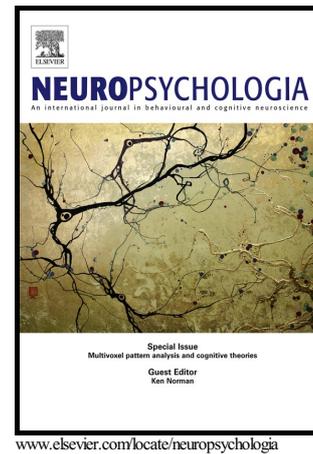


Author's Accepted Manuscript

The right hemisphere is independent from the left hemisphere in allocating visuospatial attention

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PII: S0028-3932(17)30217-8
DOI: <http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.005>
Reference: NSY6386

To appear in: *Neuropsychologia*

Received date: 27 November 2016
Revised date: 7 June 2017
Accepted date: 8 June 2017

Cite this article as: Arianna Zuanazzi and Luigi Cattaneo, The right hemisphere is independent from the left hemisphere in allocating visuospatial attention. *Neuropsychologia*, <http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.005>

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Title: The right hemisphere is independent from the left hemisphere in allocating visuospatial attention

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ABSTRACT:

The capacity to allocate visuospatial attention is traditionally considered right-lateralized according to the effects of unilateral cerebral lesions. Contralateral hemi-spatial neglect occurs much more frequently after lesions of the right hemisphere, which has therefore been dubbed as ‘dominant’. This pattern of symptoms is supported by functional models that postulate either independence or reciprocal influences between the two hemispheres. Here we specifically explored the dependency of the right hemisphere (RH) from the left hemisphere (LH) in spatial attention. We capitalized on the well-known effect of online transcranial magnetic stimulation (TMS) on the RH in healthy individuals, consisting in transient neglect-like manifestations in the left hemi-space. We assessed whether prior stimulation of the left posterior parietal cortex with a long-lasting neuromodulatory procedure (transcranial direct current stimulation – tDCS) affected the acute effects of TMS on the right posterior parietal cortex. We performed a within-subjects factorial study with two factors: LH tDCS (*sham* or *real*) and RH TMS (*sham* or *real*), resulting in a 2x2 design. The effects on spatial attention were examined separately for the two hemi-spaces by means of a modified line-bisection task. The results indicated that TMS over the RH produced a spatial attention deficit in the left hemi-space alone and the behavioural effects of TMS were not modulated by prior stimulation of the LH. Interestingly, additional analyses showed that tDCS over the LH alone produced a deficit in spatial attention to the right hemi-space. We interpret the current results as evidence for a largely independent contribution of each hemisphere to the allocation of visuospatial attention limited to the contralateral hemi-space.

Keywords: Hemi-spatial Neglect; Inter-hemispheric Interaction; Line Bisection; Parietal Cortex; Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation

1. Introduction

The brain is a largely symmetrical structure. However, some cortical functions are unevenly represented in the two hemispheres, and this asymmetry may be systematically biased towards one side. This phenomenon is known as lateralization of brain functions. Lateralized functions are therefore supported by a specialized hemisphere, referred to as the *dominant* hemisphere for that specific function (Hervé et al., 2013). The behavioural capacity to allocate visual attention to portions of space is an active process supported by a brain circuit which is traditionally considered to be lateralized to the right hemisphere (RH). Evidence for right-lateralization or right-dominance of visuospatial attention comes primarily from observations in patients with unilateral cerebral lesions who manifest contra-lesional *hemi-spatial neglect* (hSN). HSN is a neurological symptom characterized by difficulty in directing gaze, reporting or responding to stimuli in the contra-lesional (most commonly left) hemi-space, despite normal visual perception and motor performance (Corbetta et al., 2005). HSN is generally associated with unilateral brain damage (Becker and Karnath, 2007), with over 90% of individuals who develop hSN suffering from RH lesions (especially over the right superior temporal cortex and the right parietal cortex, Karnath et al., 2011; Mort et al., 2003; Verdon et al., 2010), while hSN associated with lesions of the left hemisphere (LH) is extremely rare (Corbetta et al., 2005). Two main hypotheses have been suggested to explain the asymmetry of hSN symptoms. A) It has been postulated that, while the LH controls the shift of attention towards the right side of space, the RH controls the shift of attention towards both sides and can compensate for LH damage (Heilman and Van Den Abell, 1980; Mesulam, 1981). B) Alternatively, Kinsbourne (1977)'s *inter-hemispheric competition hypothesis* suggests that LH orients attention towards the right side of space and the RH towards the left side of space, but the LH exerts a stronger bias. Thus, the attention system

would reach a balance through a reciprocal inhibition between the hemispheres. Non-invasive brain stimulation studies with hSN patients using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have provided a direct evidence in favor of the inter-hemispheric competition hypothesis (Kinsbourne, 1977). Application of TMS or tDCS to the healthy LH (generally the posterior parietal cortex) may, in fact, improve the symptoms of hSN, by restoring the inter-hemispheric balance (Koch et al., 2009; Sparing et al., 2009; for a review, see Müri et al., 2013).

More recently, Corbetta and Shulman (2011) have argued that right-lateralization observed in hSN is not a consequence of lateralization of spatial attention *per se*, but rather the consequence of an abnormal functioning of the interaction between two different but connected networks. The ventral frontoparietal network (temporoparietal junction - ventral frontal cortex) is indeed right-lateralized and controls for arousal, reorienting of attention and detection of behaviourally relevant target; the dorsal frontoparietal network (intraparietal sulcus – dorsal frontal cortex) is distributed bilaterally and controls for endogenous orienting of attention. According to this framework, the damage of ventral frontoparietal regions would generate abnormalities in the intact dorsal frontoparietal region, thus affecting the inter-hemispheric balance which underlies hSN (Corbetta et al., 2005; Corbetta and Shulman, 2002, 2011).

In support of this framework, fMRI data on healthy individuals have shown that, when participants perform a spatial attention task, lateralization of visuospatial attention processes can be observed for the ventral but not for the dorsal attentional network, which shows instead bilateral activation, although stronger for contralateral stimuli (Corbetta et al., 2000, Shulman et al., 2010). It has to be noted that, despite being symmetric, the activation of left and right dorsal frontoparietal regions might yet have different functions, e.g. there might be an asymmetric influence upon remote brain areas (such as upon visual cortices which

represent peripheral fields), with right frontoparietal regions exerting a stronger influence (Ruff et al., 2009; Shulman et al., 2010; see also Vossel, Geng, & Fink, 2014).

Ideally, investigating inter-hemispheric interplays in attentional mechanisms should include modulation of activity of both hemispheres in the same individual. However, this is impractical in patients. Neurostimulation techniques offer a unique opportunity to modulate focal neural activity of one or both hemispheres to produce behavioural changes in healthy individuals. On one hand, previous neurostimulation studies with healthy individuals have shown that unilateral stimulation of the RH may produce ‘hSN-like’ effects (Babiloni et al., 2007; Bjoertomt et al., 2002; Fierro et al., 2001; Giglia et al., 2011; Hilgetag et al., 2001; Meister et al., 2006; Muggleton et al., 2006; Nyffeler et al., 2008; Oliver et al., 2009; Thut, 2004). Moreover, bilateral stimulation brings evidence in favour of the competition hypothesis, i.e. ‘hSN-like’ effects produced by concurrent left- and right-hemisphere inhibition cancel each other out (Dambeck et al., 2006; Szczepanski and Kastner, 2013). On the other hand, multimodal studies measuring functional activity contralateral to the stimulated hemisphere have shown contrasting results, some of them contradicting the competition hypothesis, i.e. showing a decrease in neural activity for the stimulated RH and also for of the homologous LH (Bagattini et al., 2015; Ricci et al., 2012), others favouring it, i.e. showing a reduction in neural activity for the stimulated RH but an increase in neural activity for the homologous LH (Petitet et al., 2015; Plow et al., 2014).

In the present study we adopted a novel approach to investigate inter-hemispheric interplays. Rather than using simultaneous bilateral stimulation, we induced a long-lasting neuromodulatory effect on the left posterior parietal cortex by means of tDCS. The well-known online effects of TMS over the right posterior parietal cortex were then tested, superimposed on the after-effect of tDCS over the left posterior parietal cortex. Our study design is asymmetrical between the two hemispheres, i.e. we assessed the effects of prior LH

modulation on the way RH TMS affects spatial attention, given that our ad-hoc interest was that of assessing the effects of stimulation of the LH on the predicted ‘hSN-like’ effects of TMS over the RH. This design, in our view, allows us to collect information in favour of one of the possible hypotheses of inter-hemispheric dynamics in the allocation of spatial attention. We hypothesized two possible alternative outcomes on behaviour: 1) *Dependent pattern*: the behavioural effects of TMS over the RH depend on the concurrent cortical state of the LH (i.e. whether tDCS has been previously applied or not to the LH). 2) *Independent pattern*: the cortical state of the LH induced by tDCS does not influence the behavioural effects of TMS over the RH. In our study, we used a *tachistoscopic forced-choice landmark task* to assess the allocation of spatial attention. This task resembles the *line bisection task* (Bisiach et al., 1983) used to test hSN, but in the present case the transector mark is always central and the length of the left and right line segments vary. This task allows relatively independent analysis of the left and right hemi-spaces and has been previously validated as a sensitive tool to neurostimulation (Bjoertomt et al., 2002; Fierro et al., 2001; Giglia et al., 2011).

2. Methods

2.1. Participants

Sixteen healthy participants took part in Experiment 1 (5 M; mean age: 26.06; range: 19 – 39). Handedness was assessed with the Edinburgh Handedness Inventory questionnaire (Oldfield, 1971): 14 participants were right-handed and two were ambidextrous (mean laterality index: 0.89 ± 0.33 ; range: -0.26 – 1). Data from two participants were not included in the analysis because they did not fulfil the inclusion criteria (see 2.3). A different group of

16 healthy participants took part in Experiment 2 (5 M; mean age: 25.16; range: 19 – 35); 15 participants were right-handed and one was ambidextrous (mean laterality index: 0.90 ± 0.21 ; range: 0.15 – 1). Data of all 16 participants were included in the analysis as they all fulfilled the inclusion criteria (see 2.3). All participants had normal hearing and normal or corrected-to-normal vision. They were not informed of the purpose of the experiment until the end of the experiment. Participants were screened for any relative or absolute contraindications to TMS or tDCS. None had a history of neurological or psychiatric disorders or any contraindications to TMS (Rossi et al., 2009). Informed written consent was obtained from each participant. The study was conducted in the Neurostimulation Laboratory of the University of Trento (Italy) and was approved by the local ethical committee (protocol n. 2013-030).

2.2. *Stimuli and behavioural task*

Visual stimuli consisted of nine black 1 mm thick horizontal lines, transected by a 1 mm thick and 3 mm high vertical transector always coincident with the centre of the screen, so that the lines' start-points and end-points changed depending on the length of the lines. This manipulation was meant to minimize the use of the start- and end-points as a reference for the relative lengths of the two sides. Lines were pre-transected at one of nine locations, with intervals of ± 2 mm (see fig.1). In order to minimize potential bias, increase sensitivity and make the task more demanding, participants were not told about the presentation of an exactly bisected line.

<Figure 1 approximately here>

Each trial was presented an equal number of times for each stimulation condition: 10 times in Experiment 1 (only line 5 was presented 20 times) and 20 times in Experiment 2, for an overall total of 200 trials in Experiment 1 and 720 trials in Experiment 2. The order of line's length appearance was pseudo-randomized within each TMS condition. This reduced errors of habituation and expectation, making the level of the next stimulus unpredictable for participants.

The task consisted of a tachistoscopic landmark task. As mentioned in the Introduction, line-bisection task is often used as an effective measure of hSN in patients, who show a rightward bias in line bisection (Bisiach et al., 1983). Moreover, compared to manual method-of-adjustment, tachistoscopic forced-choice testing approaches were shown to be a better measure of bisection error (Jewell and McCourt, 2000). Participants were instructed to press the left or the right key as accurately and quickly as possible, to judge the respective length of the two segments of the bisected line: left key if the left segment was longer than the right segment (the line was longer on the left side of the transector), or right key if the right segment was longer than the left segment (the line was longer on the right side of the transector).

2.3. *Inclusion/exclusion criteria*

Potential participants were excluded from the experiment if they presented contraindications to TMS or tDCS as highlighted in the safety questionnaire. Additionally, participants were excluded post-hoc if they were not sufficiently proficient in the task. As a cutoff measure for task proficiency we used d -prime scores: participants with a normalized d -prime score in the *sham* condition which was lower than 1.64 SD (equal to the 95th percentile point of the normal distribution) below the group mean were excluded from the data analysis.

After the application of the exclusion criteria, data of two participants of Experiment 1 were not included in the data analysis. Data of all participants of Experiment 2 were included in the data analysis.

2.4. TMS and tDCS

2.4.1. Localization on the scalp of the target of stimulation

All stimulation targets were localized on the scalp according to the international 10 – 20 system for EEG coordinates. TMS was performed over the right posterior parietal region localized between the CP4 and the P4 coordinates (see Ashbridge et al., 1997; Bardi et al., 2013; Dambeck et al., 2006; Hilgetag et al., 2001; Pourtois et al., 2001; Sparing et al., 2009; Thut, 2004) (see fig.2, panel A). CP4 has been previously shown to overlie PPC in close proximity to the intraparietal sulcus (Herwig et al., 2003; Hilgetag et al., 2001; Oliver et al., 2009). P4 overlies the cortex ventral to the intraparietal sulcus, specifically the angular gyrus, as shown in probabilistic cranio-cerebral correlations (Okamoto et al., 2004). During tDCS, the cathode was centred over the left homologous area of CP4-P4 coordinate, i.e. over the CP3-P3 position, and the anode (reference electrode) was placed over the ipsilateral supraorbital region (see fig.2, panel B). According to the model proposed by Corbetta and Shulman (2002, 2011), the region we targeted is located within the dorsal frontoparietal attentional network.

<Figure 2 approximately here>

2.4.2. TMS

Before the experiment, the individual visual resting motor excitability threshold of stimulation was established as the lowest stimulation intensity applied over the right primary motor cortex capable of evoking a visible twitch of the left hand on around five out of ten consecutive stimulations. Single biphasic TMS pulses were applied with a figure-of-eight coil (diameter 65 mm) and a MagPro stimulator (MagVenture Company, Denmark) over the right stimulation site with the coil handle oriented at 45° from the mid-sagittal axis. The stimulation intensity used during the experiment was set at 200% of the individual motor threshold (mean stimulation intensity: 90% and 93% of maximal stimulator output for Experiment 1 and 2, respectively). As a control condition, single biphasic TMS pulses were applied with a sham figure-of-eight coil (diameter 65 mm) and a second MagPro stimulator (Magventure Company, Denmark) over the frontal region of the RH, immediately rostral to the TMS coil that stimulated the parietal cortex. The stimulation intensity was the same of the real TMS. The sham coil was a factory model designed to visually resemble the actual coil and to produce a similar sound and similar percussive stimulation of the scalp. Sham and real TMS coils were attached to two mechanical arms fixed to the chinrest and placed tangentially to the scalp. It should be noticed that both real and sham coils were always simultaneously present on the scalp, and were triggered alternatively by the E-Prime software (Psychology Software Tools, Pittsburgh, PA) through a parallel port. Sham and real TMS were delivered in an event-related fashion, time-locked to the presentation of visual stimuli. Sham and real single pulses were always delivered after 150 ms from the onset of the target line, interleaved in a stimulus-type sequence which was previously pseudo-randomized. The stimulation timing of 150 ms has been proven to be optimal for inducing ‘hSN-like’ effects by means of TMS (Dambeck et al., 2006; Fierro et al., 2001).

2.4.3. *tDCS*

A battery-driven, constant current stimulator (Neuroconn, Germany) was used, connected to two surface electrodes (5x7 cm). During real stimulation, tDCS current ramped up for the first 10 seconds to a maximum of 1 mA, remained on for the remainder of the 10-minute stimulation period and then ramped down for other 10 seconds. As a control condition, sham stimulation was performed. The electrodes were placed on the same sites on the scalp as real stimulation. The sham control stimulation was identical to the real stimulation, with two ramps, one at the beginning and one at the end of the stimulation, except that after 15 seconds of stimulation the experimenter reduced the current to zero (Gandiga et al., 2006). A tingly or itchy sensation which faded away after a few seconds was reported for both real and sham tDCS; none of the subjects were capable of distinguishing the two modalities after the experiment. Given the little predictability of the duration of the after-effects of tDCS, the two modalities (sham and real) were delivered to the participants in two sessions, separated by five days. The order of the sessions was counterbalanced across subjects, to control for learning effects. To assess participants' well-being and the possible side effects of tDCS, Warwick-Edinburgh Mental Well-being Scale (WEMWBS) (Tennant et al., 2007) and on the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) were administrated before the experiment (baseline), after sham tDCS stimulation and after real tDCS stimulation. No significant difference was found in the rating between sham and real stimulation (after subtracting the baseline rating).

2.5. *Experimental procedures*

Experiment 1 consisted of a 1-minute training session and a 10-minute experimental session. During the training and the experiment, participants were seated in a comfortable

chair in front of a computer, which was positioned at a viewing distance of 50 cm (see Bjoertomt et al., 2002) and the centre of the screen was positioned with respect to the mid-sagittal plane of each participant. The screen refresh rate was 75 Hz. The brightness and contrast were previously set at 23% and 50% respectively. The seat could move up or down to fix the participant's position and head orientation were controlled using a chinrest. Participants rested the index and the middle finger of the right hand on a response box with only two keys (left and right keys). Key orientation corresponded to the axis of perceptual discrimination (i.e., the left response key was on the left of the right response key). Participants were given both oral and written instructions and were asked to respond as accurately and quickly as possible. Stimuli were presented in a two-alternative forced-choice tachistoscopic landmark task on a white background. Before each stimulus, a fixation grey square appeared for 4000 ms and was supplanted by one of the nine possible pre-bisected lines. Stimulus presentation lasted 40 ms. Response time was limited to 2000 ms, after which a grey screen appeared as a 'response given' feedback (see fig.3).

<Figure 3 approximately here>

The procedure of Experiment 2 was identical to that of Experiment 1 except that, after the 1-minute training session, the experimental session lasted 30 minutes and it was preceded by 10-minutes of tDCS without any task. During the tDCS session, participants were instructed to rest the head over the chinrest and to start with the task as soon as the 10-minutes of tDCS concluded. Electrodes remained on the participant's head until the end of the experiment, but the stimulator was turned off during the TMS part (see fig.4).

<Figure 4 approximately here>

2.6. Data analysis

For each condition, data with reaction times exceeding 2000 ms or above and below two standard deviations from each subject's mean were excluded from all the analyses. For each condition, a Shapiro-Wilk's test ($p > .05$) (Shapiro and Wilk, 1965) was run to verify that the residuals were approximately normally distributed.

2.6.1. Response analysis

In order to obtain a measure of the perceived symmetric line (α), independent psychometric functions were fitted to individual datasets (Logistic sigmoidal function, see the equation in [1], Shen and Richards, 2012; Wichmann and Hill, 2001).

$$[1] \Phi(x; \alpha, \beta, \gamma, \lambda) = \gamma + (1 - \gamma - \lambda) / (1 + e^{-\beta(x - \alpha)})$$

with $x \in [0, +\infty)$, and parameters $\alpha \in (0, +\infty)$ $\beta \in (0, +\infty)$. x is defined by line types. The dependent measure was the proportion of trials on which participants indicated that the line was longer on the left side (meaning that the left segment was longer than the right segment), for each line type. α is equal to $F^{-1}(y)$ (being F the psychometric function fitted to individual datasets) where y is 0.5. We chose to consider subjective thresholds as a measure of symmetric lines, instead of using the veridical bisected line, given the great importance it has been previously attributed to individual differences in spatial bias (McCourt and Olafson, 1997; Szczepanski and Kastner, 2013).

Further, cubic interpolation was performed for each subject for each condition (*sham* TMS, *real* TMS in Experiment 1; *sham* tDCS – *sham* TMS, *sham* tDCS – *real* TMS, *real*

tDCS – *sham* TMS, *real* tDCS – real TMS in Experiment 2). To obtain a global measure of proportion of trials on which participants indicated that the line was longer on the left side for each line type (right- and left-elongated lines), the area under the interpolated data was calculated, for each subject, for each condition and for the two line types (over the intervals $[1, \alpha]$, for right-elongated lines, and $[\alpha, 9]$ for left-elongated lines). For each participant, α , previously estimated in the *sham* condition, was considered as the subjective midpoint, which discriminates between right- and left-elongated lines. This method permits assessment of changes in line-length perception from subjective midpoint independently for left- and right-elongated lines, which in previous line-bisection studies has not been consistently done at a behavioural level.

The obtained areas were analysed by means of a 2-way ANOVA (2x2 design) with the factors TMS (2 levels: *sham*, *real*) and LINE (2-levels: *right-elongated*, *left-elongated*) in Experiment 1, and by means of a 3-way ANOVA (2x2x2 design) with the factors tDCS (2 levels: *sham*, *real*), TMS (2 levels: *sham*, *real*) and LINE (2-levels: *right-elongated*, *left-elongated*) in Experiment 2.

2.6.2. *d*-prime and criterion analysis

D-prime and *criterion* analyses were performed in both experiments for each condition. *D*-prime was calculated as $[Z(\text{hit rate}) - Z(\text{false alarm rate})]$, where *Z* is the inverse of the cumulative Gaussian distribution. *Hits* were ‘left’ responses to left-elongated lines and *False Alarms* were ‘left’ responses to right-elongated lines. *Criterion* was calculated as $- [Z(\text{hit rate}) + Z(\text{false alarm rate})] / 2$ (Stanislaw and Todorov, 1999). The obtained *d*-prime scores and *criterion* scores were analysed by means of a two-tailed paired-sample t-test in the first experiment, and by means of a 2-way ANOVA (2x2 design) with the factors tDCS (2 levels: *sham*, *real*) and TMS (2 levels: *sham*, *real*) in the second experiment.

3. Results

3.1. Experiment 1

Overall, 8.6% of the responses were excluded from the analysis of Experiment 1. Group mean threshold (mean α) was 4.42 (SD: 0.78). The 2-way ANOVA carried out for the Response analysis showed a significant TMS by LINE interaction ($F(1, 13) = 21.97, p = 0.000$). A post-hoc Tukey HSD test revealed that, only for left-elongated lines, the area under the interpolated data of *sham* TMS was significantly bigger than the area of *real* TMS ($p = 0.005$). No significant difference was found for right-elongated lines ($p = 0.111$). This result shows that TMS applied over the RH has an effect only on left-elongated lines, reducing the ‘left’ responses when lines are actually left-elongated (with respect to the subjective symmetrically transected line). Group mean areas for right- and left-elongated lines and areas for right- and left-elongated lines for each participant are illustrated in figure 5, panel A and B.

<Figure 5 approximately here>

D-prime analysis showed a significant difference between the two conditions ($t(13) = 2.52, p = 0.025$): when TMS was *real*, the *d*-prime was lower, suggesting a general less accurate discrimination between right- and left-elongated lines. This difference is driven by a significant increase of *Misses* (‘right’ response for left-elongated lines) ($t(13) = -3.22, p = 0.007$). No significant difference was found in the *criterion* analysis.

Mean and Standard Deviation (in parenthesis) for the area under the interpolated data, d -prime and criterion for each condition are summarized in table 1 and table 2.

<Table 1 approximately here>

<Table 2 approximately here>

3.2. Experiment 2

Overall, 5.3% of the responses were excluded from the analysis of Experiment 2. Group mean threshold (mean α) was 4.76 (SD: 0.79). The 3-way ANOVA carried out for the Response analysis showed a significant main effect of TMS ($F(1, 15) = 6.74, p = 0.020$) and a significant tDCS by TMS by LINE interaction ($F(1, 15) = 6.76, p = 0.020$).

In order to address the hypothesis of a *dependent pattern*, we reasoned that a significant tDCS by TMS interaction would be expected. In fact, if tDCS changes the cortical excitability of the RH (inhibition or excitation), and this effect is behaviourally measurable when interfering with the activity of the RH through TMS, the ‘hSN-like’ effect (i.e. the bias towards the right hemi-space) should be significantly different compared to the condition where tDCS is *sham*. In particular, the ‘hSN-like’ effect should increase if RH cortical excitability was previously decreased by LH neuromodulation, and should decrease if RH cortical excitability was previously increased. Our analysis revealed no significant tDCS by TMS interaction ($F(1, 15) = 0.031, p = 0.864$). Considering that in Experiment 1 we found that the effect of TMS was line-specific, we unpacked the 3-way ANOVA into two 2-way ANOVAs for further analysis, one for left- and one for right-elongated lines, with the factors tDCS (2 levels: *sham, real*) and TMS (2 levels: *sham, real*). This analysis permits to account for the effects of tDCS on the ‘hSN-like’ effects of TMS for left- and right-elongated lines,

separately. The ANOVA run for left-elongated lines showed a significant main effect of TMS ($F(1, 15) = 6.76, p = 0.020$), with the area under the interpolated data of *sham* TMS being significantly bigger than the area of *real* TMS. This result confirms the ‘hSN-like’ effect of RH TMS found in Experiment 1: TMS applied over the RH reduces the ‘left’ responses when lines are left-elongated (with respect to the subjective symmetrically transected line). No main effect of TMS was found for right-elongated lines ($F(1, 15) = 4.02, p = 0.063$). Moreover, no main effect was found for tDCS neither for left-elongated lines nor for right-elongated lines ($F(1, 15) = 0.107, p = 0.748$ and $F(1, 15) = 2.21, p = 0.166$, for left- and right-elongated lines respectively). More importantly, neither of the two ANOVAs showed a significant tDCS by TMS interaction (left-elongated lines: $F(1, 15) = 0.947, p = 0.346$; right-elongated lines: $F(1, 15) = 2.72, p = 0.119$). These results suggest that the TMS ‘hSN-like’ effect observed for left-elongated lines was not modulated by tDCS previously applied over the LH.

Given that the significant tDCS by TMS by LINE interaction cannot be explained by our *dependent pattern* hypothesis (as showed in the previous analysis), we further explored the 3-way interaction via a comprehensive post-hoc Tukey HSD test. Results are reported in table 3.

<Table 3 approximately here>

The Tukey HSD test revealed that, when tDCS was *sham or real*, for left-elongated lines, the area under the interpolated data of *sham* TMS was significantly bigger than the area of *real* TMS ($p = 0.002$ and $p = 0.043$, respectively). No significant difference was found for right-elongated lines ($p = 0.889$ and $p = 1$, respectively). These results reflect the significant main effect of TMS found for left-elongated lines but not for right-elongated lines. A similar result, but in the opposite direction, was found in the *sham* TMS condition only for right-

elongated lines: the area under the interpolated data of *sham* tDCS was significantly smaller than the area of *real* tDCS ($p = 0.012$). No significant difference was found for left-elongated lines ($p = 0.992$). Taken together, these results indicate that both TMS and tDCS had an inhibitory effect over the stimulated hemisphere (tDCS only in the condition where TMS was *sham*), biasing towards the ipsilateral hemi-space (left hemi-space for TMS and right hemi-space for tDCS) the judgment of lines longer on the contralateral hemi-space. In accordance with these results, we attributed the significant tDCS by TMS by LINE interaction to the independent inhibitory effects of TMS and tDCS over left- and right-elongated lines, respectively.

Group mean areas for right- and left-elongated lines are illustrated in figure 6, where the independent and opposite effects of TMS and tDCS are indicated.

<Figure 6 approximately here>

This line of reasoning allows us to explain also the significant difference between the ('hSN-like') effect of stimulation over one hemisphere for lines longer on the contralateral hemi-space and the (null) effect of stimulation of the opposite hemisphere on the same lines (i.e., *sham* tDCS *real* TMS vs *real* tDCS *sham* TMS for left-elongated lines: $p = 0.011$ and *real* tDCS *sham* TMS vs *sham* tDCS *real* TMS for right-elongated lines: $p = 0.001$). Finally, it seems plausible that the 'hSN-like' effect of TMS for right-elongated lines in the *real* tDCS condition (*real* tDCS *sham* TMS vs *real* tDCS *real* TMS: $p = 0.013$) might be a result of the effect of RH TMS on right-elongated lines after they are perceived more frequently as left-elongated due to LH tDCS application (which preceded the application of TMS). A similar effect of LH tDCS on left-elongated lines is not observed as RH TMS was applied only after

tDCS. Nevertheless, this conclusion remains somewhat speculative as the reverse stimulation order would be needed to confirm this hypothesis.

D-prime analysis showed a significant TMS by tDCS interaction ($F(1, 15) = 5.68, p = 0.030$). Further post-hoc Tukey HSD test revealed no significant results. The *criterion* analysis showed a significant main effect of TMS ($F(1,15) = 5.66, p = 0.031$), indicating that when TMS was *real* the criterion was higher compared to *sham* TMS. Mean and Standard Deviation (in parenthesis) for the area under the interpolated data, *d*-prime and criterion for each condition are summarized in table 4 and table 5.

<Table 4 approximately here>

<Table 5 approximately here>

4. Discussion

In this work we explored whether the behavioural effects of TMS applied to the RH changed with respect to the concurrent functional state of the LH. The baseline excitability of LH was manipulated by means of tDCS, which produces a long-lasting after-effect on cortical physiology and behaviour. TMS was applied during such after-effect.

As a necessary preliminary step we conducted Experiment 1, which showed that TMS applied over the RH does indeed produce an ‘hSN-like’ bias towards the right hemi-space when lines are left-elongated. Data showed that participants gave less frequently a ‘left’ response for left-elongated lines following effective RH *real* TMS compared to *sham* TMS over the same hemisphere. This result replicates previous studies that showed a similar visuospatial bias (Babiloni et al., 2007; Bjoertomt et al., 2002; Fierro et al., 2001; Giglia et al., 2011; Hilgetag et al., 2001; Meister et al., 2006; Muggleton et al., 2006; Nyffeler et al.,

2008; Oliver et al., 2009; Thut, 2004; see Duecker and Sack, 2015 for a review about ‘hSN-like’ and ‘extinction-like’ effect of TMS and Harvey and Kerkhoff, 2015 for a review of studies investigating the effect of neurostimulation on attention).

The novelty of our study arises from the results of Experiment 2. We showed that the ‘hSN-like’ behavioural effects induced by RH TMS were not modified by application of LH tDCS. These primary results argue against the hypothesis of dependency of behavioural effects of RH TMS on the current state of the contralateral LH. Neuropsychological and neuroimaging studies which have previously investigated inter-hemispheric interplays have shown contradictory findings. To our knowledge, the present study is the first ever manipulating the baseline excitability state of the LH prior to RH stimulation.

Further, a secondary explorative post-hoc analysis revealed another result of interest. tDCS over the LH alone induced a deficit in spatial attention allocation to the right hemi-space, i.e. right-elongated lines were identified correctly less frequently. The ‘hSN-like’ effects produced by RH stimulation and that produced by LH stimulation appeared independently and only for lines longer on the hemi-space contralateral to the stimulated hemisphere. Line specificity was already reported in previous studies, which showed a separate effect for left- and right-elongated lines in a similar tachistoscopic forced-choice landmark task (see Bjoertomt et al., 2002; Kim et al., 2005). These results are, in our view, supportive of functional independence of the RH from the LH in allocating visuospatial attention. Hence, they support our initial *Independent pattern* hypothesis and in addition show a contribution of both LH and RH to the allocation of visuospatial attention. It has to be noted that ‘HSN-like’ effects of LH stimulation have been previously reported, although not as often as those from RH stimulation (see Babiloni et al., 2007; Battelli et al., 2009; Hilgetag et al., 2001; Sparing et al., 2009). Moreover, the model proposed by Corbetta and Shulman (2011), supported by fMRI data on healthy participants (Shulman et al., 2010), suggests that

spatial attention is indeed represented bilaterally in the dorsal frontoparietal network, with each hemisphere showing higher activation for the contralateral hemi-space. Thus, our secondary results are not at odds with a model which assumes that both hemispheres are involved in spatial attention processes.

Some critical aspects regarding the effects of tDCS deserve consideration. First, even though our behavioural results show an independent pattern, we cannot completely rule out the possibility that this pattern was observed because the effect of tDCS remained limited to the LH and no transcallosal modulation took place, as we did not measure the cortical activity of the RH. Nevertheless, we are inclined to exclude this hypothesis, as previous studies brought data in favour of inter-hemispheric effects of offline tDCS on the homologous hemisphere (see Pellicciari et al., 2013; Romero Lauro et al., 2014). Thus, assuming inter-hemispheric effects of offline tDCS, an alternative explanation for the absence of interaction between LH tDCS and RH TMS behavioural effects could be ascribed to the specific polarity of tDCS stimulation we used or to weak transitory cortical excitation or inhibition effects via transcallosal pathways (compared to the acute inhibitory effects of TMS applied over the site itself).

Second, the current literature on tDCS highlights the difficulty in establishing *a priori* a predictable polarity (gain or loss) of the neurophysiological and physiological changes induced by this type of stimulation. Our model of independent behavioural effects of stimulation does not make predictions in the sense of a gain or a loss of function to tDCS, as long as a change of any type is produced. While behavioural results in favour of our *behavioural dependency* hypothesis would reasonably entail that the homologous RH is either excited or inhibited via inhibition of LH (as Ricci et al., 2012, Bagattini et al., 2015, and Petit et al., 2015 demonstrate), the hypothesis that behavioural effects of LH neuromodulation and RH neurostimulation are independent makes no specific assumption

regarding the cortical state of the RH after LH tDCS application. Thus, our experimental hypotheses are impermeable to the potential ambiguity in the polarity of the effects of tDCS.

Third, our conclusion that tDCS over the LH produced a behavioural change is based on a secondary explorative post-hoc analysis which we ran to further interpret the significant tDCS by TMS by LINE interaction that we found. However, a main effect of tDCS for lines longer on the contralateral hemi-space was not found. This result clearly suggests that, in our study, tDCS applied to the LH produced less strong and less effective behavioural effects than TMS to the RH. The reason behind weak behavioural effects could be ascribed to the inefficacy of tDCS or to the site of stimulation itself.

For the aforementioned reasons, we should resist the temptation to discuss our findings in general terms, i.e. independently from type of stimulation, from stimulation polarity and from the specific site of stimulation, as we investigated state-dependent effects of TMS only with cathodal tDCS and in only one direction (LH to RH). Such generalization would probably require a symmetrical experimental paradigm in terms of stimulation technique (e.g., LH tDCS/RH TMS and LH TMS/ RH tDCS), stimulation polarity (e.g., cathodal and anodal LH tDCS preceding RH TMS) or in terms of stimulation site (e.g., RH offline stimulation preceding LH online stimulation and vice-versa).

While acknowledging the potential limits of our methodological approach, we believe that our results can point to further interpretation. Although the main aim of our experimental manipulation was to investigate interhemispheric interplays rather than to compare the effects of LH tDCS and RH TMS on behaviour, the fact that LH stimulation produced contralateral 'HSN-like' effects and failed to modulate the behavioural effects of TMS led us to discuss our primary and secondary results altogether. Importantly, the 'hSN-like' bias was not only independent but also hemi-space specific, i.e. a deficit in spatial attention allocation was found only for lines longer on the contralateral hemi-space. Thus, we reasoned that the

absence of interaction between LH tDCS and RH TMS behavioural effects could be more convincingly interpreted in light of the tachistoscopic forced-choice landmark task we employed. This task involves the monitoring of two segments located one in the left and one in the right hemi-space, to decide which one is longer, and may resemble a multifocal spatial attention task, where attention is split into multiple foci (i.e. left and right hemi-spaces). In a set of experiments with healthy participants, Alvarez and Cavanagh (2005) and Alvarez et al. (2012) investigated how attention is spatially divided and demonstrated that attentional resources are allocated independently in the two visual hemi-fields. Importantly, they showed that hemi-field independence is associated to location-based attention (thus only limited to spatial features) and it is peculiar to early attentional processing, such as spatial attentional selection and tracking. Independent attentional resources for the two hemi-fields are explained in terms of neuronal mechanisms underlying spatial attention. Contrarily to feature-based attention, location-based attention operates at a local spatial scale (i.e. local groups of neurons) and involves parietal regions strongly connected to ipsilateral lower level regions, within the same hemisphere (Alvarez et al., 2012; Cohen and Maunsell, 2011). Thus, according to this hypothesis, our behavioural results would reflect the impact of tDCS and TMS on intra-hemispheric mechanisms involved in the spatial attention task we used, rather than on inter-hemispheric connections. This account would explain why, in our study, the effects of LH and RH stimulation were independent and specific to the contralateral hemi-space.

Concluding, our novel bi-hemispheric neurostimulation approach brings new evidence in favour of independent contribution of the right and the left hemispheres in spatial representation, thus going beyond the already questioned traditional framework which defines the RH as *dominant* for visuospatial attention (for a review, see Corbetta and Shulman, 2011). When a multifocal spatial attention task is employed, behavioural effects of

RH and LH stimulation may reflect the impact of such stimulation on intra-hemispheric mechanisms, which independently control spatial attention allocation to the contralateral hemi-space.

Acknowledgements

We would like to thank Guido Barchiesi for his helpful insights into this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

	right-elongated lines		left-elongated lines	
	sham TMS	real TMS	sham TMS	real TMS
mean area	0.66	0.84	3.97	3.67
	(0.20)	(0.34)	(0.71)	(0.61)

Table 1. Experiment 1: mean and standard deviation of the area under the interpolated data for each condition.

	mean d -prime		mean criterion	
	sham TMS	real TMS	sham TMS	real TMS
	2.51	2.14	-0.35	-0.21
	(0.49)	(0.36)	(0.32)	(0.32)

Table 2. Experiment 1: mean and standard deviation of d -prime and criterion for each condition.

		right-elongated lines				left-elongated lines				
		sham tDCS	sham tDCS	real tDCS	real tDCS	sham tDCS	sham tDCS	real tDCS	real tDCS	
		sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS	
right-elongated lines	sham tDCS		0.889	0.012	1.000	sham tDCS		0.002	0.992	0.043
	sham TMS					sham TMS				
	sham tDCS			0.001	0.872	sham tDCS			0.011	0.791
	real TMS					real TMS				
	real tDCS				0.013	real tDCS				0.167
	sham TMS					sham TMS				
	real tDCS					real tDCS				
	real TMS					real TMS				

Table 3. Experiment 2: *p*-values of the comprehensive Tukey post-hoc pairwise comparisons for the significant interaction tDCS by TMS by LINE. Comparisons by LINE are not reported for the sake of readability (as expected, the difference between any right- and left-elongated line comparisons resulted significant, given the measure we used for data analysis).

	right-elongated lines				left-elongated lines			
	sham tDCS	sham tDCS	real tDCS	real tDCS	sham tDCS	sham tDCS	real tDCS	real tDCS
	sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS
mean area	0.75	0.69	0.95	0.76	3.51	3.28	3.48	3.35
	(0.16)	(0.27)	(0.35)	(0.40)	(0.73)	(0.91)	(0.84)	(0.89)

Table 4. Experiment 2: mean and standard deviation of the area under the interpolated data for each condition.

mean d -prime				mean criterion			
sham tDCS	sham tDCS	real tDCS	real tDCS	sham tDCS	sham tDCS	real tDCS	real tDCS
sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS	sham TMS	real TMS
2.27	2.16	2.06	2.24	-0.15	0.02	-0.18	-0.08
(0.46)	(0.50)	(0.39)	(0.42)	(0.35)	(0.46)	(0.36)	(0.49)

Table 5. Experiment 2: mean and standard deviation of d -prime and criterion for each condition.

Figure legends

Figure 1. The nine lines used as visual stimuli. Lines 1, 2, 3 and 4 are right-elongated; line 5 is exactly bisected (72 mm left and 72 mm right); lines 6, 7, 8 and 9 are left-elongated.

Figure 2. Panel A. Stimulation spot of Experiment 1: TMS was delivered over a spot between CP4 and P4 (according to the 10-20 EEG system). Panel B. Stimulation spots of Experiment 2: during tDCS, the cathode was applied over a spot between CP3 and P3 (black pad) and the anode over the ipsilateral orbita (gray pad). TMS was then delivered over a spot between CP4 and P4 (according to the 10-20 EEG system).

Figure 3. Experiment 1, procedure. Single pulse TMS was delivered after 150 ms from the onset of the target line, which remained on the screen for 40 ms. Response time was limited to 2000 ms.

Figure 4. Experiment 2, procedure. Cathodal tDCS was delivered for 10 minutes. Then, single pulse TMS was delivered after 150 ms from the onset of the target line, which remained on the screen for 40 ms. Response time was limited to 2000 ms.

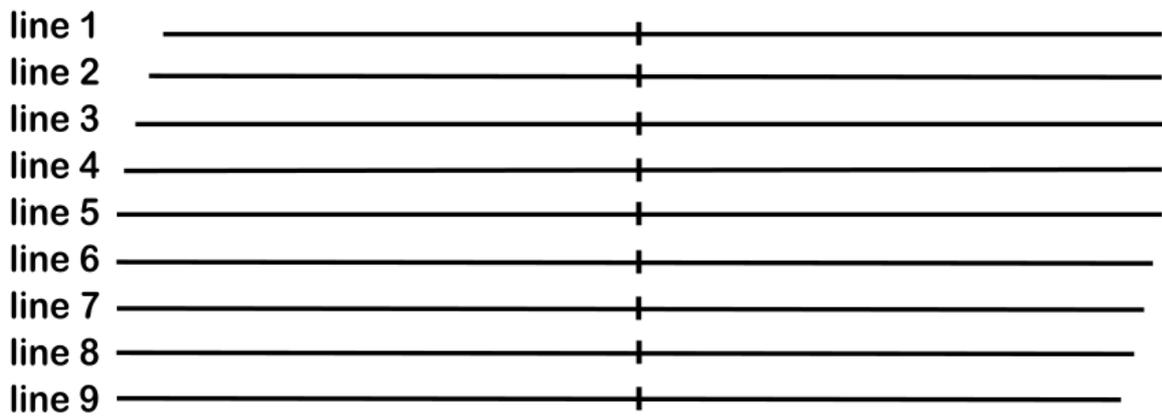
Figure 5. Panel A. Group results for right- and left-elongated lines for each TMS condition. Panel B. Individual results for right- and left-elongated lines for each TMS condition. Error bars indicate 95% confidence intervals of the mean.

Figure 6. Group results for right- and left-elongated lines for each tDCS-TMS condition. Error bars indicate 95% confidence intervals of the mean.

Highlights

- Symptoms of hemispatial neglect suggest that spatial attention is right-dominant
- Studies investigating inter-hemispheric interplays show contradictory findings
- In healthy volunteers we stimulated the left and right parietal cortices
- No interaction between left and right hemisphere stimulation was observed
- Left and right hemispheres seemingly contribute independently to spatial attention

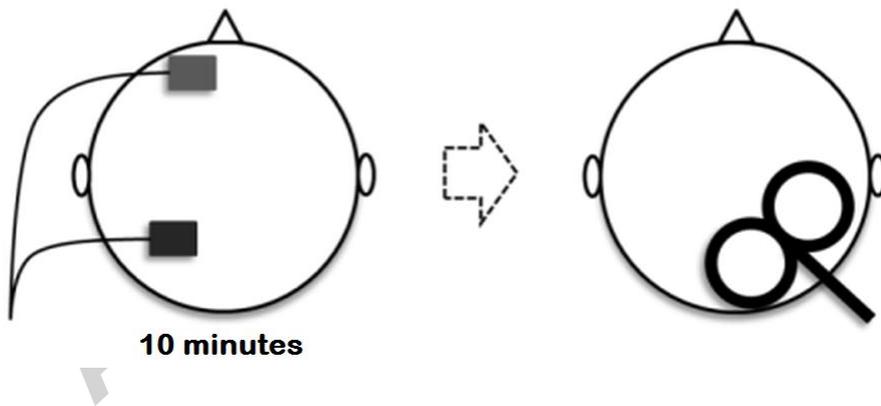
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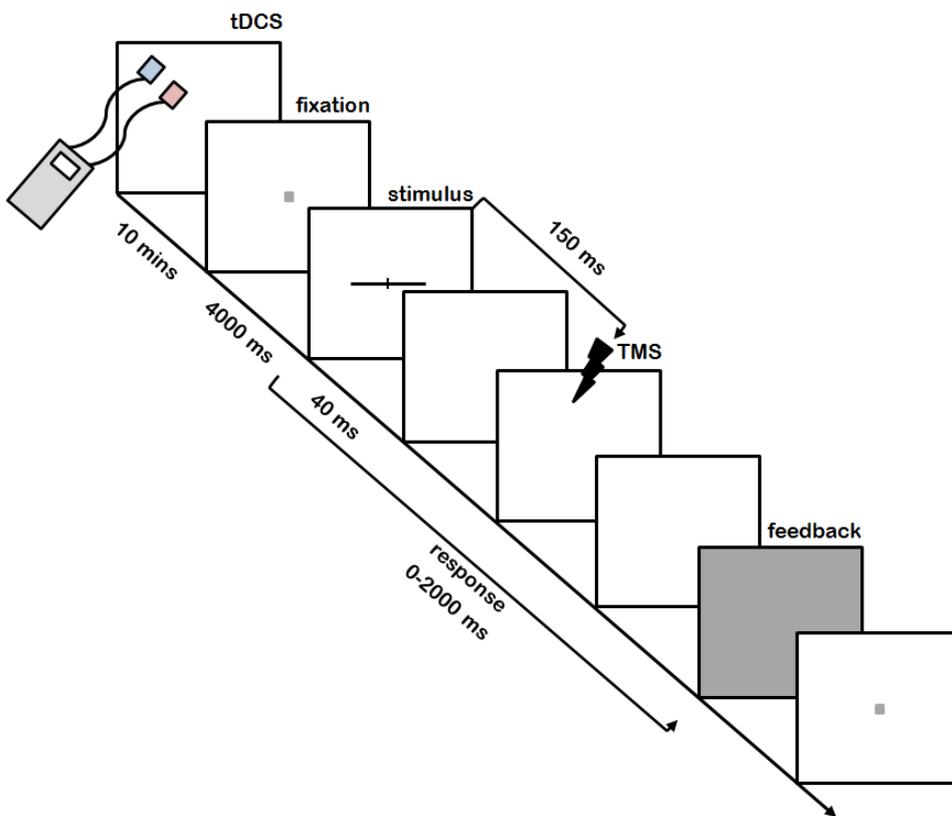
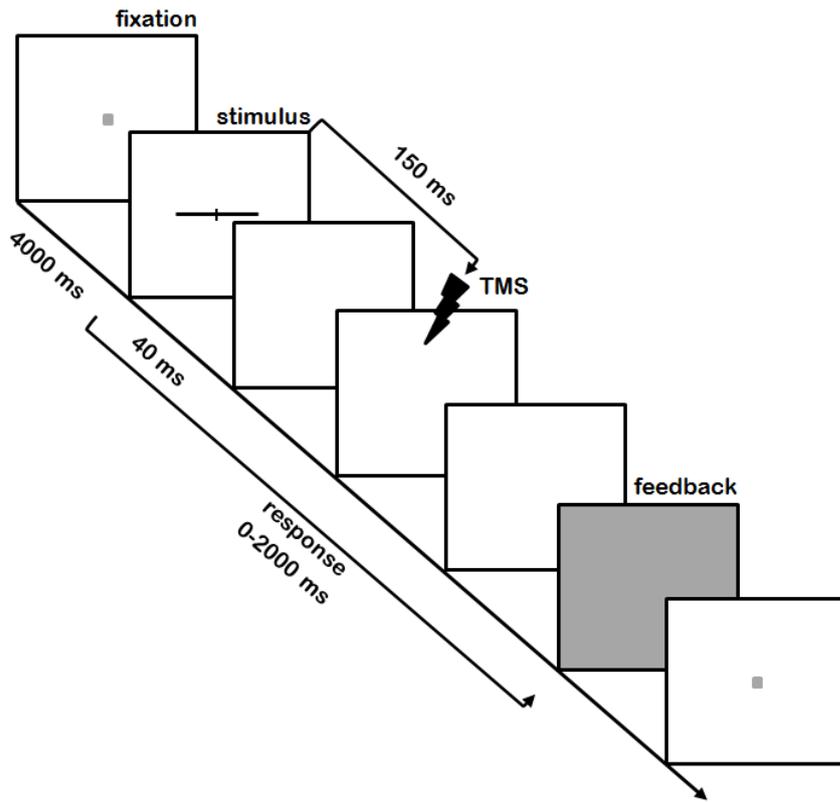


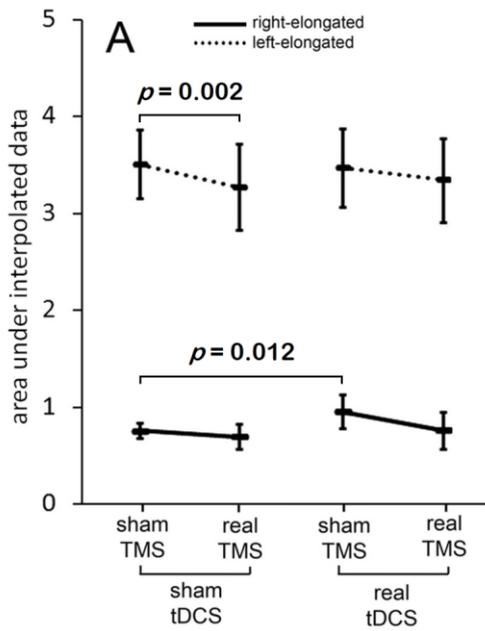
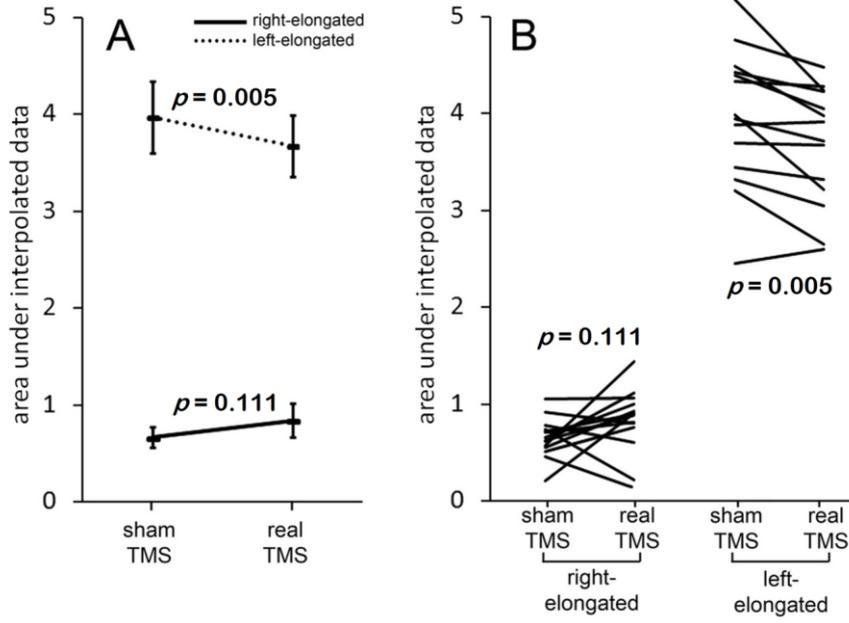
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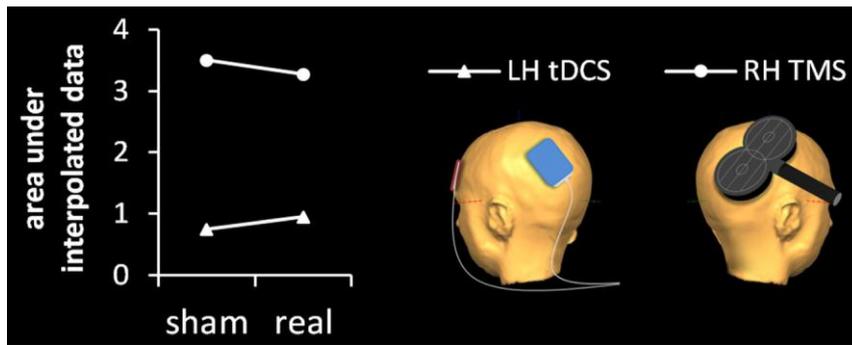


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Graphical abstract

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