Event-related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference

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The right posterior parietal cortex (PPC) is implicated in visuo-spatial processing, as illustrated by patients with visuo-spatial neglect, but the precise time-course of its contribution is still an open question. In the present study we assessed whether single-pulse transcranial magnetic stimulation (TMS) can interfere with the performance of normal subjects in a standard visuo-spatial task. Participants had to perform a landmark task while TMS was applied over the right PPC, the homologue region in the left hemisphere or the right primary motor cortex. Stimulation was time-locked to the stimulus presentation with a stimulus onset asynchrony (SOA) varying between 50 and 200 ms. Our results indicate that TMS interfered mainly with the visuo-spatial task when applied over the right PPC at an early stage (50 ms post-stimulus). The interference effect of single-pulse TMS in the present visuo-spatial processing is revealed by a processing cost for ipsilateral targets. These results are in agreement with neuropsychological and brain imaging studies showing a right hemispheric dominance in visuo-spatial processing but add crucial information about the time-course of visuo-spatial processing within the right PPC. *NeuroReport* 12:2369–2374 © 2001 Lippincott Williams & Wilkins.

Key words: BA7; Hemispheric dominance; Posterior parietal cortex; Single pulse TMS; TMS–MRI co-registration; Visuo-spatial

INTRODUCTION

Our study explored the interference induced by transcranial magnetic stimulation (TMS) applied over the right posterior parietal cortex (PPC) (BA7) on the performance of normal adult subjects in a standard visuo-spatial task. Line bisection is widely used as a clinical test of spatial cognition in patients with visuo-spatial neglect [1]. Patients are asked to manually bisect a line drawn on paper by indicating the subjective line centre. Patients with left neglect typically bisect lines (in the azimuthal plane) significantly to the right of actual centre or are poor at judging whether lines are correctly bisected in perceptual judgement tasks [2]. Here we used a modified computer version of the classical line bisection task known in the literature as the landmark task [3–7]. This task offered the opportunity to record reaction times from stimulus onset and to manipulate concurrently three main visuo-spatial variables: the length of line (the smaller the line the shorter the reaction time), the side of target (left or right side compared to the mid-point), and the distance of target from the mid-point (the larger the distance the shorter the reaction time).

TMS, which consists of the induction of a local electric field consecutive to the application of a brief magnetic pulse through the human scalp (single-pulse technique), is able to produce reversible functional impairments or improvements at the behavioural level in a wide range of cognitive tasks (see [8,9] for recent reviews). The major contribution of TMS as a technique for the investigation of visual cognition consists in the possibility to apply single pulses delivered according to time and space characteristics [10–12] in order to validate or invalidate functional hypotheses about the anatomical and temporal organization of the visual system. Facilitatory effects of single-pulse TMS applied over the posterior parietal and frontal cortex have been demonstrated in brain-damaged patients [13,14] and confirmed the involvement of the parietal cortex together with the frontal cortex in directing attention to spatial locations. Using repetitive TMS in normal subjects, Fierro and colleagues [15] recently demonstrated the possibility of inducing contralateral hemispatial neglect while stimulating the right parietal cortex, but did not provide information about the time-course of the transient interference in the parietal lobe. Previous electrophysiological studies [16] have demonstrated an early contribution (100 ms post-stimulus) of the parietal lobe for visuo-spatial processing.

In this study, we used single-pulse TMS applied over the right PPC of 10 normal subjects with the aim of confirming the right PPC preference in visuo-spatial processing (for reviews see [17–19]) and to investigate its time-course. In order to investigate the speed of visuo-spatial processing within the PPC, the stimulation was time-locked to the stimulus onset with an SOA of 50, 100, 150 and 200 ms. Two control conditions were used in order to test for the specificity of TMS interference in the right PPC. TMS was also applied either over the primary motor cortex (M1) in the right hemisphere or over the homologue PPC in the left hemisphere while subjects performed the same landmark task. In neither case did we expect to uncover interactions between SOAs and the visuo-spatial variables manipulated (i.e. length of line, spatial distance between target and mid-point and side of target) mainly because of the time-window of the different SOAs (right frontal site compared to right parietal site) or because of the pre-supposed hemispheric dominance of visuo-spatial processing (left parietal site compared to right parietal site). We used a co-registration technique between TMS and structural magnetic resonance imaging (MRI) providing offline accurate location of the pre-selected sites for magnetic stimulation.

MATERIALS AND METHODS

Subjects: Participants were 10 right handed subjects (5 males and 5 females) from the University of Louvain aged between 21 and 27 (s.d. 1.7 years) who took part in the present TMS study following approval of the local ethical commitee. Participants had normal or corrected to normal vision, and had no neurological history (all were screened for epilepsy and for the presence of metallic implants). They were given an extensive information form and gave written consent before participation. They were paid for their participation. Two subjects (one male and one female) were not included in statistical analyses because their errors were not normally distributed (leaving some conditions without the possibility to compute an average for correct responses).

Stimuli: Twelve pre-bisected lines served as visual stimuli (Fig. 1). Stimuli were generated using Superlab software running on a PC Pentium II (Windows 98). A line was either 10 or 20 cm long on the horizontal axis (thickness: 1 pixel) subserving 9.5 or 18.9° of visual angle, respectively. All lines were presented in the centre of the screen (17 inches; 25×32 cm), with the mid-point appearing exactly in the centre of the screen (right and left horizontal segments equal in length). A vertical segment of 2 cm (thickness: 1 pixel) perpendicular to the horizontal line was always presented (1 cm above and 1 cm below the horizontal line). For each line length (10 or 20 cm) and each side (left or right), the segment was located 2 (close), 8 (intermediate) or 32 mm (far) away from the mid-point leading to three distances for each side and length of line. The mislocation was 0.19, 0.76 or 3.06° left or right of the centre.

TMS: The equipment consisted of a Magstim model 200 Magnetic stimulator (Magstim, UK). We used a figure-of-eight coil, each winding measuring 7 cm (maximum output 2 T) producing the maximum electric field below its center and so the zone of stimulation is more focal [20]. The

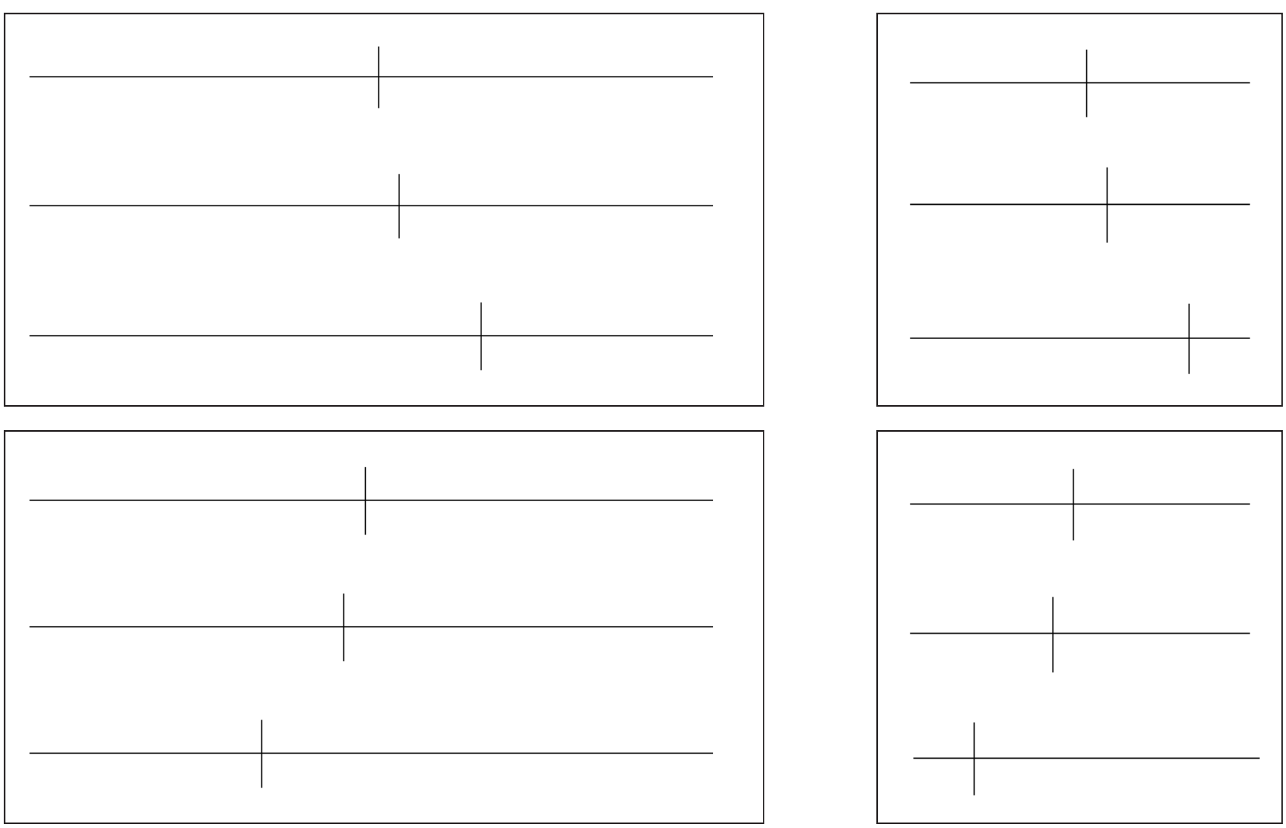

Fig. 1. The 12 pre-bisected lines used as stimuli. Lines were either 20 (left) or 10 (right) cm long on the horizontal axis. The vertical segment appeared in the right (upper) or left (lower) visual field. The segment was located 2, 8 or 32 mm away from the mid-point.

center of the coil was positioned over the cortical site to be stimulated (left parietal, right parietal or right frontal) in a parasagittal line with the handle pointing posteriorly. Rate of stimulation did not exceed 0.3 Hz. Using a CIO-DIO 24 card interface, the stimulator and the PC were interconnected, allowing us to trigger TMS time-locked to the stimulus onset. The SOA between stimulus onset and TMS was 50, 100, 150 or 200 ms. The point over which low intensity TMS evoked a visible twitch in the contralateral hand muscles was considered as the location of the primary motor area (M1). Motor thresholds were determined as the TMS intensities that evoked a visible twitch in the contralateral hand muscles in 50% of the stimulations applied over M1. The motor threshold of each subject was re-calculated between each experimental block but did not vary. Magnetic single pulses were delivered at an intensity of 10% above the motor threshold measured in the ipsilateral M1 before each block.

Selection and confirmation of TMS sites: Participants wore a closely fitting EEG cap. Using the International 10-20 system [21], the PPC was located and marked over the EEG cap on the left (P3) and right side (P4) of the head. TMS was therefore applied over a region thought to correspond to BA7 in the right and left hemisphere. Right primary motor cortex (M1) was also marked for each participant after detection by TMS. The accurate localisations of TMS pulses were next confirmed for three out of 10 subjects (Fig. 2) using a method that allows co-registration between TMS site and structural MRI [22]. The precise positions of the coil was tracked with a 3D coordinates system (Polhemus Isotrak II system, Kaiser Aerospace Inc.). This system gives the x, y and z coordinates of each point relative to a fixed radio-frequency magnetic field transmitter. Stimulation sites were recorded with a digitizing receiver pen, relative to a second receiver fixed to the subject's forehead that allowed head movements. Then, $\geqslant 60$ points were digitized over the scalp surface. This contour of the scalp was plotted in a 3D space and matched semi-automatically with the 3D reconstruction of the surface of the head from MR images, using a software developed in the laboratory and based on the Visual Tool Kit (VTK) library. A transformation matrix was calculated, that computed any point of the 3D coordinate system into the MR system. Since position of the coil over P3, P4 and right M1 was digitized during the last trials, the transformation matrix allowed thus location of the coil relative to the head. A line normal to the plane of the coil was drawn from the centre of the coil through the scalp and skull until it crossed the brain surface. This cortical impact point was considered as the site where TMS was maximal. Depending on the cortical region of interest, co-registration accuracy of a few mm is attainable [23].

Procedure: Within each of the three TMS sites, each stimulus type (2 lengths $\times$ 2 sides $\times$ 3 distances $\times$ 4 SOAs) was randomly presented five times in five separate blocks. In total, 15 blocks were randomly presented. Within a block (48 trials), TMS was constantly applied by one experimenter over the same site. All trials (720) were performed under magnetic stimulation. For each trial an alerting symbol appeared in the centre of the screen for 500 ms and was followed by the presentation of one of 48 pre-bisected lines. Stimuli were shown until a response was made. The interval between stimuli was kept constant at 3 s, respecting the recommendations for the practice of single pulse TMS [24]. Reaction times were calculated from stimulus onset. Subjects were seated comfortably on a chair 60 cm in front of the screen and were positioned so that eye level was at the middle of the display monitor that was centred on their sagittal midplane. The centre of the stimulus fell therefore in line with the subject's midsagittal

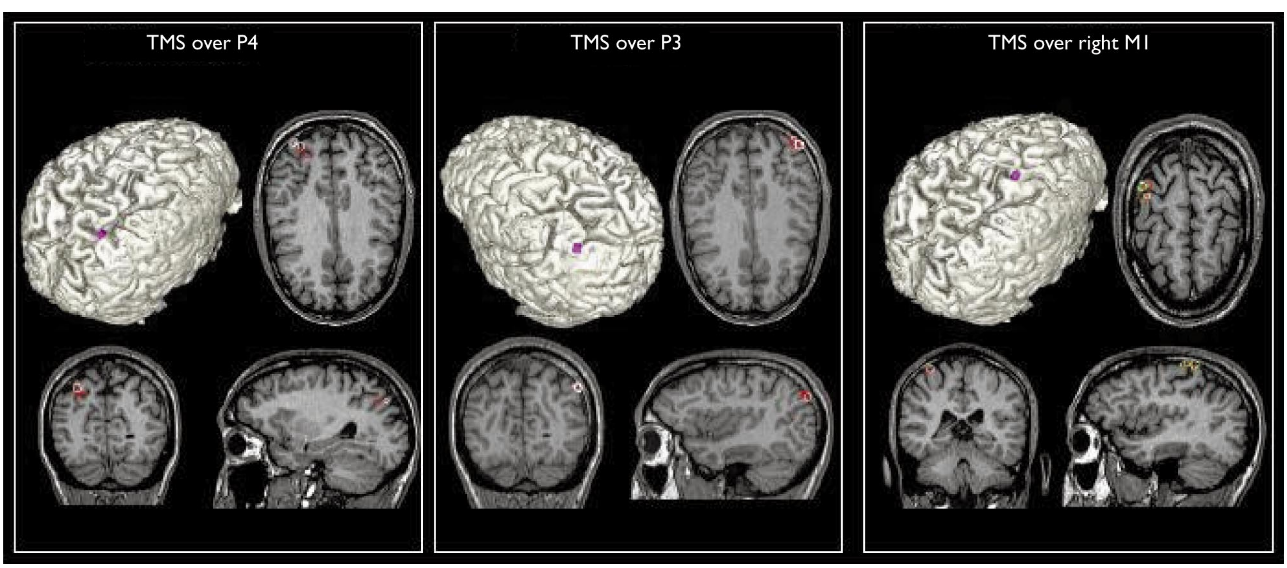

Fig. 2. Co-registration between TMS and MR images. Axial, sagittal, coronal sections and 3D reconstruction of the brain surface of participant 9, showing the presumed cortical sites (left parietal-P3, right parietal-P4 and right frontal-M1) of magnetic stimulations. A beam perpendicular to the surface of the figure-of-eight coil was computed from the center of the coil (under which the induced current is the strongest) and the impact point on the 3D-reconstructed cortical surface was considered as the point of stimulation. Each circle (sections) is one impact point and the magenta cube (3D reconstruction) is the computed mean impact point.

plane. Subjects were instructed to make a two alternatives forced choice with their dominant right hand using two buttons of a reponse box (RB 400, Cedrus): the vertical segment (the target) appeared leftward to the subjective mid-point or rightward. Before the start of the experiment, a block of 48 training trials was presented.

RESULTS

A repeated measure ANOVA with five within-subject factors was computed on the mean reaction times with correct responses as the dependent variable (Table 1): site of stimulation (left parietal, right parietal or right M1), side (left or right compared to the mid-point), length of line (small or large), distance of target from mid-point (close, intermediate or far) and SOA between stimulus onset and TMS (50, 100, 150 or 200 ms). The ANOVA revealed a significant main effect of length ($F(1,7) = 12.3$, $p < 0.01$), a significant effect of distance ($F(2,14) = 16.3$, $p < 0.001$), a significant interaction between these two independent variables ($F(2,14) = 7.9$, $p < 0.005$), and a significant interaction between the five factors ($F(12,84) = 1.86$, $p = 0.05$). Moreover, there was a trend towards significance for the interaction site of stimulation $\times$ side of target ($F(2,14) = 2.9$, $p = 0.086$), as well as for the interaction length $\times$ distance $\times$ SOA ($F(6,42) = 1.95$, $p = 0.095$). Two supplementary ANOVAs confirmed the selective interference within the right PPC in the landmark task when compared to the left PPC or the right M1 separately (see Table 1). When compared to the left parietal cortex, the 2 (site of stimulation) $\times$ 2 (side of target) $\times$ 2 (length of line) $\times$ 3 (distance) $\times$ 4 (SOA) ANOVA revealed a significant interaction between these five variables ($F(6,42) = 2.62$, $p < 0.05$), suggesting a selective interference within the right PPC. The same conclusion holds for the comparison between right parietal and right M1, as suggested by a significant interaction site of stimulation $\times$ side of target ($F(1,7) = 6.93$, $p < 0.05$). When TMS was applied over the right PPC (Fig. 3), subjects were significantly slower for targets appearing on the right side (ipsilateral) than for targets appearing on the left side (contralateral) ($t_7 = 2.36$, $p = 0.05$), a laterality effect which is non-significant when TMS was applied over the left PPC ($t_7 = 0.66$, $p > 0.5$). Moreover, when right PPC was directly compared with left PPC for the effect of SOA (Fig. 4), the analysis showed a significant difference for 50 ms SOA ($F(1,7) = 4.05$, $p = 0.057$) and a difference that almost reaches significance for 100 ms SOA ($F(1,7) = 3.65$, $p = 0.07$).

The same repeated measure ANOVA with five within-subject factors (site of stimulation, side of target, length of line, distance of target from mid-point and SOA between stimulus onset and pulse triggering) was computed on the mean error rates as the dependent variable (Table 1). The ANOVA revealed a significant effect of length ($F(1,7) = 38.32$, $p < 0.001$), indicating that subjects made more errors with long lines than short lines, a significant effect of distance ($F(2,14) = 50.41$, $p < 0.001$), indicating that subjects made more errors with targets close to the mid-point than far, and more errors with intermediate targets than far targets, and a significant interaction between these two independent variables ($F(2,14) = 11.73$, $p = 0.001$), indicating that the distance effect is stronger with long lines than short lines.

Table 1. Mean error rates and mean ($\pm$s.d.) reaction times for the four visuo-spatial variables and the three sites of stimulation.

Stimulation site	Length		Distance			Side		SOA			
	Long	Short	Close	Intermediate	Far	Left	Right	50	100	150	200
P3											
Reaction time for correct response	610 ± 235	581 ± 224	749 ± 303	564 ± 137	474 ± 95	590 ± 218	601 ± 241	587 ± 231	592 ± 241	602 ± 221	602 ± 227
Error rate	10	8.4	25	2.5	0.63	7.7	11	10	10	10	7
M1											
Reaction time for correct response	626 ± 278	569 ± 204	758 ± 318	558 ± 162	476 ± 108	603 ± 240	592 ± 251	589 ± 236	601 ± 268	592 ± 246	607 ± 232
Error rate	12	8.3	26	3.8	0.94	9.5	11	11	10	9	10
P4											
Reaction time for correct response	624 ± 238	600 ± 252	772 ± 323	574 ± 155	491 ± 104	593 ± 216	631 ± 271	611 ± 278	614 ± 252	616 ± 237	608 ± 213
Error rate	11	7.4	25	2.81	0.31	7.9	11	10	10	9.8	7.5

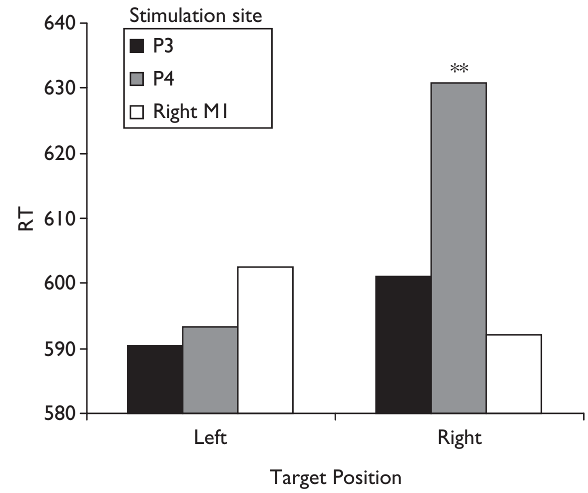

Fig. 3. Mean reaction times for targets appearing in the left or right visual hemifield for the three TMS conditions (M1 for magnetic stimulation in right frontal cortex, P3 in left parietal cortex and P4 in right parietal cortex).

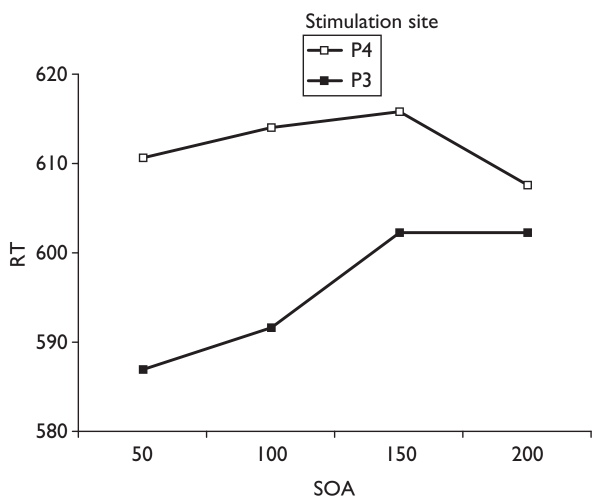

Fig. 4. Mean reaction times for the four SOAs (50, 100, 150 or 200 ms asynchrony between stimulus onset and single pulse onset) for the two TMS parietal sites (P3 for left parietal and P4 for right parietal).

The TMS–MRI co-registration algorithm used to visualize the putative location of the stimulation zone over the PPC (Fig. 2) confirmed that the stimulation zone actually corresponded to the PPC (e.g. BA 7) near the intraparietal sulcus.

DISCUSSION

In the present study, we assessed the TMS interference effects with visuo-spatial processing using a computer version of a widely used clinical test (i.e. the landmark task) highly relevant to screen for hemi-spatial neglect [6]. When TMS was applied over the right PPC, a transient interference in the landmark task was clearly evidenced and mainly revealed by increased processing cost for ipsilateral targets. We therefore confirmed the right-hemispheric dominance in visuo-spatial processing [25] when compared to the homologue region in the left hemisphere and/or to right M1. We found significant interactions between site of stimulation and the visuo-spatial variables (length of line, side of target, target eccentricity and SOA) directly manipulated in the present study.

The involvement of the right PPC in visuo-spatial processing has already been widely documented both in the lesion and brain imaging literature [19]. Here we showed that single-pulse TMS applied over the right PPC mainly corresponding to BA7 is able to selectively interfere with visuo-spatial processing at an early stage (50 ms post-stimulus). The use of the TMS–MRI co-registration algorithm indicated that stimulations in the right (P4) and left (P3) PPC do not overlap the post-central gyrus, as previously suggested by others [13,15].

The early contribution of the right PPC has already been demonstrated using paired TMS in brain-damaged patients [14], EEG recordings [16] and wavelet analysis of fMRI time-series [26], and may suggest a starter effect of the right parietal lobe in visuo-spatial processing. In our study the TMS interference in the landmark task manifested for P4 scalp-position as early as 50 ms post-stimulus might be explained by long-lasting effects (i.e. effects that last as long as 50 ms after the single pulse) at the cortical level induced by single-pulse TMS [27,28]. Our results are consistent with a previous TMS study [15] showing it is possible to interfere with visuo-spatial processing by stimulating the right PPC although repetitive TMS and different parietal zones of stimulation (P5 and P6 instead of P3 and P4 in the present study) were used in this earlier experiment.

CONCLUSION

The present study adds crucial information about the speed of visuo-spatial processing in the right parietal lobe. The interference from TMS is manifested by a processing cost for ipsilateral targets, suggesting that the impairment produced by single pulse TMS applied over the right PPC is qualitatively different from the contralateral impairment produced by repetitive TMS applied over the same lobe (see [15] for a comparison). Our results are compatible with previous neuropsychological studies [29] showing that some patients with damage in the right parietal lobe show ipsilesional neglect on line bisection tasks. The results of the present study contribute to establish further the methodological relevance of single-pulse TMS when studying the modular organization of the visual cortex [8]. Further single-pulse TMS investigations of visuo-spatial processing will need to test other time-windows of magnetic stimulation over differents cortical sites in both hemispheres as well as other visuo-spatial tasks.

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