

A matter of hand: causal links between hand dominance, structural organization of fronto-parietal attention networks, and variability in behavioural responses to transcranial magnetic stimulation

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ABSTRACT

Considerable evidence suggests that, on a group level, human visuospatial attention is asymmetrically organized, with a right-hemispheric dominance. The asymmetrical organization of the superior longitudinal fasciculus (SLF) has been shown to account for the right-hemispheric dominance in visual attention. However, such account is by no means universal, and large individual differences in asymmetrical performance on visuospatial tasks have been reported. Furthermore, the variability in the SLF lateralization has been shown to correlate with behavioural asymmetries. Continuous theta burst stimulation (cTBS) enables to temporarily interfere with cortical activity. cTBS applied over the posterior parietal cortex (PPC) has been previously used to systematically study attentional asymmetries. Interestingly, large individual differences in the effectiveness of stimulation have been reported. In accordance with earlier both animal and human studies, one possible cause underlying these striking individual differences might lie in the structural organization of frontoparietal pathways subserving visuospatial attention. Thus, the current study employed diffusion tractography to examine the relationship between the variability in the structural organization of the SLF and the individual differences in attentional shifts induced by a **modified cTBS (cTBS_{mod}; triplets of pulses at 30Hz, repeated at 6Hz)** applied over the IPS, as measured by a line bisection task. Consistent with previous studies, on a group level, **cTBS_{mod}** applied over the right intraparietal sulcus (IPS) triggered a rightward bisection bias shift, and there were no significant effects of **cTBS_{mod}** applied over the left IPS. However, further analyses demonstrated that both handedness and structural variability (as assessed based on hindrance modulated orientational anisotropy) within the middle and the ventral branches of the SLF predicted individual differences in the **cTBS_{mod}**-induced attentional shifts. Our study thus suggests that the effects of **cTBS_{mod}** over the IPS may depend on intra-hemispheric interactions between cortical loci controlling visual attention. **To conclude, our findings provide converging evidence for the notion put forward previously that inter-individual variability in the structural organization of intra-hemispheric frontoparietal connections has important implications for the functional models of human visual attention. Moreover, we hypothesize that this may also be relevant for the understanding of attentional disorders and their rehabilitation.**

keywords: individual differences; continuous theta burst stimulation; superior longitudinal fasciculus; visual attention; spatial bias

1. INTRODUCTION

A considerable amount of evidence suggests that visuospatial attention is asymmetrically organized in the human brain, with a right-hemispheric dominance (Corbetta and Shulman, 2002; Kinsbourne, 1987; 1993; Mesulam, 1981). The empirical support for hemispheric asymmetries in visuospatial attention stems from behavioural and functional neuroimaging studies in healthy controls, and from neuropsychological studies in right-hemispheric stroke patients suffering from hemispatial neglect syndrome (Corbetta and Shulman, 2002, 2011; Shulman et al., 2010). Neglect patients fail to direct attention towards the side of space contralateral to the damaged (most commonly right) hemisphere (Corbetta and Shulman, 2011; Heilman and Valenstein, 1979; Heilman and Van Den Abell, 1980; Vallar, 1998). In contrast, healthy participants generally respond faster to targets appearing in the left visual field, and/or display a variable degree of leftward deviation (so-called pseudoneglect) when identifying the midpoint of a line (Jewell and McCourt, 2000; McCourt and Jewell, 1999; Sosa et al., 2010). It has been suggested that – during visuospatial tasks – a preferential activation of the dominant, right hemisphere leads to the above-mentioned leftward attentional bias in healthy participants, and that a pathological hyperactivity of the contralesional, left hemisphere results in the neglect syndrome (Corbetta et al., 2005; Corbetta and Shulman, 2002, 2011; Shulman et al., 2010).

Human visuospatial attention relies on the function of the so-called dorsal and ventral attention networks (Corbetta and Shulman, 2002; Mesulam, 1981, 1990), subserved by three branches of a long frontoparietal association pathway, the superior longitudinal fasciculus (SLF; (Thiebaut de Schotten et al., 2011). The projections of the first and third branches of the SLF (SLF I and SLF III) interconnect cortical areas within the dorsal and ventral attention networks, respectively, whereas the middle branch of the SLF (SLF II) provides connections between both networks (Bartolomeo et al., 2007; Doricchi et al., 2008; Schmahmann et al., 2007; Thiebaut de

Schotten et al., 2011). Numerous studies, both structural (diffusion imaging studies) and functional magnetic resonance imaging (fMRI studies), indicate that the dorsal network is organized bilaterally, whereas the ventral network is strongly lateralized towards the right hemisphere (Corbetta and Shulman, 2002; Doricchi et al., 2010; Shulman et al., 2010; Thiebaut de Schotten et al., 2011). Nevertheless, while this right-hemispheric dominance in visuospatial attention suitably reflects general principles of the human brain organization, it fails to account for the observed individual differences in spatial biases. Reports of rightward biases in healthy controls, and of neglect affecting the right side of space following left-hemispheric damage suggest that, indeed, this general model is not invariable across the human population (Cai et al., 2013; Chechlacz et al., 2015a; Jewell and McCourt, 2000; Petit et al., 2015; Suchan et al., 2012; Thiebaut de Schotten et al., 2011). Subsequently, it has been suggested that both the extent of lateralization and the lateralization patterns in the human attention networks (i.e., left- or right-hemispheric dominance, or bilateral organization) not only determine the degree of behavioural asymmetries on the individual level, but also the susceptibility to lateralized attentional deficits following unilateral brain lesions. Recent studies demonstrated that the individual structural variability in the organization of the SLF is linked to behavioural attentional asymmetries (Chechlacz et al., 2015a; Marshall et al., 2015a; Thiebaut de Schotten et al., 2011). Moreover, the extent of fronto-parietal disconnections – emerging as a result of SLF damage – has been associated with the severity of neglect symptoms and with the degree of neglect recovery (Lunven et al., 2015; Thiebaut de Schotten et al., 2014). Finally, while some studies suggest that the degree of hemispheric lateralization of the attentional networks might be causally linked to handedness, other reports strongly contradict such a link, or at least indicate that this relationship is not straightforward (Bryden et al., 1983; Cai et al., 2013; Chechlacz et al., 2015a; Floel et al., 2005a; Floel et al., 2005b; Mazoyer et al., 2014; Petit et al., 2015; Somers et al., 2015b; Szaflarski et al., 2002; Szczepanski et

al., 2013; Whitehouse et al., 2009; Willems et al., 2014).

Transcranial magnetic stimulation (TMS) provides a powerful tool to study the functional organization of the brain, and this technique has been frequently used to investigate basic principles of visuospatial attention control (for a review see Szczepanski and Kastner, 2009). TMS can be employed to temporarily interfere with cortical processing, in a so-called “virtual lesion” approach. The application of TMS over the right posterior parietal cortex (PPC) has been used to alter the spatial allocation of visual attention, and to induce neglect-like behaviour in healthy participants (Cazzoli et al., 2009; Fierro et al., 2000; Hilgetag et al., 2001; Hung et al., 2005; Sack et al., 2007). On the other hand, in stroke patients, TMS applied over the intact, left PPC has been used to ameliorate neglect symptoms, by reducing the pathological hyperexcitability of the contralesional hemisphere (for review see Cazzoli et al., 2010). Though, both in healthy participants and neglect patients, large individual differences in the effects of TMS have been reported, either in the direction and/or in the extent of the induced attentional shifts (Chechlacz et al., 2015b; Plow et al., 2014; Rizk et al., 2013; Szczepanski and Kastner, 2013; see also the review by Nicolo et al., 2015). Despite the individually varying behavioural responses across neglect patients, TMS is being considered as potential add-on therapy in neglect rehabilitation. Thus, understanding how individual differences in behavioural responses to TMS arise represents not only a relevant question for basic science, but also for clinical applications (Cazzoli et al., 2010; Nicolo et al., 2015).

In the current study, we employed diffusion magnetic resonance imaging tractography to examine the relationship between individual differences in the attentional shifts induced by TMS applied over the PPC and the variability in the structural organization of the fronto-parietal attention pathways, namely the SLF I, SLF II, and SLF III. We used a **modified** continuous theta burst stimulation (**cTBS_{mod}**) protocol, which has been shown to exert robust neural inhibition when

applied over the PPC, affecting the spatial distribution of visual attention (Cazzoli et al., 2012; Cazzoli et al., 2009; Chechlacz et al., 2015b; Nyffeler et al., 2009; Nyffeler et al., 2008). To date, numerous studies, in both animals and humans, provide evidence that the micro- and macrostructural organization of white matter connections, including fronto-parietal networks, mediates the effects of TMS induced changes in brain activity and in behavioural performance on visual perception and motor-learning tasks (Valero-Cabré et al., 2005; Valero-Cabré et al., 2007, Neubert et al., 2010; Quentin et al., 2013; Quentin et al., 2015a,b; Rodríguez-Herreros et al., 2015). Specifically, it has been shown that, for instance, the structural variability of the fronto-tectal tract and the SLF I predicts the magnitude of top-down modulated conscious visual perception (Quentin et al., 2013; Quentin et al., 2015a,b). Interestingly, combined TMS-fMRI studies have demonstrated that TMS application results in compensatory changes in both contra- and ipsilateral brain activity, across several functionally connected brain regions, suggesting that the TMS-induced behavioural changes may be a result of not only the direct effect on the stimulated region, but also of the influence on remote but interconnected brain regions (Plow et al., 2014; Ruff et al., 2008; Ruff et al., 2009; Sack et al., 2007). For example, Sack and colleagues (Sack et al., 2007) have shown that TMS applied over the PPC results in bilateral changes in the activity of several fronto-parietal regions affecting performance in a spatial judgement task. Furthermore, two studies by Ruff et al. (2008, 2009) have demonstrated that the right parietal TMS triggers remote changes in the bilateral visual cortex activity associated with the presentation of simple visual stimuli. Based on those earlier reports, indicating that the structural properties of the white matter pathways (e.g., Quentin et al., 2013; Quentin et al., 2015a,b) and the compensatory activations in remote cortical areas (e.g., Plow et al., 2014; Ruff et al., 2008; Ruff et al., 2009; Sack et al., 2007) mediate the effects of TMS on visual perception in humans, we previously tested the hypothesis that the effects of TMS applied over the PPC may depend on

inter- and/or intra-hemispheric interactions between cortical loci controlling visual attention, and would thus be predicted by the variability in the structural organization of white matter pathways subserving visual attention (Chechacz et al., 2015b). In a former study, we demonstrated that individual differences in response to cTBS_{mod} over the PPC could be predicted by the variability in the structural organization of the corpus callosum, but we found no reliable evidence for the variability of the cTBS_{mod} effects to hinge on intra-hemispheric fronto-parietal pathways (Chechacz et al., 2015b). While in the previous study we measured the overt allocation of spatial attention by means of a free visual exploration paradigm, in the present study we purposefully employed a manual line bisection task. Although a manual line bisection task may present some limitations (i.e., it cannot be individually titrated in order to enhance sensitivity; presentation time cannot be strictly controlled; left vs. right, or combined bilateral left vs. right, attentional orienting effects cannot be specifically disentangled), this task also presents several advantages, which guided our decision. First, as handedness has been previously linked to attentional asymmetries, the line bisection test, which can be performed with both hands, provides a suitable approach to examine the effects of hand dominance on the measured behavioural performance. Second, a recent study directly compared the effects of TMS on performance (manual line bisection vs. a landmark task), and showed a greater sensitivity of the manual line bisection task (Varnava et al., 2013). Third, previous work indicates a robust correlation between deviations from the centre in the line bisection task and the structural lateralization of the SLF II (Thiebaut de Schotten et al., 2011). Fourth, the line bisection task is one of the most frequently used tools to measure behavioural asymmetries in human spatial attention (i.e., pseudoneglect), and to diagnose neglect symptoms in clinical settings. Hence, this approach could be potentially adopted in the future to address similar questions in neglect patients, e.g., in the context of neurostimulation applied as an add-on therapy.

2. MATERIAL AND METHODS

2.1. Participants. Twenty-four healthy participants (12 men; mean \pm SD age = 26.5 ± 5.1) volunteered to take part in the study, consisting of one magnetic resonance imaging (MRI) and three brain stimulation sessions. Exclusion criteria included any previous history of neurological or psychiatric disorders, and contraindications to magnetic resonance imaging (MRI) or TMS (Rossi et al., 2009). For the purpose of the current study we did not use handedness as an exclusion criterion. Based on self-report, we recruited seventeen right-handed and seven left-handed participants. Subsequently, we used the Edinburgh handedness inventory (Oldfield, 1971) to formally assess hand dominance. In right-handed participants the mean age was 26.71 years old (standard error of the mean, SEM = 1.17) and 27 years old (SEM = 2.16) in left-handed participants. There was no significant difference in age between left- and right-handed participants ($t_{22} = -.129$, $p = .899$).

The study was conducted in accordance with the latest version of the Declaration of Helsinki, and all participants provided written informed consent, in compliance with relevant protocols approved by the University of Oxford Central University Research Ethics Committee.

2.2. Behavioural testing and Line bisection task. To date, it is unclear whether and to what extent handedness affects the lateralization of brain functions. Published reports provide both evidence for and against an atypical lateralization of visual attention and language in left-handed participants (Badzakova-Trajkov et al., 2010; Bryden et al., 1983; Cai et al., 2013; Floel et al., 2005b; Mazoyer et al., 2014; Sommer et al., 2002; Szaflarski et al., 2002; Whitehouse and Bishop, 2009; for a recent comprehensive review, see Willems et al., 2014). Consequently, left-handed participants are typically excluded from the majority of studies. As our aim was to focus on individual differences (as opposed to reducing variance in the data), we did not select our

participants according to their handedness. At recruitment, participants were asked to state their hand preference (self-report). Subsequently, the Edinburgh handedness inventory (Oldfield, 1971) was used to objectively assess their handedness. The Edinburgh handedness inventory score ranges from -100 (extremely left-handed; a score below -40 indicating left-handedness) to +100 (extremely right-handed; a score above +40 indicating right-handedness), with the scores between -40 to +40 indicating ambidexterity.

All participants were tested on a manual line bisection task. In this task, participants were asked to mark with a pen the midpoint of a twenty cm long and one mm thick black line, presented horizontally, at the centre of a white, landscape-oriented A4 sheet of paper. During testing, participants were seated in front of a table, and were presented with ten such lines, each sheet of paper being sequentially positioned in front of the participant, with the centre of the paper sheet aligned with the participant's midsagittal plane. Out of the ten lines, each participant marked five with the right hand, and five with the left hand, always starting with the self-reported dominant hand.

Participants were tested with this manual line bisection task at several time points. First, the task was performed prior to the MRI session, in order to evaluate the distribution of the bisection bias/pseudoneglect in the studied group. Subsequently, we used this task twice during each brain stimulation session, i.e., before and after application of brain stimulation, in order to assess whether the respective stimulation condition (see below) would induce changes in the bisection bias (Figure 1A). Participants were tested on the line bisection task in close proximity to the start and the end of each stimulation session. Specifically, participants were first tested (pre stimulation test) before the motor threshold was determined and the stimulation point was identified (see below for details concerning the stimulation sessions). Following the application of stimulation, the **computer program** controlling stimulation and the stimulator were turned off, and

participants were asked to move back to the table where they were presented with the second set of ten lines (post stimulation test).

2.3. Repetitive transcranial magnetic stimulation (rTMS). All participants performed the line bisection task at three different rTMS sessions, separated by at least one week: (i) with active stimulation over the right IPS; (ii) with active stimulation over the left IPS; and, (iii) with sham stimulation over the right IPS; (Figure 1A). The order of the rTMS sessions was counterbalanced across participants. rTMS was applied by means of a **modified** continuous Theta Burst Stimulation (**cTBS_{mod}**) protocol described previously (Cazzoli et al., 2012; Cazzoli et al., 2009; Chechlac et al., 2015b; Nyffeler et al., 2009; Nyffeler et al., 2008), modified from the **standard protocol** (**cTBS_{std}**; Huang et al., 2005; **3 pulses at 50 Hz, repeated at 5 Hz**). The protocol was composed of a total of 801 pulses, delivered in a continuous train of 267 bursts, each burst consisting of 3 pulses at 30 Hz, repeated at 6 Hz. The effects of this **cTBS_{mod}** protocol have been shown to last at least 30 minutes when applied over the PPC (Nyffeler et al., 2008) and over the primary motor cortex (Goldsworthy et al., 2012). **We decided to use this protocol because, when applied over the PPC, cTBS_{mod} has been reliably shown to exert inhibitory effects (i.e., effects that interfere with performance, on an individual behavioural level, and on a group level) on the spatial allocation of visual attention (Cazzoli et al., 2009; Chechlac et al., 2015b; Nyffeler et al., 2008, Nyffeler et al., 2009). Moreover, a recent study has shown that cTBS_{mod} has greater suppressive effects, and more consistent across subjects, than cTBS_{std}, at least when applied over the primary motor cortex, and as measured by motor evoked potentials (MEP; Goldsworthy et al., 2012). The probable basis for the differences in response to the two cTBS protocols is hypothesised to be represented by the variations in the inter- and/or intra-burst frequencies (Goldsworthy et al., 2012). Although the mechanisms leading to cortical excitability suppression after cTBS_{mod} have not been extensively investigated, there is some evidence that these mechanisms are cortical in nature and, like for cTBS_{std}, it is hypothesized**

that these are due to long term depression (LTD)-like changes (Goldsworthy et al., 2012).

cTBS_{mod} was performed by means of a Magstim Rapid stimulator, connected to four booster modules (Booster Module Plus, Magstim). For the two real cTBS_{mod} conditions (i.e., cTBS_{mod} over the left and the right IPS, respectively), a commercially available figure-of-eight coil, with a diameter of 70 mm (Magstim), was connected to the stimulator. For sham stimulation, a figure-of-eight coil was connected to a commercially available placebo coil system (Magstim). With this sham setup, the coil produced discharge noises as in the real stimulation conditions, and elicited mild cutaneous sensations, but did not produce active stimulation of the underlying cortical tissue. It should be noted that, in the present study, sham stimulation was only applied over the right IPS. The cueing effect represented by lateralized sensations (e.g., tapping, clicking) during sham stimulation are thought to be less relevant for experiments using offline stimulation, as it was the case in the present study, since behavioural tasks are administered after (and not during) stimulation. However, participants may better infer the type of stimulation received (i.e., real or sham), since they are not engaged in a behavioural task during stimulation. A more comprehensive experimental design would have also included sham stimulation over the left IPS. We decided against additionally applying sham stimulation over the second (left IPS) site for practical reasons, i.e., this would have meant a fifth experimental session, in addition to four prior sessions (one MRI session and three randomised stimulation sessions).

The stimulator setup was connected to a laptop (Dell), controlling the above-mentioned stimulation parameters by means of a script programmed in E-Prime 2.0 Pro (Psychology Software Tools). Stimulation intensity was set at 80% of the individual resting motor threshold (rMT) of the participants' contralateral small hand muscles. The rMT was defined as the minimal stimulator output of single TMS pulses that was able to consistently elicit (i.e., at least three out of five consecutive trials) motor responses in the contralateral, relaxed small hand muscles. The mean

rMT in right-handers was 50.12 % stimulator output (s.o.) (SEM = 1.55) for the left hemisphere and 50.35 % s.o. (SEM = 1.55) for the right hemisphere, and in left-handers was 49.86 % s.o. (SEM = 2.42) for the left hemisphere and 50 % s.o. (SEM = 2.41) for the right hemisphere. There was no significant main effect of handedness ($F_{1,22} = .013, p = .910$) or of hemisphere ($F_{1,22} = .034, p = .856$), and no significant interaction between these two factors ($F_{1,22} = .002, p = .965$). The stimulation intensity (i.e., 80% rMT) in right-handers was 40 % s.o. (SEM = 1.25) for the left hemisphere and 40.24 % s.o. (SEM = 1.23) for the right hemisphere, and in left-handers was 39.87 % s.o. (SEM = 1.95) for the left hemisphere and 40.14 % s.o. (SEM = 1.92) for the right hemisphere. There was no significant main effect of handedness ($F_{1,22} = .003, p = .957$) or of hemisphere ($F_{1,22} = .092, p = .764$), and no significant interaction between these two factors ($F_{1,22} = .001, p = .977$).

Positioning of the coil was performed by means of MRI-guided neuronavigation (frameless stereotactic system BrainSight, Rogue Research). The stimulation sites for the left and the right IPS (posterior part of the IPS, left and right IPS1/2; Silver and Kastner, 2009) were identified using slice- and 3D-rendered information from the individual MRI anatomical scans acquired for every participant (see “MRI data acquisition and preprocessing” section for the scan details). This approach was chosen because previous studies have shown that employing MRI-guided TMS neuronavigation with individually determined anatomical landmarks of the IPS yields larger behavioural effect sizes than using group-based normalized stereotaxic coordinates derived from prior fMRI experiments (Sack et al., 2008). Neuroanatomical sites were co-registered with landmarks on the participants’ scalp surface by means of the neuronavigation system. The mean estimated skull thickness over the IPS target site in right-handers was 8.08 mm (SEM = .23) for the left hemisphere and 7.71 mm (SEM = .25) for the right hemisphere, and in left-handers was 7.37 mm (SEM = .36) for the left hemisphere and 7.46 mm (SEM = .39) for the right hemisphere. There was no significant main effect of handedness ($F_{1,22} = 1.269, p = .272$) or of hemisphere ($F_{1,22} =$

1.512, $p = .232$), and no significant interaction between these two factors ($F_{1,22} = 3.82$, $p = .063$).

The mean coil-to-target Euclidian distance in right-handers was 29.59 mm (SEM = 1.04) for the left hemisphere and 29.98 mm (SEM = .96) for the right hemisphere, and in left-handers was 27.53 mm (SEM = 1.62) for the left hemisphere and 27.26 mm (SEM = 1.5) for the right hemisphere.

There was no significant main effect of handedness ($F_{1,22} = 1.22$, $p = .281$) or of hemisphere ($F_{1,22} = .385$, $p = .542$), and no significant interaction between these two factors ($F_{1,22} = .058$, $p = .811$).

The experimenter held the coil in position during the **cTBS_{mod}** protocol (44 sec). The handle of the coil was pointing backwards, at angle of 45° with respect to the sagittal plan of the participant (with the apparatus and coil orientation used in the present study, the current induced in the brain tissue had thus a posterior-anterior direction, as defined with respect to the first phase of the biphasic pulses).

2.4. Behavioural data analyses. For each bisected line, we first measured the deviation from the true midpoint in millimetres (mm), with negative values corresponding to a leftward deviation (i.e., the indicated bisection point was to the left with respect to the centre of the line), and positive values corresponding to a rightward deviation (i.e., the indicated bisection point was to the right with respect to the centre of the line). For the purpose of statistical analyses, for each testing time-point, we first averaged performance across all ten bisected lines, i.e., performance averaged across the dominant and the non-dominant hand. In addition, the performance with only either the dominant or the non-dominant hand was calculated.

To assess the effects of the respective stimulation conditions (**cTBS_{mod}** over the left IPS, **cTBS_{mod}** over the right IPS, and sham), a bisection bias shift was calculated as follows: bisection bias measured as averaged deviation from the true midpoint after stimulation (post) minus bisection bias measured as averaged deviation from the true midpoint before stimulation (pre). Hence, negative values indicated a leftward bias shift, and positive values a rightward bias shift.

First, data were analysed *without* taking into account handedness (across all participants), by means of a one-way repeated-measures analysis of variance (ANOVA), with the within-subjects factor stimulation (levels: sham, cTBS_{mod} left IPS, cTBS_{mod} right IPS). Second, data were analysed taking into account handedness, by means of a mixed-model repeated-measures ANOVA, with the within-subjects factor stimulation (levels: sham, cTBS_{mod} left IPS, cTBS_{mod} right IPS) and the between-subjects factor handedness (levels: right-handers, left-handers). Third, in order to evaluate the influence of the dominant and the non-dominant hand, the same mixed-model repeated-measures ANOVA approach as in the previous point was re-run separately for the performance with the two hands. All subsequent post-hoc tests were performed by means of Fisher's least significant difference-corrected t-tests.

2.5. MRI data acquisition and preprocessing. For all participants, we acquired T1-weighted and diffusion-weighted scans at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), using a 3T Verio scanner with a 32-channel head coil (Siemens, Erlangen, Germany). T1-weighted structural scans were acquired using magnetization prepared rapid acquisition gradient echo sequence (MPRAGE), with the following parameters: TR = 2040 ms, TE = 4.7 ms, flip angle of 8°, and a resolution of 1x1x1mm. These scans were employed for MRI-guided neuronavigation, i.e., to target the left and the right IPS during cTBS_{mod} stimulation (see above). Diffusion magnetic resonance imaging data were acquired using single-shot echo planar imaging (EPI), and a monopolar sequence with a voxel size of 2x2x2mm with the following parameters: TR = 9600 ms and TE = 87 ms, in plane parallel imaging (GRAPPA) factor=2. The diffusion weighting was isotropically distributed along 60 directions ($b = 1500 \text{ s/mm}^2$), and our acquisition also included 4 volumes without diffusion weighting. For each participant, two sets of whole brain diffusion-weighted data were acquired, with reversed phase-encoding directions (anterior-posterior vs posterior-anterior). Such protocol was employed to improve the signal-to-noise ratio,

and to allow correction of geometric distortion resulting from EPI acquisition (Andersson et al., 2003; Chang and Fitzpatrick, 1992). All diffusion-weighted scans were pre-processed for distortion correction, using the pipelines developed for the Human Connectome Project (Glasser et al., 2013; Sotiropoulos et al., 2013), and the latest FSL tools (FMRIB Centre Software Library, Oxford University; Smith et al., 2004). First, pairs of phase-reversed images were used to correct for susceptibility-induced distortions (Andersson et al., 2003) with the FSL topup tool. Subsequently, eddy currents and subject motion were corrected using a generative model approach with the FSL EDDY tool (Andersson and Sotiropoulos, 2015, 2016). All distortion corrections were performed in a single re-sampling step, using spline interpolation.

2.6. Spherical Deconvolution and Tractography. To reconstruct the three branches of the SLF, we employed a previously published and widely used method, based on spherical deconvolution and whole brain tractography combined with virtual dissections (Thiebaut de Schotten et al., 2011). First, we applied spherical deconvolution based on the damped Richardson-Lucy algorithm, to model the diffusion signal as a distribution of multiple fiber orientations as implemented in the StarTrack software (www.natbrainlab.com; Dell'acqua et al., 2010; Dell'Acqua et al., 2013). Subsequently, the StarTrack software was used to perform whole brain tractography, and the streamlines were propagated with an Euler integration algorithm, with a step size of 0.5 mm and an angular threshold of 45°. Finally, we employed TrackVis (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital) to carry out virtual dissections of the three SLF branches (SLF I, SLF II, and SLF III), based on a multiple regions of interest (ROIs) approach (Thiebaut de Schotten et al., 2011). Briefly, four target ROIs were first defined around the superior, middle, and inferior frontal gyri, and posteriorly in the parietal region, within both hemispheres. To isolate the three branches of the SLF, we retained the streamlines that went through these ROIs, while excluding fibers of the arcuate fasciculus using a

single ROI defined in the temporal lobe of each hemisphere (see Figure 1B for further details).

Following virtual dissections, a hindrance modulated orientational anisotropy (HMOA) index was estimated for each tract. This index characterizes white matter diffusion properties, and thus reflects white matter organization and microstructure (Dell'Acqua et al., 2013). In addition, the volume was calculated based on the number of voxels intersected by all the streamlines of each tract, denoting the space occupied by each reconstructed pathway (macrostructural organization). Tractography was performed in the native space. Thus, to control for the variability in brain/hemisphere size (which could affect the estimated tract volume; i.e., larger brain = larger tract), for each participant we normalized the tract volume by the total hemisphere white matter (WM) volume (i.e., according to the formula: tract volume/hemisphere WM volume). Finally, we calculated a lateralization index (LI) for all the reconstructed SLF branches (separately for the HMOA index and for the normalized volume), according to the following formula: $LI = (Right - Left) / (Right + Left)$. Thus, negative values indicated a leftward asymmetry, and positive values a rightward asymmetry.

2.7. Neuroimaging data analyses. Statistical analyses were performed using either Matlab 7.14/R2012a (The MathWorks, Natick, MA, USA) or SPSS 21 (IBM SPSS Statistics, NY, USA). One-sample t-tests were used to assess the lateralization of the three branches of the SLF.

Independent-sample t-tests were used to compare group differences (right versus left-handers) concerning the lateralization of the SLF branches.

Based on Shapiro-Wilk tests (Shapiro and Wilk, 1965), we were unable to confirm the Gaussian distribution for all the variables derived from either behavioural performance/*cTBS_{mod}* stimulation (bisection bias, bisection bias shift) or neuroimaging data (HMOA, volume, lateralization index). Therefore, we used the Spearman's method for all correlation analyses, in order to examine the link between the structural variability within the SLF branches and the individual differences in

either the pseudoneglect (bisection bias) or the **cTBS_{mod}**-induced changes in the bisection bias (i.e., the bisection bias shift). To correct for multiple comparisons in the correlation analyses, we applied the FDR correction, based on the Benjamini–Hochberg FDR method, using the `mafdr` function as implemented in the Matlab Bioinformatics toolbox (Benjamini and Hochberg, 1995). This procedure estimates false discovery rate (FDR) from p values of multiple hypothesis testing. Unless specified otherwise, we report FDR-corrected p values. Finally, to provide a proof of the robustness of the statistically significant correlations reported here, we have included additional permutation testing (as described by Groppe et al., 2011 and as implemented in the Matlab `mult_comp_perm_corr` function) based on the Spearman’s rank correlation coefficient with 5000 random permutations. Specifically, for the analyses looking at the link between the bisection bias and SLF II lateralization, the lateralization indices based on both volume and HMOA index as well as bisection bias were permuted across the entire group of participants and all correlations were recalculated with each new version of the modified dataset. Subsequently, for the analyses examining the link between structural variability of the SLF and the effects of **cTBS_{mod}**, we first permuted, across the entire group of participants, the HMOA of the SLF II and SLF III in each hemisphere as well as the bisection bias shift triggered by **cTBS_{mod}** over the right IPS and then all correlations were recalculated with each new version of the modified dataset. Such permutation approach allowed us to test the null hypotheses that correlations obtained with initial order are as likely as the correlations obtained with random permutations. This method is used for adjusting the p-values of each variable for multiple comparisons in a way that controls the family-wise error rate (Groppe et al., 2011).

3. RESULTS

3.1. Behavioural Results. We acquired data from a group of 24 participants. Based on the self-report at recruitment, 17 participants were classified as right-handers and 7 participants as left-

handlers. The further assessment with the Edinburgh handedness inventory (Oldfield, 1971) overall confirmed the self-reported hand preference with respect to writing and drawing, although 2 out of the 17 right-handers and 3 out of the 7 left-handers should be regarded as ambidextrous when also considering other activities included in the inventory.

All participants were first tested on the line bisection task prior to the MRI session. While we observed large individual differences in both the direction and the extent of the bisection bias, consistently with previous studies (for an extensive review, see Jewell and McCourt, 2000), at the group level our participants showed a left-sided bisection bias (left pseudoneglect; -2.0 ± 2.3 mm for the performance averaged across both hands, and -2.6 ± 3.2 mm for the performance with the dominant hand only). We also compared the performance on the line bisection task between the right-handed and the left-handed participants, and no significant differences were found with respect to either the performance averaged across both hands or the performance with the dominant hand only (all p values > 0.5).

The participants' performance on the line bisection task without application of any brain stimulation was measured on four different occasions (prior to the MRI session and prior to the three stimulation sessions). A repeated-measures ANOVA indicated no significant differences between these four occasions, neither when considering performance averaged across both hands, nor when considering performance with the dominant hand only (all p values > 0.5).

We next analysed the bisection bias shifts, i.e., the changes in bisection performance after application of **ctBS_{mod}**. When handedness was *not* taken into account (i.e., performance averaged across the dominant and the non-dominant hand), the analysis of the bisection bias shift revealed a significant main effect of the factor stimulation ($F_{2,46} = 4.421$, $p = 0.018$). As shown in Figure 2A, and as assessed by subsequent *post-hoc* tests, **ctBS_{mod}** over the right IPS triggered a significant rightward shift of the bisection bias in comparison to sham stimulation ($p = 0.005$), whereas

cTBS_{mod} over the left IPS had no significant effect in comparison to sham stimulation ($p = 0.183$).

However, subsequent analyses revealed that, when handedness was taken into account, there were differential stimulation effects for right- and left-handed participants. The analysis of the bisection bias shift (performance averaged across the dominant and the non-dominant hand) revealed no significant main effect of the factor handedness ($F_{1,22} = 0.012$, $p = 0.912$), but a significant main effect of the factor stimulation ($F_{2,44} = 3.757$, $p = 0.031$) and a highly significant interaction between factors stimulation x handedness ($F_{2,44} = 5.943$, $p = 0.005$). As shown in Figure 2B, and as assessed by subsequent post-hoc tests, in the group of right-handers, cTBS_{mod} over the right IPS triggered a significant rightward shift of the bisection bias in comparison to sham stimulation ($p = 0.001$), whereas cTBS_{mod} over the left IPS had no significant effect in comparison to sham stimulation ($p = 0.941$). Moreover, for the right-handed participants, the effects of cTBS_{mod} over the left and the right IPS were significantly different ($p = 0.002$). In contrast, in the group of left-handed participants, cTBS_{mod} over the left IPS triggered a significant rightward shift of the bisection bias in comparison to sham stimulation ($p = 0.011$), whereas cTBS_{mod} over the right IPS had no significant effect in comparison to sham stimulation ($p = 0.461$). Moreover, the difference between the effects of cTBS_{mod} over the left and over the right IPS showed a trend towards significance ($p = 0.064$).

Finally, to evaluate not only the influence of participants' handedness, but also the effect of performance with the dominant versus the non-dominant hand, we re-run two separate analyses. Interestingly, the analysis of the bisection bias shift based on the performance with only the dominant hand revealed a significant interaction between the factors stimulation x handedness ($F_{2,44} = 4.416$, $p = 0.018$). In contrast, the analysis of the performance with only the non-dominant hand revealed no significant interaction between the factors stimulation x handedness ($F_{2,44} = 1.808$, $p = 0.176$). These findings indicate that the effect of the interaction between the factors

stimulation x handedness on the bisection bias shift, observed when bisection performance was averaged across the dominant and the non-dominant hand, was likely driven by the dominant hand.

3.2. Neuroimaging Results. Based on tractography reconstructions of the three SLF branches, and on the measures of tract volume and HMOA index, we first evaluated the lateralization of the SLF. Consistently with previous reports based on measured tract volume (Chechlacz et al., 2015a; Marshall et al., 2015a; Thiebaut de Schotten et al., 2011), only the SLF III was right-lateralized at the group level ($t_{23}=7.52$, $p<0.0001$; Figure 3B), while the SLF I and the SLF II were symmetrically organized ($t_{23}<1$). Interestingly, based on the HMOA index measures, both the SLF III ($t_{23}=6.71$, $p<0.0001$) and the SLF II ($t_{23}=4.09$, $p<0.0001$) were right-lateralized (Figure 3C), while the SLF I was symmetrically organized ($t_{23}<1$). These findings are consistent with previous studies demonstrating a differential micro- and macro-structural organization of the fronto-parietal pathways (e.g., Chechlacz et al., 2015a).

Given that, in the current study, we included both right- and left-handers, we next examined potential links between handedness and the SLF lateralization. In the studied group of participants, there were no significant correlations between handedness (as a continuous measure, derived from the Edinburgh handedness inventory) and the lateralization indices (calculated based on either tract volume or HMOA index) of any of the SLF branches (all p values >0.5). Notably, direct group comparisons (i.e., right- versus left-handers) based on the HMOA measures revealed a stronger right lateralization of the SLF III in the left-handed participants ($t_{23}=-2.73$, $p=0.012$). Subsequent t-test indicated a significantly lower HMOA index within the left SLF III in the examined group of left-handed participants ($t_{23}=2.61$, $p=0.016$). There were no other significant group differences. It should be noted, however, that both the correlation analyses and the group comparisons were based on a disproportionately larger number of right-handed than

left-handed participants (i.e., 17 versus 7, respectively), as well as on an overall relatively small number of participants. Thus, caution should be taken when generalizing these findings in terms of a common relation between structural variability in brain organization and handedness.

In the current study, we primarily sought to determine whether the effects of **cTBS_{mod}** applied over the IPS (measured by the shift in the bisection bias) might be predicted by the variability in the structural organization of the SLF. However, in order to perform this analysis, we first confirmed that, in the studied group of participants, the measured line bisection bias itself (without application of any stimulation) was indeed related to the lateralization of the SLF (measured by the lateralization index), as this relationship, providing the anatomical basis of hemispheric lateralization in human attention and reported by earlier studies (in particular please see Thiebaut de Schotten et al., 2011) constituted the rationale behind the current study. We found a consistent link between the bisection bias and both the macro- and the micro-structural lateralization of the SLF II (but neither of the SLF I, nor of the SLF III; all p values >0.5). A larger volume and as well as a higher HMOA index of the SLF II within the right hemisphere corresponded to a stronger leftward bisection bias, i.e., a greater deviation towards the left from the true centre of the bisected line (Figure 4A,B). These findings are consistent with the results of previous studies (Chechlacz et al., 2015a; Marshall et al., 2015a; Thiebaut de Schotten et al., 2011). Specifically, we found negative correlations between the lateralization of the SLF II and the bisection bias evaluated prior to the MRI session, both when considering performance averaged across both hands (volume LI $r=-0.45$, $p=0.04$ FDR corrected; HMOA LI $r=-0.48$, $p=0.03$ FDR corrected; Figure 4A,B) and when considering performance with the dominant hand only (volume LI $r=-0.45$, $p=0.04$ FDR corrected; HMOA LI, $r=-0.49$, $p=0.03$ FDR corrected). The permutation tests confirmed the above results of the correlations between the lateralization of the SLF II and the bisection bias as evaluated prior to the MRI session (performance averaged across both hands:

volume LI $p=0.036$ and HMOA LI $p=0.022$; performance with the dominant hand only: volume LI $p=0.038$ and HMOA LI, $p=0.018$).

Importantly, these findings were consistent for the bisection bias estimated according to the performance averaged across all testing sessions without stimulation. We also found negative correlations between the macro-structural (volume) lateralization of the SLF II and the bisection bias (performance averaged across both hands $r=-0.49$, $p=0.02$ FDR corrected; performance with the dominant hand only $r=-0.49$, $p=0.02$ FDR corrected). This was also the case when examining the link between the micro-structural (HMOA index) lateralization of the SLF II and the bisection bias (performance averaged across both hands $r=-0.48$, $p=0.02$ FDR corrected; performance with the dominant hand only $r=-0.50$, $p=0.02$ FDR corrected). The permutation tests confirmed the above results of the correlations between the lateralization of the SLF II and the bisection bias as estimated according to the performance averaged across all testing sessions without stimulation (performance averaged across both hands: volume LI $p=0.023$ and HMOA LI $p=0.021$; performance with the dominant hand only: volume LI $p=0.021$ and HMOA LI, $p=0.018$).

Similarly to prior studies (e.g., Quentin et al., 2015a,b) the main analyses examined whether the variability in the structural organization of the SLF, within either the right or the left hemisphere, was associated with behavioural differences in the response to **cTBS_{mod}**. The correlation analysis indicated a link between the bisection bias shift triggered by **cTBS_{mod}** over the right IPS and the micro-structural (HMOA index) but not macro-structural (volume) organization of the SLF II and III (see Figure 4C,D). A higher HMOA index within the left SLF II corresponded to a greater rightward bisection bias shift triggered by **cTBS_{mod}** over the right IPS (performance averaged across both hands $r=0.44$, $p=0.05$ FDR corrected; performance with the dominant hand only $r=0.56$, $p=0.02$ FDR corrected). Similarly, a higher HMOA index within the left SLF III corresponded to a greater rightward bisection bias shift triggered by **cTBS_{mod}** over the right IPS

(performance averaged across both hands $r=0.57$, $p=0.02$ FDR corrected; although this correlation was not very strong when examined for the performance with the dominant hand only $r=0.36$, $p=0.04$ uncorrected/ 0.18 FDR corrected). The permutation tests confirmed the above results of the correlations between the HMOA index within the left SLF II and the rightward bisection bias shift triggered by **cTBS_{mod}** over the right IPS (performance averaged across both hands $p=0.008$; performance with the dominant hand only $p=0.014$) as well as between the HMOA index within the left SLF III and the rightward bisection bias shift triggered by **cTBS_{mod}** over the right IPS (performance averaged across both hands $p=0.011$; but not for the performance with the dominant hand only $p=0.18$).

There were no statistically significant correlations ($p>0.5$) between either the micro- or macro-structural organization of any of the SLF branches and the effects of either **cTBS_{mod}** over the left IPS or sham stimulation.

4. DISCUSSION

In the current study, using diffusion tractography combined with a **modified** cTBS protocol (**cTBS_{mod}**), we demonstrate that handedness and variability in the structural organization of intra-hemispheric fronto-parietal pathways can predict the effects of the stimulation-induced shifts in the spatial allocation of visual attention, as measured by a line bisection task. Consistently with previous studies, we report that **cTBS_{mod}** applied over the right IPS triggered a rightward bisection bias shift on a group level, but there were no significant effects when **cTBS_{mod}** was applied over the left IPS. Notably, we show here strikingly opposite stimulation effects in right- versus left-handed participants. In right-handed participants, similarly to the overall group findings, **cTBS_{mod}** over the right IPS triggered a significant rightward shift of the bisection bias, whereas **cTBS_{mod}** over the left IPS had no significant effect. In left-handed participants, by contrast, **cTBS_{mod}** over the right IPS had no significant effect, whereas **cTBS_{mod}** over the left IPS triggered a significant rightward shift of

the bisection bias. Finally, our findings indicate that the structural variability (as assessed by HMOA) within the middle and the ventral branches of the SLF (SLF II and SLF III, respectively) of the left hemisphere predicts the bisection bias shift triggered by **cTBS_{mod}** applied over the right IPS, with a higher HMOA index corresponding to a greater rightward bisection bias shift.

A growing body of evidence strongly suggests that the anatomical and functional variability in the organization of neural networks needs to be taken into account to comprehend the mechanisms governing human visual attention (Chechlacz et al., 2015a; Szczepanski and Kastner, 2013; Thiebaut de Schotten et al., 2011). The variability in the structural organization of the SLF II has been linked to individual differences in spatial attention biases (Chechlacz et al., 2015a; Thiebaut de Schotten et al., 2011), while other fronto-parietal pathways such as SLF I, SLF III, and the inferior fronto-occipital fasciculus (IFOF) have been shown to mediate diverse visual attention functions, such as accuracy of target detection, visual short-term memory, and top-down control (Chechlacz et al., 2015a; Marshall et al., 2015a; Quentin et al., 2015a). Importantly, a recent combined tractography and magnetoencephalography (MEG) study not only demonstrated that the SLF I mediates top-down signals modulating occipital cortical oscillations but also suggested vital functional implications of the structural variability of fronto-parietal connections. Specifically, that the variability in the structural organization of the SLF I is linked to individual differences in exerting top-down control of neural oscillations supporting selective attention (Marshall et al., 2015a). Another recent study showed a link between individual differences in the TMS-induced modulation of performance in a spatio-temporal visual detection task and the structural variability in fronto-parietal pathways (Quentin et al., 2015a). Specifically, Quentin et al. (2015a) reported a strong association between the SLF I volume and the influence of frontal beta oscillation patterns (triggered by short, frequency-specific 30Hz TMS bursts delivered to the right frontal eye field; FEF) on conscious visual target discrimination. Furthermore, the same group also demonstrated

that similarly microstructural variability of the right SLF I mediate the observed effects of rhythmic TMS applied to the FEF on contrast sensitivity in visual performance (Quentin et al., 2015b). These two reports (Quentin et al., 2015a,b) add to a growing body of evidence based on both animals and humans studies indicating that the micro- and macrostructural organization of white matter connections mediates the effects of TMS induced changes in brain activity and performance in a variety of cognitive tasks including visual discrimination, decision making, and motor-learning (Valero-Cabré et. al., 2005; Valero-Cabré et. al., 2007; Neubert et al., 2010; Quentin et al., 2013; Chechacz et al., 2015b; Quentin et al., 2015a,b; Rodríguez-Herreros et al., 2015). While prior studies examining the link between the variability in the white matter organization and the effects of TMS on visuospatial detection focused on the frontal eye field (e.g., Quentin et al., 2013, 2015a,b), our prior report (Chechacz et al., 2015), as well as the current study, specifically looked at the effects of patterned TMS applied over the posterior parietal cortex, i.e., the stimulation site and protocol similar to those currently under investigation in studies assessing TMS as a potential add-on therapy to rehabilitate neglect (e.g., Cazzoli et al., 2012; Koch et al., 2012). Thus, more and more studies examining the mechanisms underlying visual perception and attention, including those employing TMS, strongly advocate that the variability in the structural and functional architecture of neural networks needs to be taken into account to create adequate models of human brain function. Surprisingly, studies addressing the notion that the structural variability of the white matter pathways could be potentially used to predict the therapeutic effectiveness of TMS are uncommon (although see Quentin et al., 2013; Chechacz et al., 2015b; these two studies did not directly address this notion, but explored this idea by inferring from TMS observations performed in healthy participants).

Repetitive TMS (rTMS) has been shown to alter cross-hemispheric interactions and the inter-hemispheric competition underlying the spatial allocation of visual attention and, therefore,

provides a powerful tool to study the asymmetrical organization of visuospatial attention.

Inhibitory rTMS applied over the right PPC – but not left PPC – is known to temporarily disrupt cortical processing and to trigger neglect-like behaviour in healthy participants. It should be noted that, although cTBS protocols (and inhibitory rTMS protocols in general) are commonly described as having “inhibitory/disruptive” behavioural effects on a group level, the patterns of functional activations leading to the behavioural output are likely to be more complex. For instance, recent research combining TMS and EEG showed that rhythmic TMS patterns are able to entrain local and inter-regional oscillatory synchrony, even offline (i.e., after stimulation application; Thut et al., 2011; Woźniak-Kwaśniewska et al., 2013). Further research is therefore needed to understand these patterns of functional activations and their relationship to the behavioural output, in particular on the individual level.

While rTMS studies provide strong support for the model of right-hemispheric dominance in attention (Cazzoli et al., 2009; Kinsbourne, 1987; 1993; Mesulam, 1981; Nyffeler et al., 2008), large inter-individual differences in the effectiveness of stimulation to influence the spatial allocation of visual attention have been reported. Previous combined TMS-fMRI studies indicate that inhibitory stimulation applied to either the right or the left PPC triggers a compensatory increase in activity within several fronto-parietal regions, including the ipsilateral superior parietal lobule, the bilateral temporo-parietal junction, and the bilateral visual cortex (Plow et al., 2014; Ruff et al., 2008; Ruff et al., 2009; Sack et al., 2007). While some of these previous studies reported variability in the TMS-induced compensatory activations, they did not directly address the causes underlying individual differences in the effectiveness of stimulation. Nevertheless, these studies provide important clues to understand such inter-individual differences, by exploring the neural mechanisms of TMS effects on visual attention. The findings suggest that the effects of TMS applied over the PPC depend on inter- and/or intra-hemispheric interactions between cortical

loci controlling visual attention, and mediating compensatory changes in regional cortical activity both within each hemisphere and across the hemispheres. Interestingly, a recent study using a trifocal-TMS approach has shown a link between inter-hemispheric inhibition and fractional anisotropy within the SLF and the posterior corpus callosum (Koch et al., 2011).

We previously hypothesized that the effects of brain stimulation on the spatial allocation of attention could be predicted by the variability in the structural organization of white matter pathways subserving visual attention (Chechlacz et al., 2015b). In our previous study examining the effects of **cTBS_{mod}** over the PPC on the spatial allocation of visual attention, as assessed by a free visual exploration task, we failed to find any reliable evidence for a link between individual differences in the effects of **cTBS_{mod}** and structural variability in the organization of intra-hemispheric fronto-parietal pathways (Chechlacz et al., 2015b). However, we showed that individual differences in response to **cTBS_{mod}** over the left and right IPS could be predicted by the variability in the structural organization of the corpus callosum, which is thought to be involved in maintaining inter-hemispheric dynamics underlying the spatial allocation of visual attention. There might be several reasons why we did not previously find any evidence for a link between the structural variability in the intra-hemispheric fronto-parietal pathways and the effects of **cTBS_{mod}** over the PPC. Primarily, it should be noted that, in the previous study, we also did not find any significant correlations between the variability in the structural organization of these intra-hemispheric pathways and the initial spatial bias in the free visual exploration task, which was then used to examine **cTBS_{mod}**-induced shifts in the spatial allocation of visual attention. Thus, in the present study, we purposefully employed a manual line bisection task. In agreement with previous studies, our initial analyses not only found individual differences in the bisection bias (Braun and Kirk, 1999; Cowie and Hamill, 1998; Jewell and McCourt, 2000; Manning et al., 1990), representing stable subtypes of pseudoneglect (we report no significant differences between

participants' pseudoneglect measured during four different testing sessions; see also Benwell et al., 2013), but also a robust correlation between the structural lateralization of the SLF II and the performance on the line bisection task (see Thiebaut de Schotten et al., 2011). Moreover, subsequent analyses provided evidence that the structural variability within the left (contralateral to stimulation) SLF II and SLF III can predict the bisection bias shifts triggered by **cTBS_{mod}** applied over the right IPS, with a higher HMOA index corresponding to a greater rightward bisection bias shift. The HMOA index depends on several white matter properties, such as myelination, axon density, axon diameter, and fiber dispersion (Dell'Acqua et al., 2013). Thus, while the HMOA index characterizes microstructural properties of the white matter, it is however somewhat problematic to interpret in a linear fashion, due to lack of specificity, the differences in the HMOA index measured along white matter pathways. For example, to infer that a higher HMOA index explicitly means stronger connectivity (Dell'Acqua et al., 2013; Jones et al., 2013). Nevertheless, based on our data, we speculate here that a higher HMOA index – potentially representing a surrogate of greater structural connectivity or speed of information processing – is linked to increased functional connectivity within the left hemisphere. This higher functional connectivity would trigger a more robust compensatory response within the left-hemispheric attention network when the right-hemispheric attention network is interfered with by means of **cTBS_{mod}**. In turn, this would offset the spatial allocation of visual attention, and result in a greater rightward bisection bias shift. Specifically, we found a higher HMOA index within the SLF III, interconnecting cortical loci within the ventral attention network, and within the SLF II, interconnecting the dorsal and ventral attention networks (Thiebaut de Schotten et al., 2011) in individuals with a greater rightward bisection bias shift after **cTBS_{mod}** over the right IPS. Previous fMRI studies indicate that, while the activity of the dorsal attention network underlies the ability to orient attention in space, the overall attentional bias is likely to result from the interaction between dorsal ventral attention

networks (Corbetta and Shulman, 2011; Thiebaut de Schotten et al., 2011). Accordingly, it has been postulated that unilateral neglect – caused by right-hemispheric damage to ventral attentional regions – is the result of abnormal intra-hemispheric interactions between dorsal and ventral attention networks. In turn, these interactions affect inter-hemispheric dynamics, and underlie the observed rightward bias in the spatial distribution of visual attention (Corbetta et al., 2005; Corbetta and Shulman, 2011). Based on our data, we suggest that following the changes in inter-hemispheric dynamics triggered by inhibitory stimulation of the right IPS in healthy participants, an increased (greater) intra-hemispheric communication between the cortical loci of the left-hemispheric dorsal and ventral attention networks could explain the larger rightward attention shifts.

The majority of studies examining the neural substrates of the line bisection task report activity in the inferior and the superior parietal lobules (in the vicinity of the IPS) (Cavezian et al., 2012; Cicek et al., 2009; Fink et al., 2000; Fink et al., 2001; Foxe et al., 2003). However, a recent EEG study suggests that the critical neural substrate of spatial biases in line bisection is localized in the temporo-parietal junction (TPJ), within the ventral attention network (Benwell et al., 2014). Specifically, Benwell et al. (2014) identified two event-related potentials (ERP) triggered by the experimental manipulation of bisection bias shifts: an early response within the TPJ, critical for the generation of the spatial bias per se, and a late response around the IPS, likely related to “a decisional stage of task performance”. These findings are highly relevant to the link between individual differences in the **cTBS_{mod}**-induced shifts and the structural variability within the SLF II and SLF III reported in the present study: first, both SLF II and SLF III overlap with the TPJ within the ventral attention network; second, TMS over the right PPC has been shown to trigger compensatory activity within the bilateral TPJ (Sack et al., 2007). Although our interpretations are plausible and consistent with the findings of earlier studies, they should be treated with some

caution, as they are derived from structural data and do not provide direct neurophysiological evidence.

One caveat of the present study is that, based on a priori hypothesis, we focused here on the structural properties of the SLF. However, prior neuroanatomical studies in both monkeys and humans demonstrate that visuospatial attention is dependent upon the function of large and distributed neuronal networks (Mesulam, 1990; Posner and Petersen, 1990; Corbetta and Shulman, 2002; Petrides and Pandya 2002; Schmahmann and Pandya 2006). These networks are sub-served by different white matter pathways, including long association frontoparietal pathways, such as the inferior fronto-occipital fasciculus and the three branches of the SLF examined here (Schmahmann et al., 2007; Bartolomeo et al., 2007; Doricchi et al., 2008; Thiebaut de Schotten et al., 2011). However, these frontoparietal tracts are not the only likely candidates to be considered, and it is plausible that the structural variability within other white matter pathways might be linked to the observed behavioural effects of **cTBS_{mod}** applied over the IPS. Although the parietal (IPS) and frontal (FEF) regions within the dorsal attention network are interconnected via SLF, these areas are also richly connected to other cortical and subcortical regions including the superior temporal cortex, the thalamus (pulvinar) and the superior colliculus (Schmahmann and Pandya 2006; Shipp, 2003; Shipp, 2004). Interestingly, Quentin et al. (2013) found a link between the FEF-superior colliculus connectivity and the modulation of visual contrast sensitivity when TMS was applied over the FEF during a visual detection task. Furthermore, based on a recent TMS-MEG study Marshall et al (2015b) put forward the hypothesis that oscillatory activity within the dorsal attention network might be linked to corticothalamocortical connections (see also Saalman and Kastner, 2011).

Another potential limitation of the current study is that we used a manual line bisection task. The line bisection task, and/or its equivalent landmark task have been previously used in

several studies examining pseudoneglect as well as the effects of TMS on the allocation of visual attention (e.g., Fierro et al., 2000; Varnava et al., 2013; Szczepanski and Kastner, 2013; Jewell et al., 2000). Moreover, the line bisection task is very commonly administered in clinical settings in order to assess visual neglect. Nevertheless, it should be noted that, by contrast to more sophisticated visual detection tasks with stimuli appearing within left versus right spatial locations (e.g., Hilgetag et al., 2001; Chanes et al., 2012, Quentin et al., 2013; Quentin et al., 2015a,b), the line bisection task cannot be used to differentially assess the contributions of the right versus left hemisphere to the attentional allocation in space. This is due to the fact that the final bisection bias likely represents the common final balance of inter-hemispheric interactions and is therefore ‘blind’ to the separate contributions of the right or the left hemisphere. As stated above, our choice was based on a prior study, which demonstrated strong correlation between deviations from the centre in the line bisection test and the structural lateralization of the SLF II (Thiebaut de Schotten et al., 2011). Since a recent study, directly comparing the effects of TMS on performance in a manual line bisection and a landmark task, showed a greater sensitivity of the manual line bisection task (Varnava et al., 2013), we opted for this task rather than for the more frequently used landmark task (see for review Duecker and Sack, 2015). Furthermore, while many recent reports link the individual differences in the effects of TMS on visual perception in healthy participants to the variability in structural organization of white matter pathways in healthy participants (e.g., Quentin et al., 2013; Quentin et al., 2015a,b), this aspect is far less frequently discussed in the context of the effectiveness of TMS as a potential treatment approach to attention disorders (e.g., Quentin et al., 2013; Chechlacz et al., 2015b; but see Nicolo et al., 2015). Thus, to further emphasize this point, in the current study we purposefully used a simple task often employed to diagnose neglect. Crucially, it should be noted that the line bisection test can be performed with both hands, and thus provides a suitable approach to examine the link

between hand dominance and the changes in behavioural performance following TMS stimulation. Finally, we would like to add here that in the current study we purposefully applied an offline **cTBS_{mod}** protocol. While offline **cTBS_{mod}** may be less effective in inducing changes in behavioural performance as compared to rhythmic online protocols (see for example Quentin et al., 2013; Quentin et al., 2015a,b), similar offline, patterned rTMS protocols are often applied over the PPC as an experimental approach to rehabilitate neglect (e.g., Cazzoli et al., 2012; Koch et al., 2012; for review see also Cazzoli et al; 2010).

Numerous earlier studies suggest that left-handed participants show a more atypical lateralization of brain functions, although this assumption has been disputed by other reports (Badzakova-Trajkov et al., 2010; Bryden et al., 1983; Cai et al., 2013; Floel et al., 2005b; Guadalupe et al., 2014; Mazoyer et al., 2014; Petit et al., 2015; Somers et al., 2015a; Somers et al., 2015b; Whitehouse and Bishop, 2009; for a recent, comprehensive review see Willems et al., 2014). Due to these putative differences in lateralization, left-handed participants are commonly excluded from studies examining human cognitive functions. As our study focused on individual differences in the effects of **cTBS_{mod}**, we purposefully did not select our participants based on handedness. It has been suggested that, in some individuals, left-handedness is associated with a reversed hemispheric specialization for language and attention, i.e., left-hemispheric dominance for attention, and right-hemispheric dominance for language (Badzakova-Trajkov et al., 2010; Bryden et al., 1983; Cai et al., 2013; Floel et al., 2005a). Consequently, one would expect left-handedness to be associated with a leftward lateralization of the SLF, particularly of the SLF III, and with a predominantly rightward bias in the line bisection task. Contrary to this prediction, we found no significant group differences (i.e., right- versus left-handed participants) in the bisection bias. Furthermore, the analysis based on HMOA measures revealed a stronger rightward lateralization of the SLF III in the left-handed participants. Interestingly, a recent study also attributed an overall

stronger rightward lateralization of the attention networks to left-handed participants, and not a reversed hemispheric specialization (Petit et al., 2015). Importantly, we report a strong relationship between handedness and the effects of $cTBS_{mod}$ in the manual line bisection task, with opposite effects of $cTBS_{mod}$ applied over the left and the right IPS in left-handed versus right-handed participants. As we also demonstrate that the HMOA index within the left SLF II and the left SLF III determines the magnitude of the $cTBS_{mod}$ induced bisection bias shifts, it is plausible to attribute the observed group effect in response to $cTBS_{mod}$ to the differences in the microstructural organization of the SLF. For instance, a significantly lower HMOA index within the left SLF III in the group of left-handed participants could account for the lack of significant responses to $cTBS_{mod}$ over the right IPS.

Investigations into human cognition are largely based on group studies, where attempts are made to reduce variance in the data, and conclusions are based on averaged behavioural performance. However, on the individual level, we do not all behave the same, and these discrepancies are rooted in inter-individual differences in cognitive abilities. Many reports have linked individual differences in human behaviour and cognition to the variability in brain structure and function (Boorman et al., 2007; Frost and Goebel, 2012; Mueller et al., 2013; Rademacher et al., 2001; Roberts et al., 2010; Sugiura et al., 2007). These studies raise the question whether individual differences need to be taken into consideration with respect to models of human cognition. Recently, there has been also an interest in whether these differences might have clinical implications, for instance influencing the susceptibility to neurological disorders and the potential for rehabilitation. The results of the present study support the idea that a better understanding of the behavioural variance and underlying neural mechanisms can not only extend our understanding of human brain function and the normal range of diversity, but can potentially also have a clinical relevance. While caution is needed when relating observations in healthy

participants to those in clinical populations, our findings can have implications for the understanding of the unilateral neglect syndrome and its rehabilitation. rTMS applied over the contralesional, left PPC has been shown to ameliorate neglect symptoms in stroke patients (Cazzoli et al., 2010; Cazzoli et al., 2012; Koch et al., 2012; Nyffeler et al., 2009). However, individual differences in the effectiveness of stimulation on the allocation of spatial attention have been reported. Thus, the understanding of the mechanisms underlying these differences have implications not only for generating models of visual attention, but also for the application of rTMS in neglect rehabilitation.

In conclusion, our findings support the idea put forward previously (e.g., Chechlacz et al., 2015b; Quentin et al., 2015a,b) that the structural variability within fronto-parietal pathways, and their lateralization, predict the effects of brain stimulation on visuospatial attention. This has potential bearings not only on the conceptualisation of the asymmetrical organization of visual attention, but also on the individual differences in the severity of neglect symptoms. It has been shown that right-hemispheric lesions in neglect patients trigger a hyperactivity of the intact left hemisphere, which results in a rightward bias in attentional allocation (e.g., Corbetta et al., 2005). In the current study, we only temporarily interfered with the activity of the right PPC using a “virtual lesion” approach in healthy individuals, in order to alter spatial allocation of visual attention in a manner mimicking neglect-like behaviour, i.e., inducing a rightward bisection bias shift. However, taking into account that prior combined fMRI-TMS studies have demonstrated increased activity of the contralateral (with respect to stimulation) left hemisphere (e.g., Sack et al., 2007), our findings suggest that the increased compensatory activity, contributing to the extent of biased attentional allocation towards the right hemifield, might be linked to the variability in the structural organization of the SLF, underlying intra-hemispheric interactions between cortical loci controlling visual attention. Moreover, we hypothesise that such structural

variability might be potentially relevant for the understanding of individual differences in effectiveness of brain stimulation used as an add-on therapy in neglect rehabilitation (see also Quentin et al., 2013; Chechlacz et al., 2015b). This is in line with prior studies linking neglect recovery to “push-pull” patterns within ipsi- and contralesional attentional networks, as well as linking overall stroke recovery to variability in intra-and inter-hemispheric connectivity (e.g., Corbetta et al., 2005; Carter et al., 2010; Corbetta et al., 2015; Lunven et al., 2015).

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FIGURE LEGENDS

Figure 1. (A) Schematic representation of the three testing sessions (counterbalanced order): with a modified continuous theta burst stimulation protocol (cTBS_{mod}) over the right intraparietal sulcus (IPS) (left panel), with cTBS_{mod} over the left IPS (central panel), and with sham stimulation over the right IPS (right panel). Grey rectangles represent line bisection (LB) task, which all participants performed before (Pre) and after (Post) application of the stimulation. Bolt symbols represent stimulation: real cTBS_{mod} (solid symbols) and sham stimulation (dotted symbol). **(B)** Regions of interest (ROIs) used in the tractography-based reconstruction of the SLF (Thiebaut de Schotten et al., 2011). In both hemispheres, a single parietal (Pa) region of interest (ROI) was used, in combination with frontal ROIs in the superior frontal gyrus (SFg), middle frontal gyrus (MFg), and precentral gyrus (Prg) for the reconstruction of SLF I, SLF II, and SLF III, respectively. In addition, a temporal (Te) ROI was defined in each hemisphere, in order to exclude fibers of the arcuate fasciculus. This “not” ROI was applied for the tractography of all three branches of the SLF.

Figure 2. (A) Mean bisection bias shift (i.e., bisection bias post minus pre stimulation) in the three stimulation sessions (sham stimulation, modified cTBS [cTBS_{mod}] over the left IPS, and cTBS_{mod} over the right IPS). Error bars represent the standard error of the mean (SEM). Asterisks depict significant post-hoc tests; ** $p < 0.01$. **(B)** Mean bisection bias shift (i.e., bisection bias post minus pre stimulation), in the three stimulation conditions (sham stimulation, cTBS_{mod} over the left IPS, and cTBS_{mod} over the right IPS), depending on the handedness of participants. Error bars represent the standard error of the mean (SEM). Asterisks depict significant post-hoc tests; ** $p < 0.01$; * $p < 0.05$; (*) $p < 0.07$. **(C)** Mean bisection bias shift (i.e., bisection bias post minus pre stimulation), in the three stimulation conditions (sham stimulation, cTBS_{mod} over the left IPS, and cTBS_{mod} over the right IPS) depicted for all individual participants (right- and left-handers plotted separately).

Figure 3. (A) Examples of tractography-based reconstruction of the three SLF branches within the

right and the left hemisphere (SLF I is shown in light blue, SLF II in dark blue, and SLF III in violet). Hemispheric lateralization for the three SLF branches, estimated on the basis of **(B)** the tract volume; and, **(C)** the HMOA index (group averages of the respective lateralization indices). Error bars represent 95% confidence intervals. * $p < 0.0001$.

Figure 4. The relationship between structural organization of the SLF and behavioral variability.

Correlations between bisection bias (performance averaged across both hands) and the SLF II lateralization index estimated based on **(A)** tract volume and **(B)** hindrance modulated orientational anisotropy (HMOA). Correlations between bisection bias shift triggered by the **modified cTBS protocol (cTBS_{mod})** over the right IPS (performance averaged across both hands) and HMOA measures within either **(C)** the left SLF II or **(D)** the left SLF III. * Correlation is significant after correction for multiple comparisons (FDR corrected $p < 0.05$).

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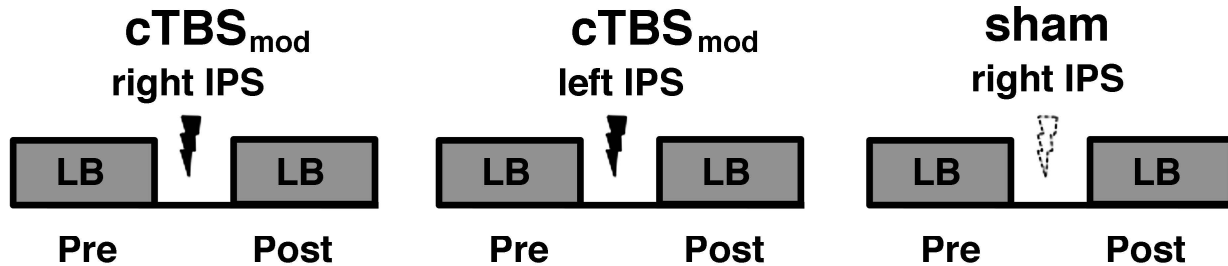
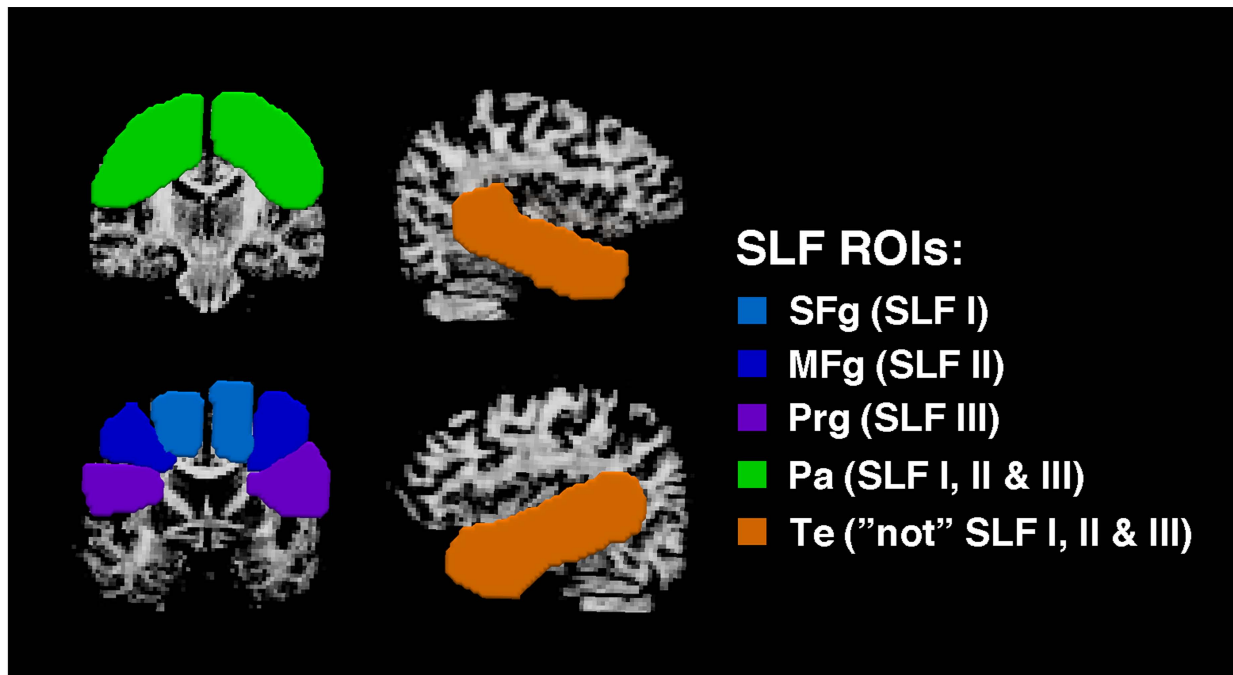
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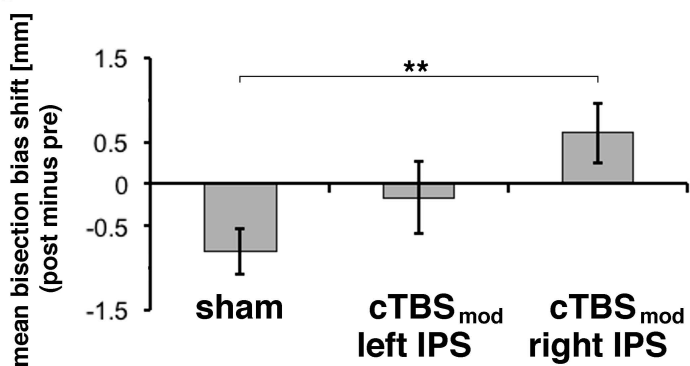
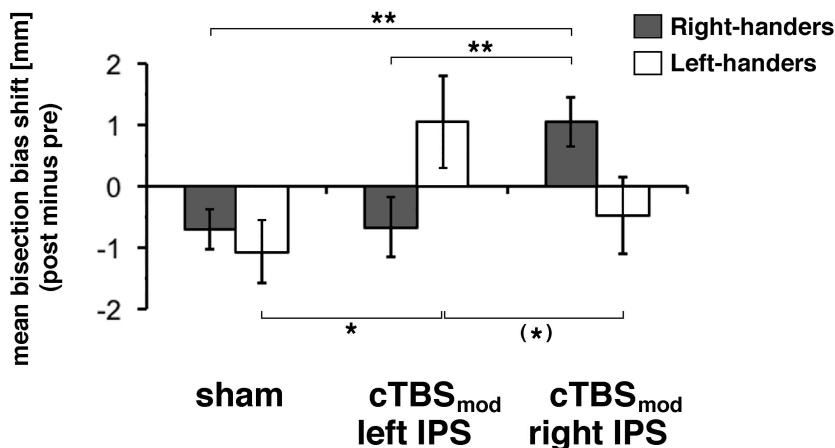
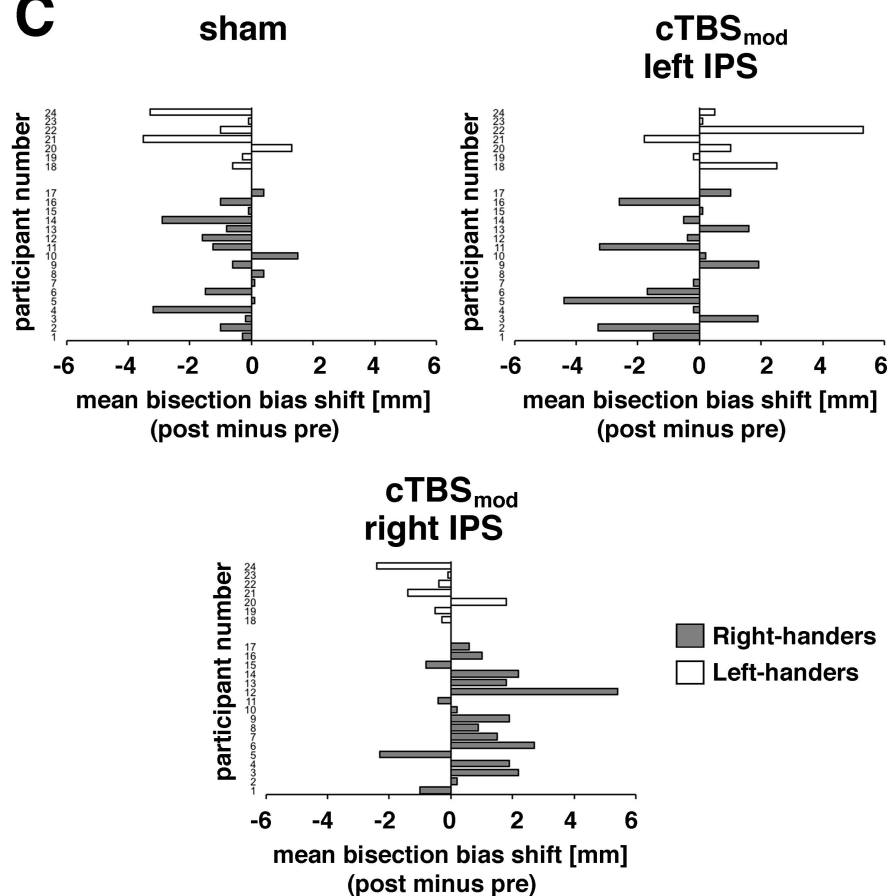
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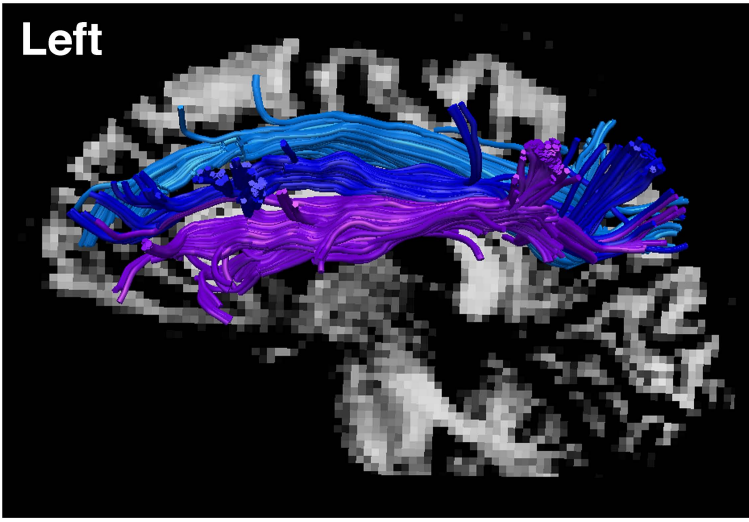
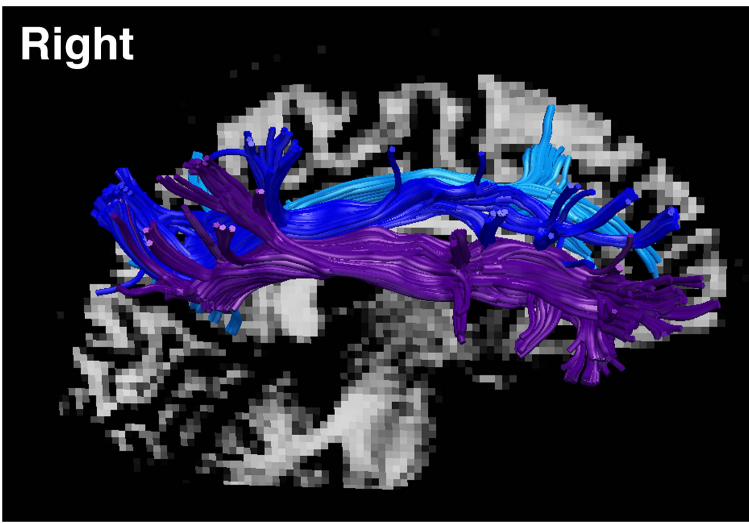
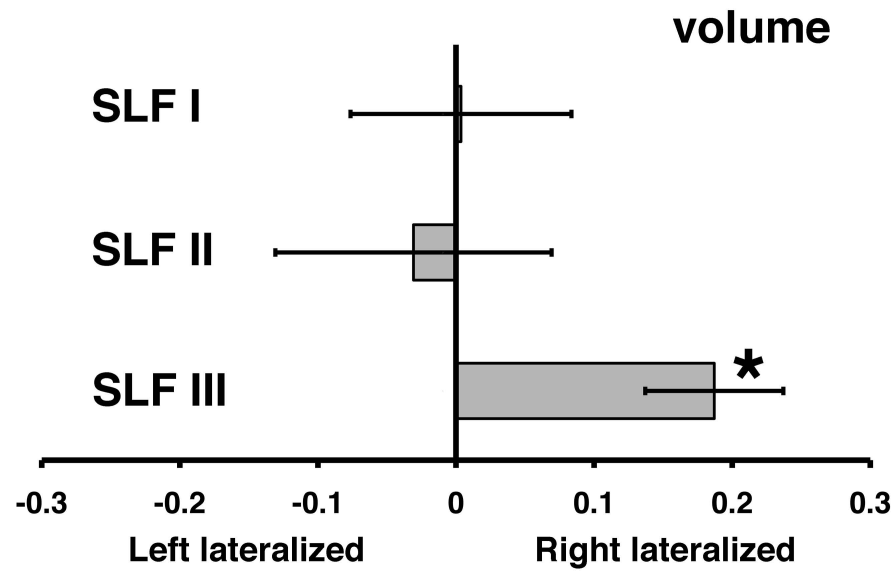
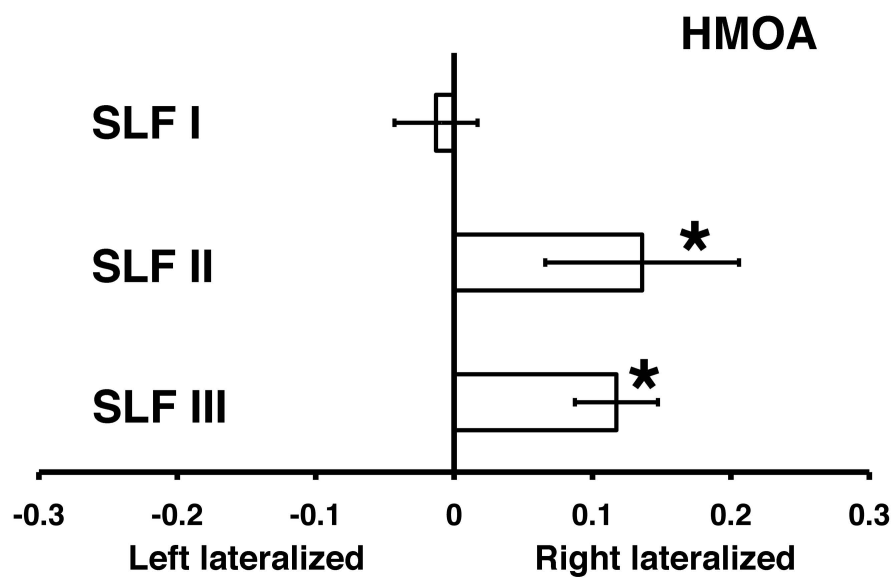
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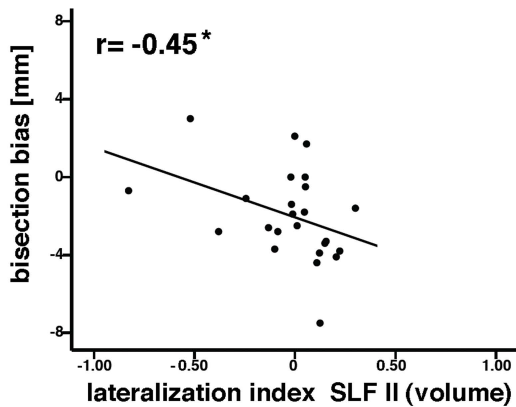
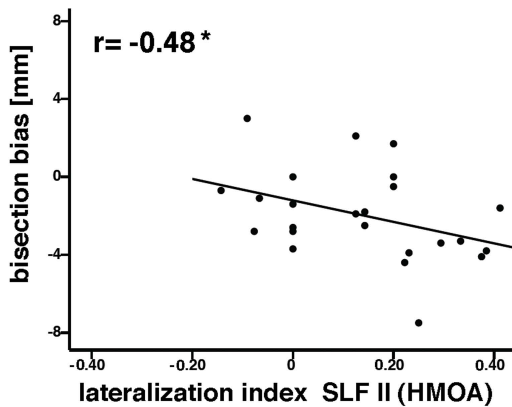
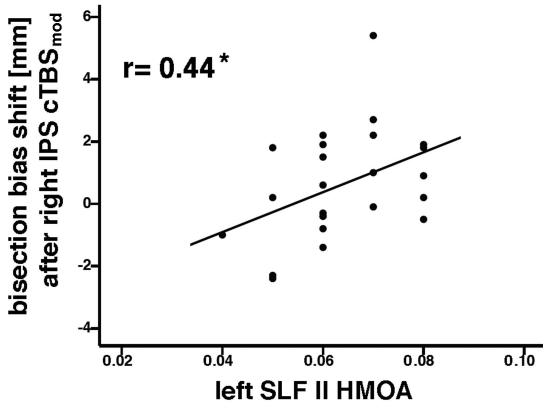
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