TMS-EEG reveals hemispheric asymmetries in top-down influences of posterior intraparietal cortex on behavior and visual event-related potentials

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Abstract

Clinical data and behavioral studies using transcranial magnetic stimulation (TMS) suggest right-hemisphere dominance for top-down modulation of visual processing in humans. We used concurrent TMS-EEG to directly test for hemispheric differences in causal influences of the right and left intraparietal cortex on visual event-related potentials (ERPs). We stimulated the left and right posterior part of intraparietal sulcus (IPS1) while the participants were viewing and rating the visibility of bilaterally presented Gabor patches. Subjective visibility ratings showed that TMS of right IPS shifted the visibility toward the right hemifield, while TMS of left IPS did not have any behavioral effect. TMS of right IPS, but not left one, reduced the amplitude of posterior N1 potential, 180-220 ms after stimulus-onset. The attenuation of N1 occurred bilaterally over the posterior areas of both hemispheres. Consistent with previous TMS-fMRI studies, this finding suggests that the right IPS has top-down control on the neural processing in visual cortex. As N1 most probably reflects reactivation of early visual areas, the current findings support the view that the posterior parietal cortex in the right hemisphere amplifies recurrent interactions in ventral visual areas during the time-window that is critical for conscious perception.

Keywords: Attention; ERP; intraparietal sulcus; visual perception; TMS; TMS-EEG

1. Introduction

Neuronal systems that guide allocation of attention are asymmetrically organized in the cerebral hemispheres. This is clearly indicated by the neuropsychological disorders of neglect and extinction, which both are more frequent after damage in the right than the left hemisphere, especially in the temporo-parietal junction and posterior parietal cortex (Bellas et al., 1988; Vallar, 1998). In unilateral neglect, the patient typically is not aware of stimuli in the contralesional hemispace. Extinction is a related disorder in which the person fails to notice a stimulus in the contralesional hemispace when one stimulus is displayed in the left hemispace and another one simultaneously in the right hemispace. Several studies have also shown that transcranial magnetic stimulation (TMS) directed to the parietal cortex in the right hemisphere can produce a behavioral pattern mimicking that in neglect or extinction (for review, see Sack, 2010).

In Kinsbourne's (1987) theory, both hemispheres orient attention towards the contralateral hemispace, but the left hemisphere has a stronger bias than the right hemisphere. According to another influential theory (Heilman et al., 1987), the right hemisphere has attentional control over the whole visual field (both left and right visual field), but the left hemisphere's attentional control is only over the contralateral right field. Thus, the right field is attended by both hemispheres, whereas only the right hemisphere controls attention over the left field. Both theories predict that lesions in the right hemisphere will produce the rightward attentional bias, whereas damage in the left hemisphere would not have equally strong asymmetrical influences on attention.

Functional brain imaging has helped to formulate more detailed theories of the cerebral organization of attention. Corbetta and Shulman (2002) suggested a model that distinguishes between two distinct

attention systems in the brain, the ventral and the dorsal attention networks. The ventral network comprises the temporo-parietal junction and ventral frontal cortex. This fronto-parietal ventral network is responsible for exogenous attention, thus it responds to unexpected task-relevant events that occur outside the current focus of spatial attention. The dorsal network comprises intraparietal sulcus (IPS) and frontal eye fields (FEF). Endogenous, top-down orienting of attention depends on this fronto-parietal dorsal network (Corbetta et al., 1993; Corbetta et al., 2000). It is assumed that the ventral system is more right lateralized, whereas the dorsal system is bilateral (Corbetta & Shulman, 2002). Therefore, the right hemisphere dominance of neglect and extinction follows from the anatomy and laterality of the ventral regions that interact with the dorsal attention network (Corbetta & Shulman, 2011).

Top-down control signals from frontal and parietal cortex modulate sensory cortical activity. Coherence analysis and fMRI showed that attention-related activity in IPS1 and IPS2, the posterior parts of IPS (Swisher et al., 2007), led activity in occipital cortical areas by a few hundred milliseconds (Lauritzen et al., 2009), implicating a top–down flow of attention signals from IPS1 and IPS2 to early visual cortex. A study that examined interregional directed influences with Granger causality found information-flow from FEF to IPS and from these both areas to visual cortex (Bressler et al., 2008). In addition, top-down Granger causality from the right IPS to bilateral intermediate-tier ventral areas was predictive of correct behavioral performance (Bressler et al., 2008). Functional magnetic resonance imaging (fMRI) combined with transcranial magnetic stimulation (TMS) revealed that TMS of right IPS led to strong BOLD changes bilaterally in V1-V4 and V5/MT+, whereas TMS of left IPS did not change the activity in any occipital area (Ruff et al., 2009). These findings challenge the idea that only the ventral attention network would be asymmetrically organized, while the dorsal attention network would be bilateral. However, it is important to keep in mind that a null-effect with TMS of left

hemisphere does not necessary imply that the left hemisphere does not have any role in the task studied. It remains possible that other, non-stimulated parts of the dorsal network are bilateral, or that the target area in the left hemisphere was inadequately localized, or the experimental task did not tap the processes that are symmetrically organized.

Causal evidence for the asymmetry in the ventral attention network is supported by TMS studies that have shown that particularly the right angular gyrus, part of the ventral fronto-parietal network in posterior parietal cortex, modulates the excitability of visual cortex (Silvanto et al., 2009) and mediates spatial reorienting of attention (Chambers et al., 2004). In addition, numerous other TMS studies examining the causal role of posterior parietal cortex have shown right hemisphere dominance in attention (for review, see Sack, 2010), but the exact stimulation location is not known, as it has been determined most often on basis of the international 10/20 electrode location system without the aid of neuro-navigation. The most commonly used locations have been the positions P3 or P4 over the left and right hemisphere respectively, which are located for most of the participants above the angular gyrus (Kim, 2007), that is, TMS has been applied on ventral fronto-parietal attention network.

Frontal eye fields (FEFs) modulate perceptual-attentional processing in asymmetric manner. Grosbras and Paus (2002) found that pre-target TMS over the left FEF facilitated responses to targets only in the right hemifield in valid, neutral, and invalid cueing conditions. TMS over the right hemisphere had a *bilateral* effect for valid and neutral conditions, but not for invalid cueing, suggesting that TMS interfered with shift of attention only in the right hemisphere stimulation. In another study (Grosbras & Paus, 2003), TMS of right FEF before target onset facilitated detection of visual stimulus in the contralateral and ipsilateral field, whereas TMS of left FEF facilitated detection in the contralateral field only. Silvanto et al. (2006) found that TMS of the right FEF changed the sensitivity of left and

right MT/V5, as measured with the intensity of MT/V5 stimulation required to elicit phosphenes; TMS of the left FEF influenced the sensitivity of the left MT/V5 only. Thus, the causal role of FEF in the fronto-parietal attention network clearly is different in the left and right hemispheres. On the other hand, posterior IPS has been shown to causally contribute to fading of contralateral stimulus from awareness (Kanai et al., 2008) and to impair conscious perception (Koivisto et al., 2014), and a TMS study showed the involvement of right IPS in both endogenous and exogenous attentional orienting (left IPS was not stimulated) (Chica et al., 2011). When left or right posterior IPS was stimulated before the onset of visual target, the response times were slowed down, but only the stimulation of right IPS decreased accuracy of responses (Capotosto et al., 2012). However, we lack causal evidence showing that the posterior part of the dorsal attention system would modulate the activity of visual system asymmetrically *during processing of visual stimuli*. Therefore, in the present study we used TMS-EEG to measure the causal influences of left vs. right IPS1 on visual event-related potentials (ERPs) during a perceptual task in which the participants were presented with bilateral stimuli in the left and right hemifields. TMS-EEG allows us to not only to study the causal role of IPS1 in attention, but also when and how activity in visual cortex is modulated by IPS1. ERP studies with clinical participants have shown that especially the posterior N1 potential, around 200 ms after stimulus-onset, is reduced in neglect and extinction (Hämäläinen et al., 2014; Marzi et al., 2000; Di Russo et al., 2008, 2013; Yordanova et al., 2017). Therefore, if IPS1 is asymmetrically organized and plays a causal role in top-down attention, we expected that TMS of right IPS1 would induce a shift of attention toward the right hemifield and would reduce the amplitude of N1.

2. Method

2.1. Participants

Twelve neurologically healthy right-handed participants (aged 19 to 28 years, 5 males) with normal or corrected-to-normal vision took part in the experiment. They received a compensation of 20e/hour for participation. Informed written consent was obtained and the study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of Hospital District of Southwest Finland.

2.2. MRI-guided localization of IPS1

For localization of the TMS stimulation areas (Figure 1A),), individual high-resolution (1 mm3 voxel size) structural T1-weighted MRI images (8.1 s TR, 3.69 ms TE, 7o flip angle, 256×256 matrix) were acquired with the Philips Ingenuity TF PET/MRI system, equipped with a 3 Tesla magnet and a head coil. Transformation parameters for spatial normalization of the images to the ICBM/MNI brain template were calculated using a unified segmentation algorithm built into the Statistical Parametric Mapping (SPM8) software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL) implemented in Matlab (MathWorks Inc., Natic, MA). The left and right IPS1 in individual brain spaces were defined in the following way. The IPS1 coordinates in the standard ICBM/MNI space were derived from an earlier study: ±23, -73, 40 for x, y, and z coordinates with standard deviation values 6, 7, and 7, respectively (Swisher et al., 2007). A 6mm radius spherical region of interest (ROI) was built for each hemisphere around these coordinates. The ROIs were transferred to the native subjects' spaces using the inverse of the individual normalization parameters calculated at the unified segmentation

step. In each hemisphere an exact focus for TMS was defined as a part of medial bank of the posterior

IPS closest to the center of the ROI.

2.3. Transcranial magnetic stimulation

Nexstim eXimia (Helsinki, Finland) stimulator and a focal biphasic 70-mm figure-of-eight coil were

used for TMS. Single TMS-pulses were applied to the left and right IPS1 and to vertex. Current

direction in the second phase of the TMS pulse during IPS1 stimulation was from lateral to medial.

During vertex stimulation, the current direction was in half of the trials from right to left and in half of

the trials from left to right. TMS intensity was 75% of the stimulator's maximal output; it was slightly

higher as compared with that used in our earlier relevant studies (e.g., Koivisto et al., 2014), to

compensate the effect of the electrode cap on the distance between the coil and skull. Music (soft epic

metal), played via earplugs, was used to attenuate the sound of TMS and to reduce noise in EEG. The

volume was adjusted together with the participant to a level that was not disturbing. While music adds

a small amount of noise to EEG, it is not in phase with the visual stimulation, and brain activity

generated by music is averaged out while reducing the amplitude of alpha noise (Woodman, 2010). The

position of the coil was continuously registered relative to the participants' anatomical brain image

using eXimia Navigated Brain Stimulation system.

--- Fig. 1 ---

2.4. Visual Stimuli and Procedure

The visual stimulus was a 4.5 x 4.5 cm Gabor patch (4.3° in diameter; 2 cycles/degree). It was presented on a gray background on a 23-inch LCD monitor set to 60 Hz (16.5 ms/frame), positioned 60 cm away from the participants' eyes.

Each trial began with a central fixation point (0.5°) presented for 2 s., followed by the stimulus (Figure 1B) or by blank screen in TMS-only trials, for 2 screen refreshes. The edge of the stimulus was positioned 15° from the fixation. In stimulus-present trials, the stimulus was displayed randomly in three visual field (VF) conditions: bilateral condition, in which one stimulus was presented in the left and one in the right VF, in the left VF or in the right VF. A single TMS pulse was applied 50 ms after the onset of the visual stimulus (or after the onset of blank screen in TMS-only trials), and EEG was recorded (for details, see section EEG recording below).

The participants were asked to fixate their eyes on the fixation point, and to make two responses after each trial. First, they had to indicate, by pressing one of the four face buttons in the response pad (Logitech F310) using their right thumb, whether they saw a stimulus in both visual fields (top button), only in the left VF (left button), only in the right VF (right button), or in neither VF (bottom button). After pressing the corresponding button in the pad, a line segment (length 18°) with a bar in the middle of it appeared on the center of the screen. The participants had to rate the relative quality of their subjective perception of the left and right VF stimulus. They indicated on which side they perceived the stimulus to be more clearly visible by moving the bar along the line segment toward the left or right side. They were instructed to move the bar as much toward the left or right side as the stimulus on that side was more visible compared to the stimulus in the opposite side. When both stimuli were equally well perceived or no stimulus was perceived, they were asked to leave the bar on the center of the line. They were told that when only a left (or right) stimulus was perceived, they could move the bar far

toward the left (or right) end of the line, whereas in most of the trials only slight fluctuations in the relative visibility of the left and right stimuli were expectable and therefore they should carefully adjust the position of the bar according their subjective perception. The bar was moved to left or right by pressing buttons under their left and right index fingers, respectively. When the bar was in the intended position, they pressed the bottom face button, which ended the task and the next trial began.

The experiment consisted of 12 stimulus blocks, presented in two separate sessions in different days (6 blocks/session). The 6 blocks given in each session consisted of 2 blocks of left IPS1 TMS, 2 blocks of right IPS1 TMS and 2 blocks of vertex TMS. Left and right IPS1 and vertex were stimulated by turns in different stimulus blocks and the order of the stimulation areas was counterbalanced across the subjects. Every block consisted of 25 trials with bilateral visual stimuli, 3 trials with right and 3 trials with left VF unilateral stimuli, and 34 TMS-only trials (i.e., TMS pulse with no visual stimulus). The unilateral stimuli were catch trials and the TMS-only trials were used to remove the TMS-induced auditory and somatosensory activity from the ERPs (Figure 2).

Before the actual experimental trials, a calibration phase, without delivering TMS, was performed to adjust the contrast of the stimulus for each participant individually to obtain about 90% correct responses in the 4-alternative choice task. The task was the same as in the experimental blocks. One calibration block consisted of 30 trials (15 bilateral, 3 LVF, 3 RVF, and 9 no-stimulus trials). Starting from a contrast level of 50%, we decreased or increased it according the obtained score in steps of 10% (if the target was perceived too easily, the contrast was decreased, if it was too difficult, it was increased). If the accuracy level was near the aimed level, but not within 86 - 93%, and could not be achieved with steps of 10% in contrast level, steps of ±5% were used instead. The calibration block

was repeated for a second time when a valid subjective rating was achieved to confirm the accuracy of calibrated level.

2.5. EEG recording

EEG was recorded continuously during the experimental blocks at 20 000 samples/second using 32 Ag/AgCl electrodes and the NeurOne Tesla amplifier (Mega Electronics). Thirty electrodes were placed on the scalp based on the International 10–20 System (FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Pz, Iz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, TP9, TP10). Two extra electrodes were placed, one below the right eye and another at the right outer canthus. Reference electrode was placed on the right side of the tip of the nose and ground electrode on the center of the forehead. Electrode impedances were kept below 5 KΩ. EEG data was processed using EEGLAB (version 11) (Delorme and Makeig, 2004), Matlab (The MathWorks, Inc., Natick, MA) and Brain Vision Analyzer 2.0 (BVA). TMS pulse artifact was removed by cutting out 10 ms of EEG (beginning 3 ms before the pulse). This "mute window" was then interpolated by a third-order polynomial curve (for a similar procedure, see e.g. Reichenbach et al., 2011), based on the signal 10 ms before and 10 ms after the TMS-pulse. The signal was then resampled to 500 Hz. After the resampling, data was imported into BVA.

Data was high-pass (0.1 Hz) and low-pass (20 Hz) filtered. Gratton & Coles algorithm (Gratton et al., 1983) was employed to remove eye movement artifacts. Trials with amplitudes +- 100 µV in one of the channels were considered artifacts and removed from further analysis. Baseline correction was performed in the time window of -200 – 0 ms preceding the stimulus onset. To remove contribution of

TMS-induced auditory and somatosensory activity to the visual ERPs, we subtracted the ERPs in TMS-only trials from the trials which involved both TMS and visual stimulus (Figure 2), separately in each stimulation condition (i.e., vertex, left IPS, right IPS). The resulting ERPs were used in the analyses reported section 3.2. The electrophysiological data from two participants were not included in the ERP analyses. The procedure described above did not work with the data of one participant and about 70% of trials were removed; the data of the other participant contained so much other EEG artifacts that the resulting waves were very noisy without any identifiable ERP components.

--- Fig. 2 ---

Visual inspection of the ERPs revealed that there were two clearly visible components: a negative potential (N1) peaking in occipital electrodes at 200 ms after stimulus-onset and a larger positive potential (P3) peaking around 400 ms in occipital and parietal electrodes. Therefore, we analyzed the mean amplitudes of N1 (180-220 ms) and P3 (350-450 ms) in occipital (O1, O2) and parietal (P3, P4) electrodes using repeated measures analysis of variance (ANOVA) with TMS (3: vertex, left IPS, right IPS), Area (2: parietal, occipital), and Hemisphere (2) as variables. In addition, there was a weak posterior deflection resembling P1 between 100 and 150 ms. As P1 may be reduced in some of the patients with neglect (Marzi et al., 2000), we analyzed P1 amplitude with the 3 x 2 x 2 ANOVA to test the potential influence of parietal TMS on P1.

3.   Results

3.1.   Behavior

The proportions of correct responses in different stimulus conditions are shown in Table 1. TMS

conditions did not influence accuracy of forced-choice responses to the unilateral left stimuli (chi = .78,

p = 0.676), unilateral right stimuli (chi = 1.00, p = 0.607), or bilateral stimuli (chi = 1.00, p = 0.607).

Thus, TMS did not suppress visual awareness of the presence of the stimuli. In TMS-only trials, the

observers did not make false alarms (mean = .004, SD = .007), indicating that they were not guessing.

Table 1. Proportion of correct responses (SD in parentheses)
to the visual stimuli in the left, right, and bilateral visual
field (VF) conditions.

		TMS		
		Vertex	left IPS	right IPS
	left	.97 (.07)	.94 (.10)	.94 (.10)
VF	right	.96 (.08)	.97 (.07)	.97 (.06)
	bilateral	.98 (.02)	.99 (.02)	.98 (.02)

Next, asymmetries in subjective visibility during the bilateral trials were analyzed as a function of TMS

condition (Figure 3). For unilateral trials, the visibility ratings were not analyzed as they were not

informative, because the participants tended to move the bar to the left or right end of the scale for the

left or right side stimuli, respectively. There was variability in bilateral trials between the observers in

their general bias toward either the left or right side, with 3 observers showing a bias to see the stimuli

on the right more clearly, whereas 5 observers reported a bias toward left. The overall non-significant group level leftward bias, particularly in the vertex stimulation, was due to the latter observers. However, independent of the general left or right-side bias in individual observers, TMS of the right IPS shifted the bias toward the right side. Due to the right skewed distribution of ratings and small sample size, we tested the difference between TMS conditions with nonparametric Friedman's test. It showed a significant difference between the TMS conditions (chi = 6.50, p = .039). Compared with the vertex stimulation, the stimulation of the right IPS biased visibility ratings toward the right side (Z = -2.75, p = 0.006), whereas the stimulation of the left IPS did not have any statistically significant effect (Z = -1.26, p = 0.209). This result mimics the behavior of patients with extinction for whom a right hemisphere lesion induces a bias toward right side in bilateral stimulus conditions.

--- Fig. 3 ---

3.2. Event-related potentials

P1 (100-150 ms). Only a relatively weak deflection resembling P1 was observable between 100 and 150 ms (Figure 4A). A TMS (3: vertex, left IPS, right IPS) x Area (2: parietal [P3/P4], occipital [O1/O2]) x Hemisphere (2: left vs. right) ANOVA on mean amplitudes in P1 range (100 - 150 ms) (Figure 4) showed an almost statistically significant TMS x Hemisphere interaction, $F(2,18)$ = 3.51, p = 0.050, η^2_p = .282. It seems that, particularly over the right hemisphere, TMS of left and right IPS enhanced rather than decreased the amplitude as compared with TMS of vertex. However, separate analyses of the data from left and right hemisphere electrode sites did not reveal any statistically significant effects for TMS.

--- Fig. 4 ---

N1 (180-220 ms). The TMS (3: vertex, left IPS, right IPS) x Area (2: parietal, occipital) x Hemisphere (2:left vs. right) ANOVA on mean amplitudes in N1 range (180 – 220 ms) (Figure 4A and 4B) revealed a significant main effect for Area, $F(1,9) = 7.90$, p = 0.020, $\eta^2_p = .47$, indicating that the amplitudes were more negative over the occipital lobe (-4.4 µV) than the parietal lobe (-2.8 µV), mean parameter estimate = -1.6, 95% CI [-2.8, -0.3]. The amplitudes were marginally more negative over the left hemisphere (-3.9 µV) than the right hemisphere (-3.3 µV), $F(1,9) = 5.12$, p = 0.050, $\eta^2_p = .36$, mean parameter estimate = -0.6, 95% CI [-1.2, 0.0]. The most important finding was the main effect for TMS, $F(2,18) = 6.48$, p = 0.008, $\eta^2_p = .42$, which suggests that the stimulation of the right IPS reduced the N1 amplitude (-1.5 µV) as compared with the vertex stimulation (-4.7 µV) ($p = 0.007$, mean parameter estimate = 3.2, 95% CI [1.1, 5.3]) and the left IPS stimulation (-4.6 µV) ($p = 0.003$, mean parameter estimate = 3.1, 95% CI [1.3, 4.8]). The amplitudes of N1 did not differ between vertex stimulation and left IPS stimulation (p = 0.911, mean parameter estimate = -0.1, 95% CI [-3.0, 2.7]. TMS did not interact with Area, $F(2,18) = 0.65$, p = 0.534, $\eta^2_p = .07$, or with Hemisphere, $F(2,18) = 0.88$, p = 0.432, $\eta^2_p = .09$, neither was the 3-way interaction significant, $F(2,18) = 2.56$, p = 0.105, $\eta^2_p = .22$.

P3 (350-450 ms). The TMS (3: vertex, left IPS, right IPS) x Area (2: parietal, occipital) x Hemisphere (2:left vs. right) ANOVA on mean amplitudes in P3 range (350 - 450 ms) did not find any main effects for Area or Hemisphere ($Fs < 1$), and none of the two way interactions was statistically significant ($Fs < 1$). The main effect for TMS, $F(2,18) = 2.81$, $p = .087$, $\eta^2_p = .24$, and the TMS x Area x Hemisphere interaction, $F(2,18) = 3.33$, p = .059, $\eta^2_p = .27$, were approaching significance. These nearly statistically

significant effects seem to originate from the decreased P3 amplitude particularly over the left parietal cortex in response to the stimulation of left IPS.

4. Discussion

The results provide causal evidence for functional asymmetry in the dorsal attention network. Stimulation of the right IPS1, 50 ms after the onset of bilateral stimuli, produced a shift in visibility ratings from the left toward the right visual field and reduced the amplitude of posterior N1. Stimulation of the left IPS did not have any effect on visibility or on N1. Thus, only the stimulation of the right hemisphere produced a pattern mimicking the rightward attentional bias that is common in the typical patients with extinction.

The finding that the TMS of right IPS1, but not left IPS1, changed the bias in subjective visibility toward right is consistent with the right hemisphere dominance in spatial attention (Heilman et al., 1987). A similar rightward shift in line-bisection task was induced by repetitive TMS of right hemisphere area near posterior IPS (electrode location P6), whereas stimulation of left area (electrode location P5) did not have any effect (Fierro et al., 2000). This phenomenon mimics the performance in extinction and neglect, in which the left-side stimulus is often not noticed. In general, there was a non-significant group level bias to rate the left-side stimulus as more visible than that in the right side. This resembles the phenomenon of pseudo-neglect (Bowers & Heilman, 1980; Mattingley et al., 2004) which refers to leftward bias for example in line-bisection tasks, or in judging the left-side stimuli to be larger or higher in luminance or visibility than the stimuli in the right side. This phenomenon is in the opposite leftward direction as compared with the rightward direction in neglect and extinction

(rightward), but it may also be explained by the right hemisphere dominance in visuospatial attention, although the exact mechanism is not clear.

The TMS-induced left-to-right shift was observed in subjective ratings of conscious perception, but not in accuracy of perception, that is, TMS did not completely suppress the visibility of the stimuli in either visual field. In neglect and extinction, following right-hemisphere damage, the contralesional left-side stimulus is usually completely unnoticed, whereas TMS induced only a weak (but significant) shift from the left toward the right side. The stronger effect in patients is understandable, because the lesion in the right hemisphere of neglect patients is typically not limited only to the posterior part of the IPS but is large (Vallar, 1998). In addition, in patients the lesion is present all the time during processing, whereas a single TMS pulse endures only a fraction of a second and has only a temporally limited influence on neural processing. In addition, we used relatively large stimuli (4.3° in diameter) which are harder to suppress with TMS than smaller ones, but which were necessary to obtain sufficiently strong EEG signal for measuring early visual ERPs. Also, the structure of the stimulus list, involving mainly bilateral trials, may have biased towards choosing bilateral responses in the 4-choice task, which explains the high accuracy level in bilateral trials.

In addition to the behavioral results, also the ERP results support the right hemisphere dominance in posterior areas of dorsal attention network. TMS of right IPS1 reduced the amplitude of N1 potential, whereas TMS of left IPS1 did not. This finding also mimics the results in neglect and extinction patients, for whom the most consistent ERP finding is the attenuation of N1 (Hämäläinen et al., 2014; Marzi et al., 2000; Di Russo et al., 2008, 2013; Yordanova et al., 2017). The impairment of N1 in neglect seems to be multisensory, observed both in response to visual and auditory stimulation (Hämäläinen et al., 2014; Tarkka et al., 2011). The P1 potential was not reliably influenced by TMS of

left or right IPS1. This is not surprising, because also patients with neglect have shown intact P1 in response to visual stimulation (Hämäläinen et al., 2014; Di Russo et al., 2008, 2013; Yordanova et al., 2017).

The stimulation of right IPS reduced the amplitude of N1 over both cerebral hemispheres. This finding is consistent with hemispheric asymmetries observed with brain imaging, showing that right but not left IPS influences the activity of visual cortex bilaterally. Top-down signals from right IPS modulate activity in the ventral areas of both hemisphere (Besser et al., 2008), and TMS-fMRI has revealed that right IPS is able to change BOLD activity in visual areas V1-V4 in both hemispheres. The generator of the posterior N1 is localized in ventral occipital sources (di Russo et al., 2002, 2005). Thus, the bilaterally reduced N1 in our study may index the influence of right IPS1 on bilateral visual processing in the ventral stream.

The timing of the TMS-induced change in ERPs (180-220 ms) and the source of the N1 in ventral stream suggest that TMS indirectly (via the IPS) interfered with the reactivation of early visual areas during recurrent processing of the stimulus information. This type of processing plays an essential role in recent theories of visual awareness. According to prevailing theories of visual awareness (Dehaene & Changeux, 2011; Lamme, 2010), feedforward processing from V1 to higher visual areas is sufficient for unconscious visual processes, whereas visual awareness requires reactivation or sustained activation of visual areas, that is, a later phase of processing in which the higher visual areas engage in recurrent processing with the early visual cortex. In ERPs, the emergence of visual awareness of stimuli correlates with enhanced posterior negativity around 200 ms in the N1-N2 latency range (for a review, see Koivisto & Revonsuo, 2010), that is, in the same time window in which TMS of right IPS1 influenced ERPs. In addition, the findings that TMS of posterior IPS interferes with conscious

perception (Kanai et al., 2008; Koivisto et al., 2014), but not with unconscious processing (Koivisto et al., 2014), suggest that posterior parietal cortex contributes to visual awareness by modulating visual processing in top-down manner, without affecting unconscious visual processing along the ventral stream during the feedforward phase (Koivisto et al., 2014). The assumption that disruption of parietal processing leaves unconscious feedforward activation of the ventral stream intact is consistent also with the observations that neglect or extinction mostly affect conscious perception, while the neglected or extinguished stimuli are able to exert unconscious effects on performance (Driver & Mattingley, 1998; Marzi et al., 1996) and activate the visual cortex in the damaged hemisphere (Rees et al., 2000; Vuilleumier et al., 2002).

A previous study (Fuggetta et al., 2006) showed that single TMS pulse delivered 100 ms after visual stimulus-onset over the right parietal cortex (electrode P4 location; left hemisphere was not stimulated) modulated ERPs during visual search 250-300 ms post stimulus. To test the effects of parietal TMS on ERPs as early as possible after the stimulus onset, we applied TMS 50 ms after the stimulus onset. Given that the majority of visual feedforward signals reach the visual cortex about 40-60 ms after stimulus onset (Foxe & Simpson, 2002), how is it possible that parietal TMS applied at 50 ms exerts top-down influence on the relatively late reactivation of visual areas? Parks et al. (2015) stimulated posterior parietal cortex with single-pulses of TMS and recorded fast optical imaging activations within occipital cortex (BA18) while no visual stimulation was presented. The occipital activations onset at 24 ms and continued 48 ms post-pulse. Because in the present experiment the TMS pulse on IPS was applied 50 ms after the onset of the visual stimuli, it can be estimated that the pulse on parietal cortex modulated occipital processing from about 75 ms until 100 ms after the onset of visual stimuli. By the end of this this time window, the whole ventral stream has been activated (Liu, Agam, Madsen, & Kreiman, 2009) and recurrent processing is initiated (Boehler, Schoenfeld, Heinze, & Hopf, 2008).

This implies that TMS of IPS may have interfered with occipital activity in the early phases of recurrent processing, which is critical specifically for visual awareness to emerge (Boehler et al., 2008; Hurme et al., 2017). This interpretation relies on the results of Parks et al. (2015) which were obtained without visual stimulation, and which thus reflect the latency and duration of distant occipital activation by the parietal TMS pulse, without any direct link to attention *per se* or to what happens directly under the TMS coil (i.e., in parietal cortex). During our task, the participants were attending to the stimuli so that top-down attention could modulate visual processing. Therefore, it is likely that the TMS pulse in the right posterior IPS interfered with the workings of the dorsal attention system in the right hemisphere, making the attention system not fully able to exert top-down modulation of ventral processing. The point is that if the attention system under the coil is disrupted and it takes some time to reset the attention, the top-down modulation would be attenuated for a longer time than the immediate distal effects of TMS pulse last (until ~100 ms), thus influencing the relatively late processes that were reflected in N1 amplitude around 180 - 220 ms.

The interpretation that the TMS-induced shift toward right in subjective ratings reflected a change in attentional or perceptual bias, however, should be considered with some caution. The participants responded by moving the bar toward left with their left-hand fingers and toward right with their right-hand fingers. Therefore, it is possible that the result reflected motor-intention bias, a failure to respond to or initiate action toward the stimulated hemisphere (for motor-intention failures in neglect, see Heilman, 2004), or a combination of perceptual-attention and motor-intention bias. In either case, the stimulation of the posterior part of the right (but not left) dorsal network induced a bias toward right side. On the other hand, the behavioral results could be argued to reflect a leftward shift of bias caused by the stimulation of vertex. The stimulation of vertex might for example induce motor activation that interferes with performance. Unfortunately, our experiment did not include trials without TMS, which

would have resolved this issue. However, the motor activation would influence more likely the first response after the onset of the target stimuli (i.e., the 4-alternative choice response) than the second response (i.e., visibility rating). Nevertheless, if true, the shift of the vertex baseline toward the left side would imply that TMS of left IPS also biased the visibility ratings toward the left side, while stimulation of the right IPS had no effect. This alternative explanation is not very plausible, because it goes against the empirically well-established and widely accepted view that the right hemisphere is dominant in attention. The straightforward interpretation, that only the stimulation of right IPS influenced performance, is consistent with the ERP results and the empirically well-established and widely accepted view stressing the importance of the right hemisphere in attention. However, this does not imply that the left IPS1 has no influence on the activity of ipsilateral visual cortex or on perception of stimuli in the contralateral field. The bilateral visual stimuli or the TMS parameters in our study simply may not have been optimal for detecting such effects on behavior or ERPs.

In summary, the present results suggest that a TMS-induced disruption of attentional top-down control mechanisms in the right posterior intraparietal area biases attention toward the right side and decreases the posterior N1 potential over both hemispheres. These findings implicate right-hemisphere dominance for top-down modulation of visual processing by the posterior part of the dorsal attention system in humans.

Acknowledgements

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Figure captions

Figure 1. A) The posterior intraparietal TMS target sites in the MRI image of one participant's brain. The cross hair shows the target IPS1 area in the right hemisphere. B) The behavioral procedure in critical bilateral trials. After the fixation cross, the visual stimulus was presented in both visual fields and the participant indicated whether he/she had seen a stimulus in both visual field, in the left field, in the right field, or in neither field. After that, he/she moved the bar to the left or right side according to the relative visibility of the stimulus in the left or right field.

Figure 2. Removal of the TMS-induced auditory and somatosensory activity from the ERPs. The ERPs to TMS-only trials in vertex, left IPS, and right IPS stimulation conditions were subtracted from those to trials involving both TMS and visual stimulus in the corresponding stimulation conditions. The resulting difference waves were the ERPs used in the statistical analyses. The figure displays the waves in electrode O1 in the left IPS stimulation condition.

Figure 3. The visual-field bias in rating either the left or the right side stimulus as more visible in the bilateral condition. Error bars show within-subjects *SEM* (Cousineau, 2007).

Figure 4. A) Event-related potentials in vertex, left IPS, and right IPS TMS conditions in response to bilateral visual stimuli in occipital (O1, O2) and parietal (P3, P4) electrodes. B) Scalp distributions of evoked potentials in vertex, left IPS, and right IPS TMS conditions in the N1 range ($180-220$ ms) to bilateral visual stimuli.