular function, and strengthen the notion that parietal and frontal structures are part of a cortical network which mediates different inputs from the visual, auditory, proprioceptive, and vestibular sensory systems in order to reach a final vestibular percept (Brandt & Dieterich, 1999; Dieterich & Brandt, 2018). The behavioral effects of parietal and frontal TMS stimulation, as well as the impact of attentional load on verticality judgment, observed in the studies of this thesis might reflect an interaction of attention and multisensory integration processes for visual-vestibular functioning, similar to that described in the integration of other sensory information (Talsma et al., 2010). Moreover, the results of the two studies presented here are in line with earlier work, which showed that the parietal and frontal cortices are crucially involved in spatial cognition and topographic memory (Dieterich & Brandt, 2018; Howard et al., 2013). These regions contribute to the establishment, remapping, and integration of egocentric and allocentric coordinate information, which are necessary steps for the creation of an internal model of one's position in space and for successful spatial perception, including verticality perception (Barra et al., 2010, 2012; Borel et al., 2008; Chechlacz et al., 2010; Clément et al., 2009; Pouget & Sejnowski, 2001). These steps can be modulated by top-down influencing factors such as attention (Barra et al., 2012), which is in accordance with the results from the studies of this thesis and the concept of higher vestibular functioning.

The findings of study 1 support the idea of a lateralization of the human "vestibular cortex" to the non-dominant hemisphere (Dieterich et al., 2003; Lopez, Blanke, & Mast, 2012). The reported TMS effects on behavioral performance and electrophysiological activity were specific to stimulation of the right IPS in right-handers whereas TMS of the homologous left-hemispheric area did not lead to any effects regarding verticality judgments. This again highlights the correspondence between the higher vestibular and attentional systems, with the spatial attention network also showing a right-lateralized dominance (Corbetta & Shulman, 2002, 2011).

## 3.3 Methodological considerations

### a. SVV measurement method and stimuli

Verticality perception as studied in terms of SVV performance can be assessed in different ways. In the clinical examination of vestibular patients and in the majority of early verticality perception research, the SVV has commonly been examined by means of different methods of adjustment (ADJ) (Baccini et al., 2014). These require the patient/participant to align a visually presented line, which is tilted away from the true vertical by a specific degree, until it is perceived as vertical. The adjustment can happen manually (e.g. by repeated button presses or rotating a dial) or verbally (by instructing the examiner to tilt the line in a specific direction until it appears vertical). In contrast, the studies of the present thesis used a computerized two alternative forced-choice (2AFC) SVV task for the assessment of verticality judgments. This approach was chosen for several reasons. First, it allowed the applied online TMS stimulation in study 1 to be precisely timed and thus, be kept constant within the trial sequence. This enabled comparisons across participants, tasks and stimulation conditions, as well as the relation of stimulation effects to specific perceptual stages. Second, this approach meant that concurrent EEG could be recorded and time-locked to the different stages of the stimulus presentation, thereby offering the possibility of ERP analysis. Lastly, this approach allowed the investigation of distinct features of SVV performance such as perceptual bias, precision, accuracy and/or reaction times. Specifically, individual SVV (and for study 1 Landmark) performance was derived by means of psychometric fitting of the observed data (see also Fig. 2 in the General introduction). To calculate SVV biases, the percentage of clockwise (CW) responses within one experimental block was plotted as a function of the orientation (tilt angle) of the line. The 50% point (i.e. point of subjective equality, PSE) obtained from the sigmoid fit to the data reflects a participant's individual SVV bias (Angelaki, 2014; Baccini et al., 2014; Dyde et al., 2006; Foxe et al., 2003; Lopez et al., 2011). The standard deviation relates to the steepness of the slope of the sigmoid and provides a measure of the participant's discrimination threshold, thus reflecting response variability or uncertainty, with a smaller standard deviation corresponding to a steeper slope, indicating less variable/more reliable discrimination performance (Angelaki, 2014; Baccini et al., 2014; Dyde et al., 2006). The importance of examining both these two features of verticality perception and the possibility to modulate them independently from each other is demonstrated by the studies of the present thesis.

Additionally, testing the SVV in a 2AFC task version offers various further advantages over ADJ SVV procedures (Baccini et al., 2014; Paci et al., 2011). Although estimates of perceptual bias and threshold can also be derived from ADJ paradigms, data gathered from 2AFC SVV tasks are thought to be more robust against artefacts and therefore more reliable (Klein, 2001; Paci et al., 2011). Specifically, it has been shown that a range of experimental variables, such as initial tilt angle of the to-be-adjusted SVV line, method of adjustment (manually or verbally), length of the line, or speed of the line motion during the adjustment, significantly affect the final SVV estimate (Baccini et al., 2014). Moreover, as opposed to 2AFC paradigms, ADJ methods do not allow the measurement of full psychometric functions, and may therefore ignore valuable aspects of behavioural performance (Baccini et al., 2014; Dyde et al., 2006; Klein, 2001; Paci et al., 2011). In addition, ADJ procedures are typically more complex, longer in duration and require a higher number of more complicated experimental instruments. Despite all the advantages of 2AFC SVV paradigms over ADJ methods, the viability of their application in SVV assessments of patients and their integration in the clinical routine still needs to be investigated. Future studies investigating the potential parameters that might influence 2AFC SVV measurement outcomes, such as trial numbers, appropriate choice of the tested tilt angle range, or test-retest reliability, are needed in order to establish standards for future SVV research and clinical work.

An important factor that must be considered when testing the SVV by means of computerized paradigms is the problem of presenting a near vertical line on a computer monitor. As the image is composed of pixels arranged on a grid, a near vertical line is actually a series of staggered vertical lines that are clearly distinguishable from a true vertical line. Most graphics software compensates for this problem by aliasing, which involves adding additional pixels in a gradient of intensity to create the illusion of a near vertical line when viewed from a sufficient distance. However, this solution is not optimal for an experimental investigation of the SVV. Firstly, the total luminance of a true vertical line is different from that of a near vertical line with additional pixels added during aliasing, and such a difference might result in ERP differences that are not truly related to verticality. Secondly, if the subject is close to the screen the differences in the image due to aliasing might serve as a cue (either conscious or unconscious) as to whether the line is vertical or not. As a solution to these problems, the SVV stimuli in the two experiments presented in this thesis were created by first calculating the true position of the line, and then assigning each pixel near this true position a random intensity within a range. The range of possible intensities decreases with distance from the line such that they reach zero (i.e. black) by a certain distance from the true line. This results in a “blurred” bar which contains no vertical edge at any point, but does have an average overall verticality, and a total luminance which is the same (i.e. the number of pixels with any given intensity is the same) regardless of the angle (Fig. 6). A white central fixation point from which the white bar emerged was present throughout the experiments. The fixation point consisted of a blurred circle, created in a similar way to the bars, i.e. each pixel was given a random intensity value within a certain range, which decreased to zero with distance from the true centre of the screen. This again ensured that the true vertical could not be perceived from looking at the fixation point.

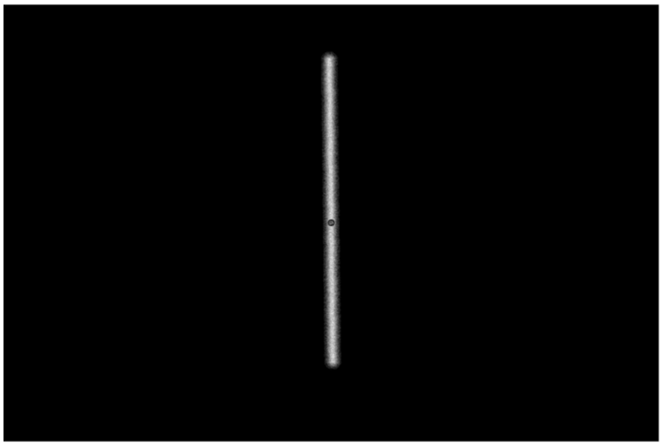

Figure 6: SVV line stimulus used for the two studies of this thesis.

### b. TMS and EEG

TMS complements and extends findings from other neuropsychological methods in the investigation of (human) brain-behavior relationships and physiology. As described in chapter 1.4a the application of TMS offers an important advantage over other neuroscientific methods: not only can it be used to investigate whether a specific brain region functionally contributes to a given task but TMS can also be used to study causal rather than merely correlational brain-behavior relationships. In general, TMS effects are strongly dependent on a variety of stimulation parameters such as stimulation site, protocol, or coil type. At present, the exact cortical action mechanisms of TMS remain unclear and potentially vary greatly across participants and brain regions (Pascual-Leone, 2000).

The human vestibular cortex encompasses several well-defined, anatomically separate cortical structures. Due to its relatively high spatial resolution, TMS can be used to study the role of these areas and their potential interactions with higher brain functions, such as attention, by interfering with a given brain region’s individual activity in a precise manner. However, as the applied pulses only reach neurons which are located just beneath the skull (Hess et al., 1987; Ridding & Rothwell, 2007), TMS doesn’t allow the study of deeper brain areas and their relevance for cognition. Regarding the question of the interaction between the vestibular and attentional or decision making systems, TMS can therefore only be used for brain regions which are close enough to the skull to be reached by the induced current. Thus, the role of deeper core areas of the human vestibular network in this interplay, such as the insula, cannot be studied by means of TMS alone. To overcome this issue, the combination of TMS with other neuroscientific techniques capable of investigating activation patterns of deeper brain regions is required. Such combined use of TMS together with other methods offering high temporal and/or spatial resolution (e.g. EEG or fMRI) would further enable the study of the neural dynamics of the applied stimulation. Despite the high variability in response to TMS, using individualized stimulation protocols that take factors such as an individual's most effective stimulation site or optimal timing of stimulation pulses during a given task into account could maximise TMS effects. Once functional and anatomical data of a participant are available, TMS can be applied to individual hotspots of the vestibular and attentional networks, respectively. Further, finding ideal stimulation sites and timings could be clinically relevant as it could help patients to gain a maximum benefit from the stimulation. In this context, neuromodulation by means of TMS might serve as a promising therapeutic tool for the treatment of vestibular patients as well as for clinical research, which is discussed in more detail below in section 3.4.

The results of this thesis demonstrate the capability of the attentional system to contribute to visual-vestibular perception. Particularly in the context of (spatial) attention studies, the inclusion of control conditions is crucial when formulating a TMS design. The clicking sound of the coil during discharge, the feeling of the coil on the head, and the sensation of the current on the scalp are all salient events, which can lead to (spatial) shifts or distraction of the participant's attention. When considering SVV tasks where the tilt direction of the stimulus line has to be rated, it is important to take spatial attention shifts due to coil position on the head into account. Ideally, such paradigms should include a control stimulation site that is located over the same hemisphere as the test site in order to control for spatial biases towards the stimulated site. As in study 1 of this thesis a control site located over the opposite hemisphere from the active test site was chosen (in order to test for hemispheric differences related to verticality judgments) follow-up work including a control stimulation site on the same hemisphere is needed.

The majority of previous human imaging work has applied fMRI to investigate verticality perception and vestibular processing, as this method allows the measurement of brain activity from any region of the brain with a good spatial resolution (Ertl & Boegle, 2019). However, due to the supine position of participants and the restriction of head and body movements during data acquisition, (f)MRI does not allow naturalistic vestibular test settings. Lying positions create biases in verticality judgments (Lopez et al., 2008; Lopez et al., 2011; Luyat et al., 2005) and interfere with neural activity related to visuospatial processing (Arzy et al., 2006). To overcome these issues and be able to record brain activity in a more naturalistic setting, study 1 of this thesis used EEG measurements to examine cortical activity related to visual-vestibular processing. EEG provides one of the highest temporal resolutions among all human non-invasive brain imaging techniques, thereby offering the possibility to draw conclusions about the timing of and temporal dynamics of perceptual events on a millisecond scale (Luck, 2005). Further, EEG can easily be combined with all common vestibular stimulation methods such as TMS or galvanic vestibular stimulation (GVS) (Ertl & Boegle, 2019), which makes it highly attractive for the investigation of the vestibular system. Still, there are some major limitations of this method. EEG only detects activation coming from superficial cortical structures while signals from deeper structures (e.g. the insula) can only be inferred by applying source reconstruction algorithms. Such reconstructions, however, have a relatively high spatial uncertainty and may lead to imprecise activity estimations (Ertl & Boegle, 2019; Michel et al., 2001). Therefore, future research on higher vestibular processing would ideally combine multiple imaging techniques with vestibular stimulation in order to compare and confirm results of the different modalities.

### 3.4 Clinical implications of presented findings and possible follow-up work

Rehabilitation interventions for patients with distorted spatial orientation (e.g. verticality perception) and spatial attention deficits (e.g. visuo-spatial neglect) focus mainly on sensory manipulations (Rode et al., 1998) and corrective exercises (e.g. for the often tilted head or body) to promote symmetrical processing of different sensory inputs and to improve the patient's perception of their own body in space, respectively (Bonan et al., 2015). At present, no therapeutic approach with the aim of manipulating the central integration of the different sensory inputs and the activity of the related cortical structures directly and non-invasively has been established. The presented studies of this thesis show that TMS has the potential to serve as both a scientific and therapeutic tool that enables interaction with crucial multisensory integration processes and a re-balancing of symmetrical spatial processing.

Spatial attention relies on balanced activity between the right and left parietal and frontal cortices (Corbetta & Shulman, 2002). The observation that spatial attention deficits are more frequent and severe after damage to right parietal structures (Corbetta et al., 2005) suggests a functional asymmetry between the two hemispheres (Mesulam, 1981). There are opposing theories regarding the right-hemispheric dominance in spatial attention: according to one model the right parietal cortex shifts attention to both hemifields while the left parietal cortex only shifts attention to the right hemifield (Heilman & Abell, 1980). In contrast, another model claims that the right hemisphere simply has a stronger bias to its contralateral (left) hemifield than the left hemisphere to the right hemifield (Kinsbourne, 1977). Moreover, TMS work has pointed to inter-hemispheric parietal competition and reciprocal inhibition related to spatial attention (Dambeck et al., 2006). In line with that, improvements in spatial attention performance by means of non-invasive brain stimulation have either focused on trying to increase activity within the lesioned hemisphere or to suppress the contralesional hemisphere and in that way decreasing its inhibitory effect on the other hemisphere (Agosta et al., 2014; Koch et al., 2012; Nyffeler et al., 2009).

A computational model of visuo-spatial attention has been introduced, which in addition addresses spatial orientation and verticality perception (Brandt et al., 2012). Based on neuroimaging and patient studies, this model proposes a bilateral organization of spatial attention and orientation, which is dominated by the right hemisphere and contains so-called “multisensory orientation/attention integration centers (MSOs)” within both hemispheres. These MSOs direct attention towards the contralateral visual hemifield and form connections with vestibular, visual, and somatosensory input structures such as the thalamus, primary visual cortices (e.g. V1), and areas MT/V5. Moreover, they are interlinked with each other via interhemispheric transcallosal pathways, which are mainly inhibitory, i.e. they exert reciprocal inhibition in order to maintain a balanced distribution of attention across both visual hemifields (Agosta et al., 2014). Given such an interhemispheric inhibition/rivalry, a lesion to one of the MSOs would not only result in an attentional inhibition within the contralesional visual hemifield, but would also lead to a “disinhibition” - and thus to increased activity levels - within the contralateral MSO. Indeed, in a recent study in right parietal patients, attentional performance levels in the contralesional (left) hemifield could be enhanced by means of inhibitory TMS of the left parietal cortex (Agosta et al., 2014). This behavioral improvement following disruption of the intact left parietal cortex might be attributed to a temporary recovery of interhemispheric balance due to a reduction of the hyperactivation of the stimulated hemisphere. Comparable results have also been found up to 32 hours following a single session of inhibitory TMS to the contralesional hemisphere, indicating a long-term effect of the stimulation and therefore, a possible therapeutic approach for neglect patients (Nyffeler et al., 2009). Consistently, after a two-week period of regular TMS stimulation, improvements of neglect symptoms lasting up to one month after the last stimulation session, as well as a reduction of the previously hyperactivity of the intact (left) hemisphere could be shown (Koch et al., 2012). Results from study 1 of this thesis agree with the model. Yet, further studies on the interplay between spatial attention and vestibular processing are needed to establish if, and how, interhemispheric inhibition gives rise to difficulties in SVV perception and/or spatial attention performance, how these two perceptual processes relate to one another, and whether TMS might be used as a clinical tool for the treatment of pathological visual-vestibular processing.

The studies described in the present thesis aimed to answer such questions in young, healthy control participants who did not report any history of neurological or vestibular disorders and who, without exception, exhibited non-pathological SVV values. In contrast, the question of whether the applied TMS stimulation leads to comparable (beneficial) behavioral effects in patients or participants that show disturbed SVV performance remains open. The studies presented in this thesis and the interhemispheric competition model suggest that future scientific work should continue to examine the role of fronto-parietal attention network structures in clinical populations. Key regions for future investigations are the right intraparietal sulcus (IPS) and its neighboring regions which have been proposed as the main integrator of visuo-spatial orientation and visuo-spatial attention (Agosta et al., 2014; Kerkhoff & Zoelch, 1998). For example, the hypothesis that disruption of left IPS activity by means of TMS would result in disinhibition of the homologous right parietal cortex, which could influence SVV as well as spatial attention performance, requires further investigation. This would provide one pathway to establish whether non-invasive brain stimulation might serve as a clinical tool for the therapeutic treatment of impaired verticality perception and related vestibular and neurological dysfunctions. Further, differences between healthy and pathological visual-vestibular processing could be examined by studying TMS effects on verticality judgments while manipulating SVV biases in healthy populations using, for example, tilted head position (Otero-Millan et al., 2018; Otero-Millan & Kheradmand, 2016) or concurrent visual flow (Dockheer et al., 2018; Reinhart et al., 2016; Schaadt et al., 2016; Thilo & Gresty, 2002).

Moreover, the present studies did not investigate the duration of the observed TMS effects on behavior but rather, focused on immediate stimulation consequences. Thus, further research is required to explore the possibility of long-term effects, or ideally improvements, in verticality perception using non-invasive brain stimulation of fronto-parietal structures. In addition, both studies of this thesis included only right-handed participants. Follow-up studies, using left handers and ambidextrous participants should be conducted in order to investigate how the proposed lateralization of the human cortical vestibular network (Dieterich et al., 2003; Lopez et al., 2012; zu Eulenburg et al., 2012) might modulate its interactions with higher cognitive functions such as attention.

Lastly, the combined results of both studies, particularly study 1, demonstrate the importance of considering the individual resting SVV bias when studying (TMS effects on) verticality judgments. No TMS-induced modulations of SVV were reported on a group level in study 1. However, after subdividing participants according to their baseline bias, into a CW and CCW bias group, normalizing effects due to the stimulation were observed. These effects would have been overlooked if individual baseline biases had been neglected in the analysis. Accordingly, missing effects of parietal TMS or other empirical interventions on verticality perception in earlier research could potentially be the result of a failure to take individual baseline bias into account. Previous studies concerning spatial attention biases regarding the horizontal plane, confirm the need to include individual spatial asymmetry at baseline as a factor when studying spatial attention and modulation by means of brain stimulation (Thomas et al., 2017; Varnava et al., 2013).

## 3.5 Conclusion

The results of the present thesis complement and enrich our knowledge of the interaction of the human attention, decision making, and vestibular systems through the use of TMS(-EEG). The findings strengthen the notion of a functional interplay of these systems during visual-vestibular tasks, such as verticality judgments. Additionally, they suggest an anatomical-functional dissociation of right dorsal parietal cortex and medial frontal cortex in verticality perception: while the right intraparietal sulcus is involved in the degree of how biased individual verticality perception is, dorsal medial frontal cortex was found to be related to perceptual precision and accuracy. Taken together these findings agree with the concept of a highly interconnected human cortical vestibular network, which is reliant on multisensory integration and modulated by higher cognitive functions such as attention. Altogether, the present thesis provides relevant theoretical and methodological implications for future clinical and scientific work in the field of higher vestibular processing.

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# LIST OF PUBLICATIONS

**Published articles:**

**Willacker**, L., Roccato, M., Can, B.N., Dieterich, M., & Taylor, P.C.J. (2020). Reducing variability of perceptual decision making with offline theta-burst TMS of dorsal medial frontal cortex. *Brain Stimulation, 13*(6), 1689-1696.

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# EIDESSTATTLICHE VERSICHERUNG / AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „Investigating the interplay of the human attentional and vestibular systems using transcranial magnetic stimulation“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation ‘Investigating the interplay of the human attentional and vestibular systems using transcranial magnetic stimulation’ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 13.07.2020

Munich, 13.07.2020

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Lina Willacker

# DECLARATION OF AUTHOR CONTRIBUTION

**Project 1: Egocentric processing in the roll plane and dorsal parietal cortex: A TMS-ERP study of the subjective visual vertical.**

Authors: Lina Willacker, James Dowsett, Marianne Dieterich, Paul C.J. Taylor

Lina Willacker and Paul C.J. Taylor conceived the experiment. Lina Willacker and James Dowsett programmed the experiment. Lina Willacker collected the data and analyzed the data with help of James Dowsett. Lina Willacker wrote the paper, which was commented and revised by Paul C.J. Taylor and Marianne Dieterich. Lina Willacker is the only first author of this paper.

**Project 2: Reducing variability of perceptual decision making with offline theta-burst TMS of dorsal medial frontal cortex.**

Authors: Lina Willacker, Marco Roccato, Beril Nisa Can, Marianne Dieterich, Paul C.J. Taylor

Lina Willacker and Paul C.J. Taylor conceived the experiment. Lina Willacker programmed the experiment. Lina Willacker collected the data with help of Marco Roccato and Beril Nisa Can. Lina Willacker analyzed the data and wrote the paper, which was commented and revised by Paul C.J. Taylor and Marianne Dieterich. Lina Willacker is the only first author of this paper. The manuscript was submitted to the journal "Brain Stimulation" on 26th November 2019.

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