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Research Report

Influence of frontal-to-parietal connectivity in pseudoneglect: A cortico-cortical *paired associative stimulation* study

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ABSTRACT

Pseudoneglect is a set of visuospatial biases that entails a behavioral advantage for stimuli appearing in the left hemifield compared to the right one. Although right hemisphere dominance for visuospatial processing has been invoked to explain this phenomenon, its neurophysiological mechanisms are still debated, and the role of intra- and inter-hemispheric connectivity is yet to be defined. The present study explored the possibility of modulating pseudoneglect in healthy participants through a cortico-cortical *paired associative stimulation* protocol (ccPAS): a non-invasive brain stimulation protocol that manipulates the interplay between brain regions through the repeated, time-locked coupling of two transcranial magnetic stimulation (TMS) pulses. In the first experiment, healthy participants underwent a frontal-to-parietal (FP) and a parietal-to-frontal (PF) ccPAS. In the FP protocol, the first TMS pulse targeted the right frontal eye field (FEF), and the second pulse the right inferior parietal lobule (IPL), two critical areas for visuospatial and attentional processing. In the PF condition, the order of the pulses was reversed. In both protocols, the inter-stimulus interval (ISI) was 10 ms. Before and after stimulation, pseudoneglect was assessed with a landmark task and a manual line bisection task. A second experiment controlled for ccPAS timing dependency by testing FP-ccPAS with a longer ISI of 100 ms. Results showed that after administering the FP-ccPAS with the ISI of 10 ms, participants' leftward bias in the landmark task increased significantly, with no effects in the manual line bisection task. The other two protocols tested were ineffective. Our findings showed that ccPAS could be used to modulate pseudoneglect by exploiting frontal-to-parietal connectivity, possibly through increased top-down attentional control. FP-ccPAS could represent a promising tool to investigate connectivity properties within

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visuospatial and attentional networks in the healthy and as a potential rehabilitation protocol in patients suffering from severe visuospatial pathologies.

1. Introduction

Pseudoneglect is a set of biases for the left side of space that naturally occurs in healthy people during perceptual judgment tasks (Bowers & Heilman, 1980; Brooks, Sala, & Darling, 2014; Jewell & McCourt, 2000). Several behavioral paradigms have been used to describe its main features, which all seem to reflect slight imbalances in allocating attention to the left versus the right side of space. The leftward spatial bias occurring in healthy people complements the rightward bias commonly observed after right hemisphere lesions in unilateral spatial neglect (Corbetta & Shulman, 2011; Halligan, Fink, Marshall, & Vallar, 2003; Heilman & Valenstein, 1979; Vallar & Calzolari, 2018). Therefore, these phenomena have been considered twin manifestations of a common underlying neural mechanism (Jewell & McCourt, 2000; Varnava, Dervinis, & Chambers, 2013) and explained with a right-hemisphere dominance for visuospatial attentional mechanisms, which is believed to arise from anatomical and functional asymmetries between hemispheres (Heilman & Van Den Abell, 1980; Mesulam, 1981). For instance, the lateralization of fronto-parietal networks has been identified as a relevant factor explaining visuospatial leftward biases (for a review, see: Mengotti, Käsbauer, Fink, & Vossel, 2020). Fronto-parietal networks comprise distributed systems subserving different facets of attentional processing. Specifically, the ventral attentional network (VAN) – which includes the temporoparietal junction and the ventral frontal cortex – is deemed to be specialized for detecting salient or unexpected stimuli (i.e., bottom-up attention). The dorsal attentional network (DAN) – which incorporates the superior parietal lobule, the intraparietal sulcus (IPS), and the dorsal frontal cortex, including the frontal eye fields area (FEF) – is thought to be involved in the voluntary control of visual attention and the selection of appropriate responses (i.e., top-down attention) (Bartolomeo, de Schotten, & Chica, 2010; Corbetta & Shulman, 2002, 2011). The communication between regions of the fronto-parietal networks is mediated by the superior longitudinal fasciculus (SLF), the most important long-range white-matter fiber tract that connects prefrontal areas to posterior regions (and vice versa) (Wang et al., 2016). SLF has been extensively studied in-vivo by tracing three anatomical branches (de Schotten et al., 2011; Makris et al., 2005; Parlatini et al., 2017): the first (SLF I) and third (SLF III) branches connect, respectively, regions of the DAN and VAN, while the second branch (SLF II) serves as a direct communication between the two attention systems.

Previous studies indicated that leftward biases emerging in line bisection and landmark tasks in healthy subjects were associated with the lateralization of the DAN (SLF I) and of the branch connecting DAN and VAN (SLF II), which showed larger structural volumes in the right – relative to the left – hemisphere (de Schotten et al., 2011; Kocsis et al., 2019). Clinical observations also corroborate the importance of fronto-parietal networks in the emergence of visuospatial biases. Several pieces of evidence highlight the relevance of the structural and functional state of intra-hemispheric connectivity (in particular of the SLF II) to the prediction of spatial neglect severity and recovery (Doricchi & Tomaiuolo, 2003; He et al., 2007; Lunven et al., 2015; Thiebaut De Schotten et al., 2014).

Several neuroimaging and electrophysiological evidence investigating landmark or line bisection tasks consistently indicated the right posterior parietal cortex (PPC) as a critical hub of the fronto-parietal attentional networks (e.g., Benwell, Harvey & Thut, 2014; Çiçek, Deouell, & Knight, 2009; Fink et al., 2000; Foxe, McCourt, & Javitt, 2003). When the activity of the right PPC was suppressed through transcranial magnetic stimulation (TMS) applied with the so-called ‘virtual lesion’ approach (Pascual-Leone, Walsh, & Rothwell, 2000), a temporary reduction of pseudoneglect and a rightward shift of bias was observed. In contrast, no effects were found when the same approach was used to interfere with left–hemisphere activity (Cazzoli & Chechlacz, 2017; Chechlacz, Humphreys, Sotiropoulos, Kennard, & Cazzoli, 2015; Fierro et al., 2000; Salatino et al., 2019). Interestingly, Cazzoli and Chechlacz (2017) found that the lateralization of SLF branches predicted the rightward shift induced by inhibitory TMS applied over the right (but not left) inferior parietal lobule (IPL) (Cazzoli & Chechlacz, 2017).

While these results yield important insight into the functional involvement of PPC in visuospatial biases, the current view of brain functioning predicts that flexible cognitive operations (such as perceptual judgment) cannot be interpreted as strict functional specializations of single cortical areas but are better accounted for by a network view of the brain (Baldassarre et al., 2014; de Schotten & Forkel, 2022). Concerning the interference approach, it is widely recognized that TMS effects on behavior reflect influences on neural processing not only at the site of stimulation, but also on remote brain regions that are part of distributed cortical networks (Bestmann et al., 2008; Ruff et al., 2006; Sack et al., 2007; Salatino, Poncini, George, & Ricci, 2014; Silvanto, Cowey, Lavie, & Walsh, 2005; Silvanto, Lavie, & Walsh, 2006; Taylor, Nobre, & Rushworth, 2007). By combining TMS with fMRI, Sack et al. (2007) were able to show that the behavioral modulation of visuospatial judgments induced by right-parietal TMS was mirrored by modulation of cortical activity not only at the site of stimulation, but also in remote and interconnected frontal regions of the same hemisphere (Sack et al., 2007). Again, Ricci et al. (2012) showed that applying TMS to the right PPC during a landmark task caused a reduction of participants' pseudoneglect accompanied, at a functional level, with decreased activity of parieto-frontal regions connected by the SLF II and of the homologous parietal region of the left hemisphere (Ricci et al., 2012). Thus, the functional inferences from studies that targeted the right PPC in visuospatial tasks deserve further investigation from a network perspective. During perceptual decision tasks, regions in the PPC (such as the IPL) are interconnected with frontal areas in the precentral cortex (such as the FEF), with signals that are supposed to flow in both directions: a frontal-to-parietal direction driving top-down attentional control versus a parietal-to-frontal direction subtending visuospatial processing (e.g., Bagattini, Esposito, Ferrari, Mazza, & Brignani, 2022; Corbetta & Shulman, 2011; de Schotten et al., 2011; Heekeren, Marrett, & Ungerleider, 2008; Mengotti et al., 2020). Because tractography investigations cannot reveal the direction of the signal responsible for the correlation between structural asymmetries and visuospatial biases, the exact contribution to visuospatial biases of fronto-parietal top-down versus parieto-frontal bottom-up connections remains to be established.

One non-invasive brain stimulation protocol that may clarify the role of intra-hemispheric connections in the right fronto-parietal system is the cortico-cortical *paired associative stimulation* (ccPAS) protocol. In this recently established dual-coil TMS protocol, the low-frequency paired stimulation of two cortical areas modulates synaptic coupling between target neuronal populations, probably through spike-timing-dependent-plasticity-like mechanisms. The inter-stimulus interval (ISI) between the two paired stimulations is chosen according to the presumed conduction delay of the target cortico-cortical pathway to ensure the synchronized occurrence of synaptic activity in one of the stimulated areas. Based on that specific timing, long-term potentiation (LTP) or long-term depression (LTD) could be induced, increasing or decreasing connectivity between target areas (Hernandez-Pavon, San Agustín, Wang, Veniero, & Pons, 2023). As a rule of thumb, a synaptic potentiation in the target neuronal population (resembling LTP) may occur when the excitatory pre-synaptic action potential is repeatedly followed by the post-synaptic one, whereas synaptic depression (resembling LTD) may occur when the repeated firing of pre-synaptic neurons follows the post-synaptic one (Caporale & Dan, 2008; Dan & Poo, 2004). PAS protocols were introduced to study the corticospinal pathway with paired peripheral-cortical stimulation, where electrical stimulation of the median nerve preceded TMS over the primary motor cortex (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000; Wolters et al., 2003; for a review, see: Suppa et al., 2017). Subsequently, they were applied to investigate the role of cortico-cortical connections in the motor and sensory domain (e.g., Arai et al., 2011; Buch, Johnen, Nelissen, O'Shea, & Rushworth, 2011; Casarotto et al., 2023; Rizzo et al., 2009; Romei, Chiappini, Hibbard, & Avenanti, 2016; Veniero, Ponzo, & Koch, 2013; for a review, see: Guidali, Roncoroni, & Bolognini, 2021b) and, more recently, in higher-order networks, investigating cognitive functions such as memory, decision-making, and emotional processing (e.g., Casula, Pellicciari, Picazio, Caltagirone, & Koch, 2016; Di Luzio, Tarasi, Silvanto, Avenanti, & Romei, 2022; Kohl et al., 2019; Momi et al., 2019; Nord et al., 2019; Santarnecchi et al., 2018; for a review, see: Guidali, Roncoroni, & Bolognini, 2021a). However, to our knowledge, PAS protocols have not yet been exploited to modulate visuospatial biases and deepen the understanding of the underlying intra-hemispheric connectivity mechanisms.

The present study used a novel ccPAS protocol to modulate pseudoneglect. We targeted right-hemisphere fronto-parietal connectivity with two different ccPAS protocols, where we manipulated the order of the *conditioning* (i.e., first) and *test* (i.e., second) TMS pulses. In a frontal-to-parietal ccPAS (FP-ccPAS), the *conditioning* pulse was delivered over the right FEF and the *test* pulse over the right IPL. These areas were selected considering the amount of literature that indicates them as core nodes for visuospatial and attentional processing (e.g., de Schotten et al., 2011; Heinen et al., 2011; Heinen, Feredoes, Ruff, & Driver, 2017). In the parietal-to-frontal ccPAS (PF-ccPAS), pulse order was reversed (i.e., *conditioning* pulse over right IPL, *test* pulse over right FEF). In both protocols, we used an inter-stimulus interval (ISI) between the two TMS pulses of 10 ms based on previous ccPAS studies that successfully targeted the connectivity between frontal and parietal lobes (e.g., Casula et al., 2016; Momi et al., 2019; Santarnecchi et al., 2018). Before and after ccPAS, the spatial bias was assessed with a landmark and a manual line bisection task. Considering recent evidence on the neurophysiological substrates of ccPAS (e.g., Casarotto et al., 2023; Turrini et al., 2023), we hypothesize that the FP protocol (acting on frontal-to-parietal connectivity) should enhance synaptic strength at IPL level (i.e., the region targeted by the second TMS pulse), thus facilitating its activity. Conversely, the PF protocol (acting on parietal-to-frontal connectivity) should induce synaptic potentiation within the FEF region. If one of these cortico-cortical pathways (or areas) plays a crucial role in pseudoneglect, we could expect behavioral modulations in the two tasks we administered. The current literature on the neural underpinnings of visuospatial biases does not support any clear a-priori hypothesis about which protocol would be effective or whether they would both be effective with different directions of modulation (i.e., rightward or leftward according to the protocol administered).

A second experiment, with an ISI of 100 ms, was carried out as a control to deepen the role of ccPAS timing. Indeed, we expected that ccPAS with an ISI of 100 ms would be ineffective in the modulation of pseudoneglect, as such a long interval should not allow the contingency between pre- and post-synaptic activations that is required to induce associative plasticity (Suppa et al., 2017).

2. Main experiment: direction of ccPAS modulation

2.1. *Methods and materials*

2.1.1. *Participants*

Twenty-six right-handed healthy volunteers took part in the *Main experiment*. One of them did not complete the second session of the experiment, resulting in a final sample of 25 participants (7 males, mean age ± standard deviation – SD = 24.9 ± 4.8 years; mean education ± SD = 15.6 ± 2.7 years).

The sample size was determined using an a-priori within-subjects repeated-measures Analysis of Variance (rmANOVA; medium effect size of $F = .25$; Alpha Error Level: $p = .05$; Statistical Power = .8, Actual Power = .81), using the software G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009), which indicated a recommended sample size of at least 24 participants to achieve enough statistical power.

Right-handedness of the participants was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971) (mean score ± SD = 96.3 ± 8.5%). None of the participants had contraindications to TMS (Rossi et al., 2021).

The experiment was performed according to the ethical standards of the Declaration of Helsinki and was approved by the Ethical Committee of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (52/2020). Before taking part in the study, participants gave their written informed consent. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures or analysis plan was pre-registered prior to the research being conducted. Task scripts, raw data, and data analysis scripts are publicly available at the Open Science Framework (OSF): https://osf.io/6mypr/.

2.1.2. *Experimental procedure*

A within-subjects experimental design was adopted. Participants underwent two sessions with the same experimental procedure except for the ccPAS protocol deployed. Session order – and hence ccPAS protocols' order – was counterbalanced between participants. Throughout the whole experiment, participants sat comfortably on a chair with their heads resting on a chinrest in a dimly lit room. At the beginning of each session, neuronavigation procedures were carried out, and the participant's resting motor threshold (rMT) was assessed. Then, participants were administered with a landmark task and a manual line bisection task. Tasks' order was fixed within and between participants. During the landmark task, all lights were turned off to achieve complete darkness. After the two tasks, the ccPAS protocol was administered according to the experimental session (FP or PF protocol). As soon as the ccPAS was over, spatial bias was reassessed using the same two tasks as before (Fig. 1a). On average, a session lasted 1 h and 30 min. The two sessions were held at the same time of day (i.e., morning or afternoon) and were separated by at least 48 h to prevent possible additive effects of PAS (Sale, Ridding, & Nordstrom, 2007).

2.1.3. *ccPAS protocol*

The experiment deployed two ccPAS protocols: a frontal-to-parietal ccPAS (FP_{10ms}) and a parietal-to-frontal one (PF_{10ms}). All stimulation parameters were identical between the two protocols, except for pulse order. In the FP_{10ms} protocol, the *conditioning* (i.e., first) TMS pulse was delivered over the right FEF, while the *test* (i.e., second) TMS pulse was delivered over the right IPL. In the PF_{10ms}, pulse order was reversed (i.e., *conditioning* pulse over right IPL and *test* pulse over right FEF). The targeted areas (i.e., right FEF and right IPL) were localized using the SofTaxic 3.4 neuronavigation software (E.M.S., Bologna, Italy, www.softaxic.com). This software allows for the reconstruction of the participant's brain based on digitized skull landmarks (nasion, inion, and two pre-auricular points) as well as 23 uniformly distributed points that are mapped on the scalp via a graphic user interface and a 3D optical digitizer (NDI, Polaris Vicra). An estimation of the single participant's cerebral volume is automatically calculated employing a warping procedure that uses a generic magnetic resonance imaging (MRI) volume based on the set of points previously digitized from the subject's scalp. The mean MNI coordinates of the right FEF ($X = 27$, $Y = 3$, $Z = 57$) and the right IPL ($X = 40$, $Y = -73$, $Z = 44$) were taken from previous functional MRI (fMRI) studies exploiting visuospatial tasks similar to ours (Heinen et al., 2011, 2017). IPL coordinates were carefully selected to be as near as possible to the IPS, considering the importance of this sulcus in visuospatial attention and SLF connectivity (Corbetta & Shulman, 2011) (Fig. 1b).

Consistently with previous literature (for a review, see: Guidali et al., 2021a), each ccPAS protocol consisted of 100 paired pulses delivered at .2 Hz for a total duration of about 9 min. Due to the Hebbian-like nature of ccPAS, precise timing is essential during its administration. Here, we used an interstimulus interval (ISI) between the two stimulation pulses of 10 ms. Although an optimal timing to probe SFL connections is yet to be established, a 10 ms ISI was successfully employed in recent ccPAS studies targeting non-motor fronto-parietal (and parieto-frontal) networks (Casula et al., 2016; Momi et al., 2019; Nord et al., 2019).

TMS was delivered using two figure-of-eight coils (Magstim model Alpha B.I. Coil Range, diameter: 70 mm) connected to two monophasic Magstim 200^2 stimulators (Magstim, Whitland, UK). TMS intensity was set at 120% of the individual resting motor threshold (rMT) for both pulses as done in previous ccPAS targeting parietal and frontal areas (e.g., Casula et al., 2016; Nord et al., 2019; Santarnecchi et al., 2018). The coil was always applied tangentially on the scalp. For FEF stimulation, it was oriented with an angle of 45° concerning the participant's mid–sagittal axis. For IPL stimulation, it was oriented at 10° with respect to the mid–sagittal axis (Fig. 1b).

To determine the participant's rMT, the motor hotspot of the left *first dorsal interosseus* (FDI) muscle was found by moving the coil in .5 cm steps around the motor hand area by using a stimulus intensity that was slightly higher than the presumed threshold. The individual rMT was then defined as the minimum TMS intensity (expressed as the percentage of maximum stimulator output) able to elicit a motor-evoked potential (MEP) of at least 50 μV by employing the parameter estimation by sequential testing (PEST) procedure (i.e., maximum-likelihood threshold-hunting approach) (Awiszus, 2003; Dissanayaka, Zoghi, Farrell, Egan, & Jaberzadeh, 2018). The average rMT during the FP_{10ms} session was 45.7 ± 8.9%, while during the PF_{10ms} session, it was 46 ± 9%. The difference between average rMTs across sessions was not significant ($t_{24} = .526$, $p = .75$).

Participants were asked to maintain fixation on a central red cross and to mentally count the number of times this cross became green (i.e., ten times during the protocol) to avoid sleepiness and keep their attention high during the ccPAS – a critical condition for protocols' effectiveness (Stefan et al.,

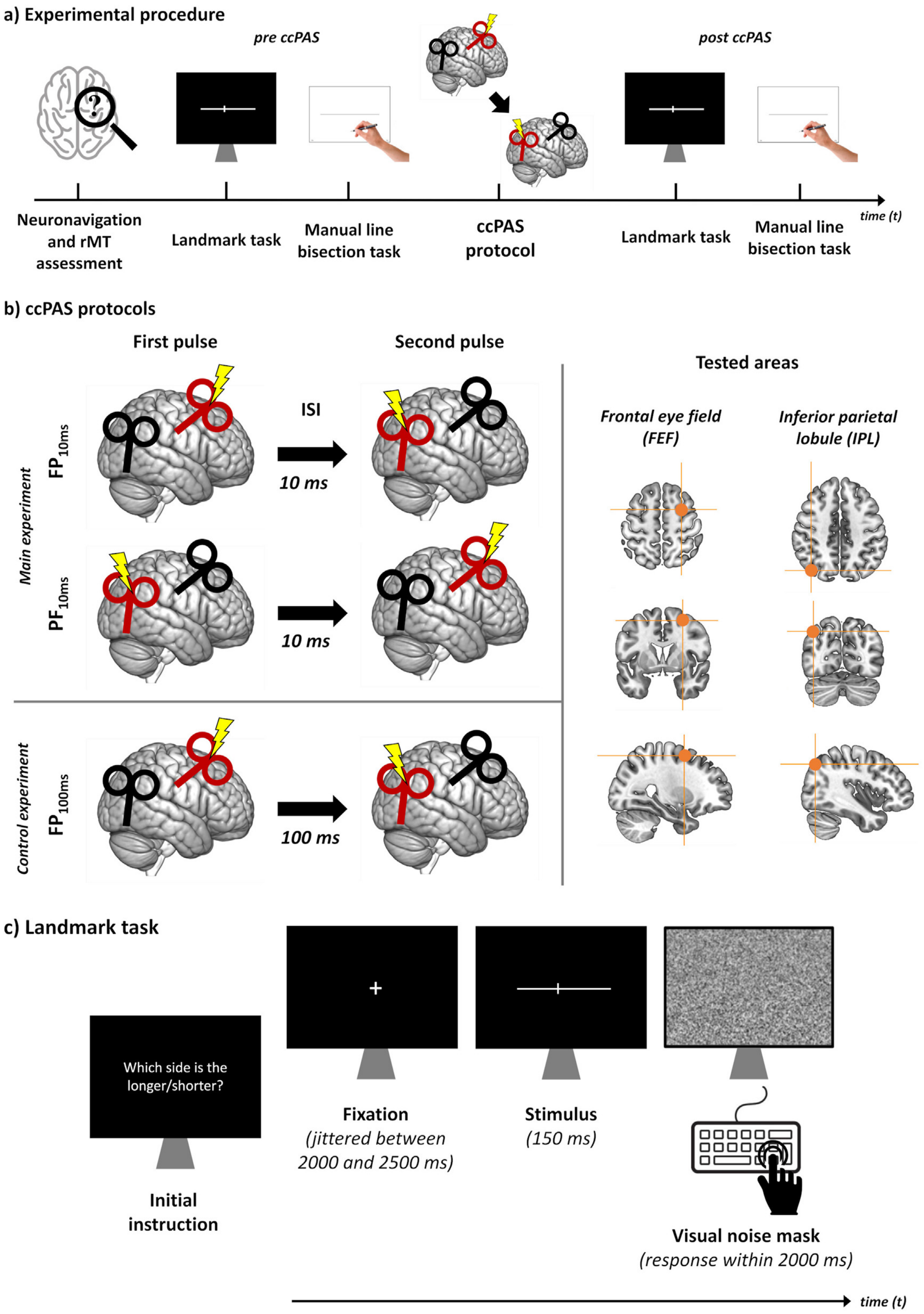

Fig. 1 – **a)** ***Experimental procedure of the two experiments.*** **b)** ***ccPAS protocols.*** **Left panel: in the *Main experiment*, frontal-to-parietal connectivity was targeted with a ccPAS stimulating the right FEF (*conditioning* pulse) and the right IPL (*test* pulse). Parietal-to-frontal connectivity was targeted, reversing ccPAS pulse order (i.e., *conditioning* pulse over IPL and *test* pulse over FEF). An ISI of 10 ms between the two pulses was used in both protocols. In the *Control experiment*, only the ccPAS targeting fronto-parietal connectivity was used, with a longer ISI of 100 ms. Right panel: axial, coronal and sagittal slices of target MNI coordinates for FEF and IPL on a standard template. The mean coordinates of the right FEF (X = 27, Y = 3, Z = 57) and the right IPL (X = 40, Y = −73, Z = 44) were taken from previous literature (see main text for further information). c) *Landmark***

2000). Trials presentation and TMS timing were controlled by a computer running dedicated software (E-Prime 2.0, Psychology Software Tool, Inc.).

2.1.4. *Landmark task*

The landmark task was a modified version of the classic landmark task introduced by Bisiach and colleagues (1998a), and it was generated using custom MATLAB code (The MathWorks, Natick, Massachusetts) and Psychophysics Toolbox functions (Brainard, 1997) and displayed on a 17-inches LCD monitor (1920 × 1080-pixel resolution, 60 Hz refresh rate).

Each experimental trial started with the presentation of a central fixation cross for a period randomly jittered between 2000 ms and 2500 ms (Fig. 1c). After this period, a white line subtending 20° (width) by .14° (height) visual angle (VA) was displayed on a black background for 150 ms. In each trial, the line could be transected in its left half, right half, or at the exact midpoint by a short vertical mark of .39° VA height. Transection points were sampled from a set of 17 points distributed along a ±2.8% (±.56° VA) range of absolute line pixel length, meaning that each point in the set was shifted by ± .35% (±.07° VA) from its neighbors (for a similar procedure, see: Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Szczepanski & Kastner, 2013). To ensure that participants did not respond randomly, two additional transection points were presented at ± 3.5% (±.7° VA) of absolute line pixel length, making them clearly detectable as transecting the horizontal line in its right versus left half. These additional transection points were not considered in subsequent task analyses, acting as mere control conditions. For the sake of completeness, accuracy at these additional points was near 100% in all conditions (i.e., pre-FP$_{10ms}$ – mean accuracy ± SD: 98.7 ± 1.4%; post-FP$_{10ms}$: 98.9 ± 1.2%; pre-PF$_{10ms}$: 98.8 ± 1.4%; post-PF$_{10ms}$: 98.9 ± 1.3%). The stimuli were always presented with the transection point centered on the participant's sagittal head midline (i.e., the line's endpoints varied, but the actual coordinates of the transection mark remained constant), preventing participants from using the coordinates of the previously displayed fixation cross as a spatial reference for the judgments. The horizontal line was kept at eye level thanks to a fixed chinrest. Responses were recorded during a full-screen mask of randomly presented grey and black pixels that disappeared after 2000 ms or upon button press, after which the subsequent trial began.

Participants were forced to choose either the longer (*instruction 1*) or shorter (*instruction 2*) line segment by pressing two adjacent keys (i.e., ‘left arrow’ if the longer/shorter side was the left one, and ‘down arrow’ if the longer/shorter side was the right one – note that keyboard symbols were covered with a colored circle to avoid confusing the participants during button pressing). Responses had to be made with the right (i.e., dominant hand) index finger. Responses for each type of instruction were collected in two randomly ordered and counterbalanced blocks. Each block contained 8 judgments for a given bisection point, for a total 152 trials and a duration of about 8 min per block. Before each block, a brief training sequence of 10 trials was presented to participants to familiarize them with the stimuli and instructions.

2.1.5. *Manual line bisection task*

The manual line bisection task consisted of the presentation of ten black lines (20 cm long, 1 mm thick) centered on a horizontal A4 white sheet (one line each sheet) aligned to the subjects' eye axis in a central position relative to the sagittal head plane. Subjects were instructed to mark the center of each line with a pencil. The task lasted about 2 min.

2.1.6. *Data analysis*

2.1.6.1. LANDMARK TASK. The primary outcome of the landmark task was the *point of subjective equality* (PSE): an objective measure of perceptual spatial bias adopted in previous studies (Benwell et al., 2014, 2015; Szczepanski & Kastner, 2013). The PSE is the line transection point that yields an estimated 50% right and 50% left responses. Because negative and positive transection points' shifts indicate that the line is transected in its left and right half (respectively), negative and positive values of PSE indicate a certain degree of leftward and rightward perceptual bias, respectively. The PSE was obtained for each participant by computing, for each transection point, the proportion of trials in which the participant gave “right is longer” and “left is shorter” responses. The points thus obtained were fit with the following cumulative logistic function:

$$y = \frac{1}{1+e^{\frac{x-\epsilon}{\sigma}}}$$

In this function, the independent variable x is the transector's location along the horizontal line, while ϵ and σ are parameters fit through a non-linear least squares procedure. In the fitted curve, ϵ is the abscissa of the point where ‘$y = .5$’ (i.e., the PSE), and σ is the curve's width: a curve shape parameter that is inversely related to slope, such that steeper curves have smaller widths (and vice versa). The fitted curve represents the proportion of right-oriented responses as a function of transector location. Thus, a subject that responded correctly at all trials would have a steep curve, while a randomly responding subject would have a horizontal line. Subjects with intermediate precision levels would have S-shaped curves of varying widths, under the general rule that the more precise the judgments, the less the width (and vice versa). *Curve width*, which measures the precision in line bisection judgments (Benwell, Thut, Learmonth, & Harvey, 2013, 2014), was considered the second dependent variable for the landmark task. The third dependent variable for the landmark task was global *accuracy*, computed as the proportion of correct responses produced by a subject irrespective of transection points.

For completeness, we have also analyzed participants' *response bias* and reaction times (RTs) (see Supplementary Materials).

task's trial procedure. Depending on the task block, participants had to indicate which side of a bisected line was longer or shorter. A visual noise mask remained on the screen until the participant pressed a key or, if no response was recorded, for a maximum time of 2000 ms.

2.1.6.2. Manual line bisection task. In the manual line bisection task, the deviation (in mm) from the presented line's true center was recorded and used as the main dependent variable. Negative and positive values of this measure indicated a certain degree of leftward and rightward perceptual bias, respectively.

2.1.7. *Statistical analysis*

For each dependent variable (i.e., PSE, curve width, accuracy for the landmark task, deviation from the true center for the manual line bisection task), a within-subjects repeated-measures analyses of variance (rmANOVA) was performed, testing the factors ‘ccPAS direction’ (FP_{10ms}, PF_{10ms}), ‘Time’ (pre-PAS, post-PAS) and their interaction, to assess possible modulation of visuospatial bias.

Statistical significance was set at $p < .05$. Normality of the distributions was checked with the Shapiro–Wilk test and further confirmed through Q–Q plots assessment. Partial eta-squared (η_p^2) was also calculated in every rmANOVA and reported as an effect size value. Significant main effects were further explored with multiple post-hoc comparisons by applying the Bonferroni correction. Unless otherwise specified, mean ± standard error (SE) is reported for each variable. Statistical analyses were performed using the software Jamovi (version 2.3.19, www.jamovi.org).

2.2. *Results*

2.2.1. *Landmark task*

The rmANOVA conducted on PSE values showed a significant ‘ccPAS direction X Time’ interaction ($F_{1,24} = 7.57$, $p = .011$, $\eta_p^2 = .24$), as well as a main effect of factor ‘Time’ ($F_{1,24} = 4.3$, $p = .049$, $\eta_p^2 = .15$). Factor ‘ccPAS direction’ did not reach statistical significance ($F_{1,24} < .001$, $p = .99$, $\eta_p^2 < .01$). Post-hoc analyses showed that selectively after the administration of the FP_{10ms} protocol, the PSE significantly shifted towards the left (pre-ccPAS PSE $= .01 \pm .13$ *vs* post-ccPAS PSE: $-.26 \pm .14$; $t_{24} = 3.5$, $p = .011$). Crucially, the administration of the PF_{10ms} did not induce modulation of PSE values (pre-ccPAS PSE $= -.14 \pm .10$ *vs* post-ccPAS PSE: $-.11 \pm .12$; $t_{24} = -.33$, $p = .99$). PSE recorded before the two ccPAS did not differ between the two sessions ($t_{24} = 1.31$, $p = .99$) (Fig. 2a,b).

Considering curve width values, rmANOVA showed neither a statistically significant interaction ‘ccPAS direction X Time’ ($F_{1,24} = .33$, $p = .57$, $\eta_p^2 = .01$), nor a main effect of factors

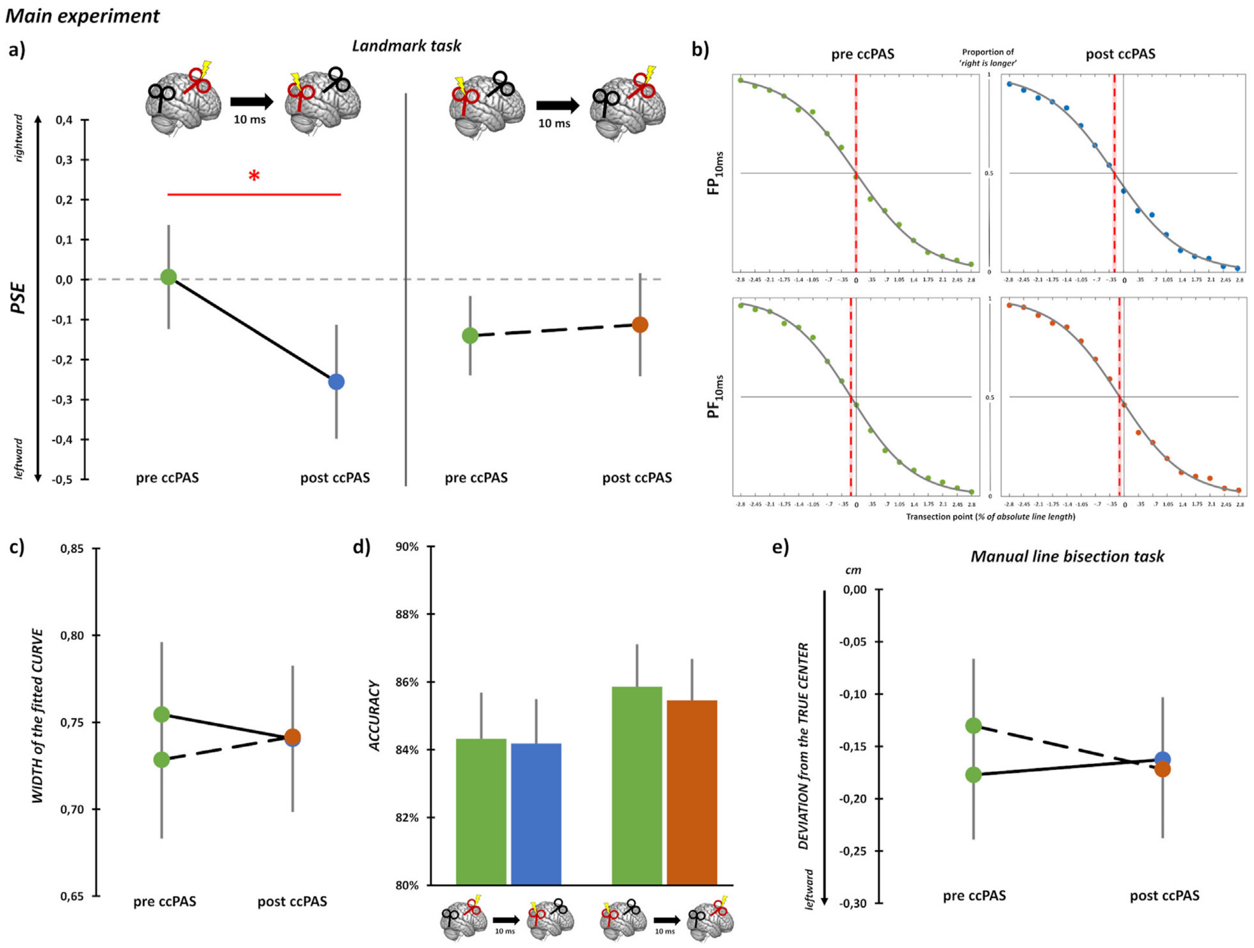

Fig. 2 – *Results of the Main experiment*. Considering the landmark task, the PSE significantly shifted leftward selectively after the administration of the FP_{10ms} ccPAS. PF_{10ms} protocol was ineffective (a). Fitted psychometric functions in the different experimental conditions (b). No effects were found for the width of the fitted curve (c) nor the accuracy (d). Considering performance in the manual line bisection task, both protocols were ineffective in modulating the perceived center of the depicted line (e). Error bars = SE; *$p = .011$ (Bonferroni corrected).

'ccPAS direction' ($F_{1,24} < .01$, $p = .99$, $\eta_p^2 < .01$) and 'Time' ($F_{1,24} = .044$, $p = .513$, $\eta_p^2 = .02$) (Fig. 2c). Thus, the participants' precision in task judgments did not differ among experimental conditions.

Considering accuracy, the rmANOVA showed a similar pattern of results as the previous analysis on curve width – namely, no effect of the interaction 'ccPAS direction X Time' ($F_{1,24} = .05$, $p = .818$, $\eta_p^2 < .01$), as well as of the main factors 'ccPAS direction' ($F_{1,24} = 3.03$, $p = .095$, $\eta_p^2 = .11$) and 'Time' ($F_{1,24} = .3$, $p = .587$, $\eta_p^2 = .01$), highlighting the absence of a general modulation of performance accuracy after the administration of the two ccPAS protocols (Fig. 2d).

2.2.2. *Manual line bisection task*

The rmANOVA conducted on the distance between the true center of the presented lines and the transection points drawn by the subjects showed no effects of main factors 'ccPAS direction' ($F_{1,24} = .1$, $p = .76$, $\eta_p^2 < .01$) and 'Time' ($F_{1,24} = .23$, $p = .634$, $\eta_p^2 < .01$), nor of their interaction ($F_{1,24} = 1.53$, $p = .229$, $\eta_p^2 < .01$). This evidence shows that no ccPAS protocol was able to modulate performance in the manual line bisection task (Fig. 2e).

3. Control experiment: timing of ccPAS effect

In this second experiment, participants underwent a single session with a modified version of the FP protocol, which was found to be effective in the *Main experiment* (i.e., *conditioning* pulse over the right FEF and *test* pulse over the right IPL with an ISI of 10 ms; FP_{10ms}). The difference between this version and the previous one was the ISI between the two paired pulses, which was lengthened to 100 ms to control for the timing dependency of the protocol (FP_{100ms}) (Fig. 1a and b). This ISI should be too long to achieve contingency between *conditioning* and *test* pulses, so we expected the protocol not to be effective in inducing plastic phenomena within the fronto-parietal network. Except for the ISI, the experimental procedure was the same as the *Main experiment*: before and after the ccPAS protocol, participants underwent the landmark and the manual line bisection tasks.

3.1. *Methods and materials*

3.1.1. *Participants*

Twenty healthy volunteers who had taken part in the *Main experiment* were recruited for the *Control experiment* (6 males, mean age ± SD = 25.3 ± 4.9 years; mean education ± SD = 15.7 ± 2.8 years). According to the Edinburgh Handedness Inventory (Oldfield, 1971), they were all right-handed (mean score ± SD = 95.8 ± 9.2%), and none had contraindications to TMS (Rossi et al., 2021).

Participants presented an average rMT of 47.6 (SD = ± 8.1). The difference in average rMTs between FP_{100ms} and FP_{10ms} sessions was not significant ($p = .49$).

3.1.2. *Statistical analysis*

The same dependent variables used in the *Main experiment* were calculated for the landmark task (i.e., PSE, curve width, accuracy) and the manual line bisection task (deviation of drawn transection point from the line's true midpoint). This experiment aimed at controlling the timing dependency of FP-ccPAS and was run on participants who had already participated in the *Main experiment*. Thus, we compared the results obtained with the FP_{100ms} protocol with the ones from the *Main experiment*'s FP_{10ms}. We performed a within-subjects rmANOVA testing the factors 'ccPAS ISI' (10 ms, 100 ms), 'Time' (pre-PAS, post-PAS), and their interaction.

Statistical analyses were performed using the software Jamovi (version 2.3.19, www.jamovi.org) following the same methodology described for the *Main experiment*.

3.2. *Results*

3.2.1. *Landmark task*

The rmANOVA conducted on PSE values showed a significant 'ccPAS ISI X Time' interaction ($F_{1,19} = 5.42$, $p = .031$, $\eta_p^2 = .22$), as well as a main effect of factor 'Time' ($F_{1,19} = 5.52$, $p = .03$, $\eta_p^2 = .23$). Factor 'ccPAS timing' did not reach statistical significance ($F_{1,19} < .833$, $p = .373$, $\eta_p^2 = .04$).

Post-hoc analyses showed that PSE shifted towards the left side after the administration of the FP_{10ms} protocol ($t_{19} = 3.37$, $p = .019$). Crucially for proving the timing specificity of the protocol, PSE was not modulated after the administration of the FP_{100ms} protocol (pre-ccPAS PSE = −.01 ± .17 *vs* post-ccPAS PSE: −.02 ± .17; $t_{19} = .11$, $p = .99$) (Fig. 3a, b).

Considering PSE curve width values and accuracy, in line with the *Main experiment*, the rmANOVAs showed no significant effect of the interactions 'ccPAS ISI X Time' (curve width: $F_{1,19} = 1.93$, $p = .181$, $\eta_p^2 = .09$; accuracy: $F_{1,19} = .65$, $p = .429$, $\eta_p^2 = .03$), as well as of the main factors 'ccPAS ISI' (curve width: $F_{1,19} = .02$, $p = .896$, $\eta_p^2 < .01$; accuracy: $F_{1,19} = .11$, $p = .743$, $\eta_p^2 < .01$) and 'Time' (curve width: $F_{1,19} = .33$, $p = .571$, $\eta_p^2 = .02$; accuracy: $F_{1,19} = .4$, $p = .536$, $\eta_p^2 = .02$) (Fig. 3c, d).

3.2.2. *Manual line bisection task*

In line with the first experiment, considering participants' performance in the line bisection task, the rmANOVA showed no effects of main factors 'ccPAS ISI' ($F_{1,19} = 3.99$, $p = .06$, $\eta_p^2 = .17$) and 'Time' ($F_{1,19} < .01$, $p = .967$, $\eta_p^2 < .01$), as well as of the interaction 'ccPAS ISI X Time' ($F_{1,19} < .01$, $p = .923$, $\eta_p^2 < .01$) (Fig. 3e).

4. Discussion

The results of our study showed that targeting right hemisphere connectivity between the FEF (first pulse) and the IPL (second pulse) with an ISI of 10 ms is effective in modulating an objective measure of perceptual spatial bias (i.e., perceived line midpoint in a landmark task – PSE) (Benwell et al., 2014, 2015; Benwell et al., 2013), making ccPAS a valuable tool to investigate visuospatial bias.

After administering the FP_{10ms} version of the ccPAS, participants' leftward bias in the landmark task increased significantly. Namely, with respect to the baseline, they tended to overestimate the size of the leftward segment, shifting the PSE towards the left side of the space.

The increased leftward bias found after our protocol was not due to an overall improvement/worsening of

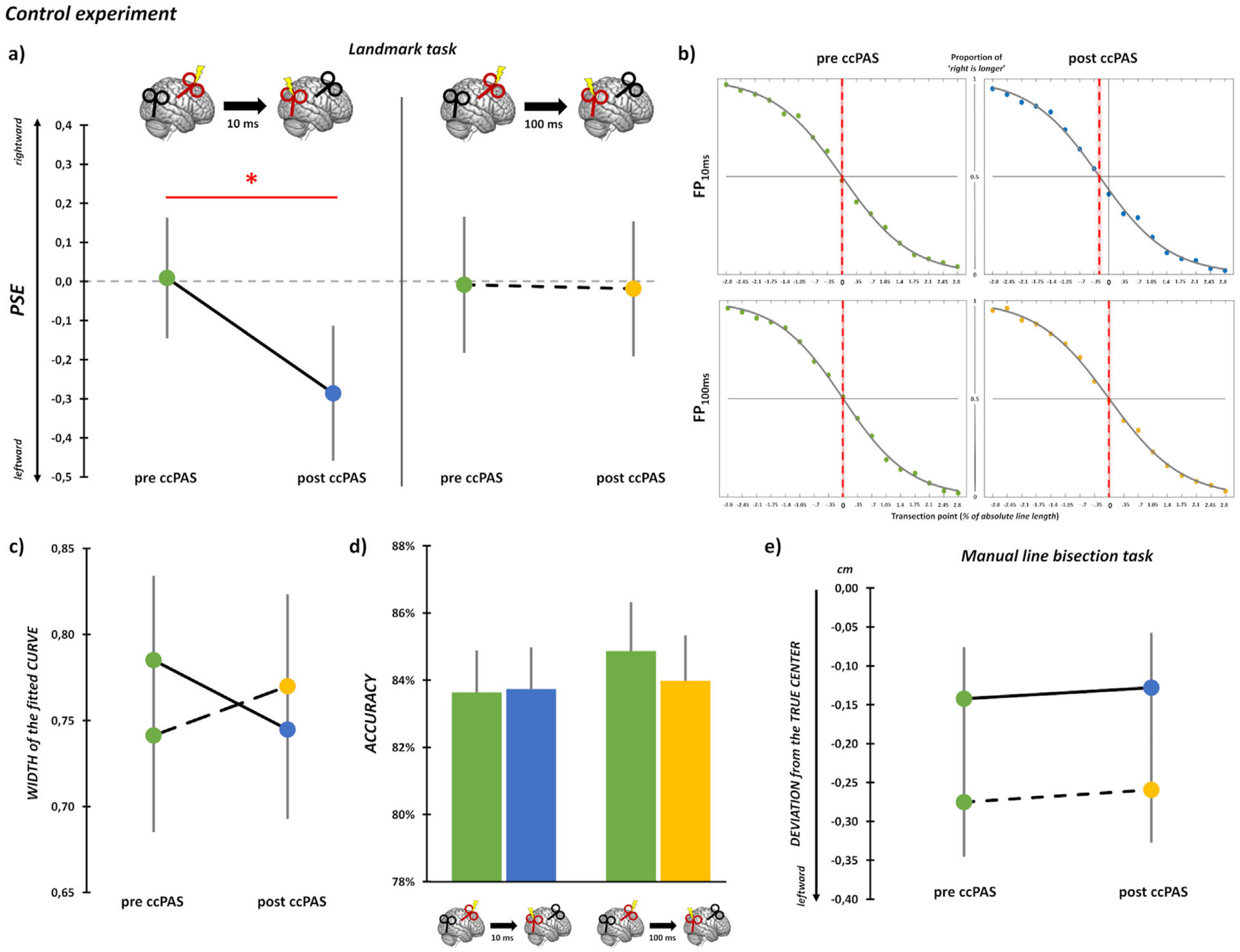

Fig. 3 – ***Results of the Control experiment.*** **Considering the landmark task, FP$_{100ms}$ ccPAS was ineffective in modulating PSE (a). Fitted psychometric functions in the different experimental conditions (b). No effects were found for the width of the fitted curve (c) nor the accuracy (d). In line with the previous experiment, this protocol was ineffective in modulating the manual line bisection task (e). Error bars = SE; ****p*** **= .019 (Bonferroni corrected).**

participants' performance, as shown by the null effects on accuracy and curve width. This evidence suggests that the induced effect was specific to the visuospatial bias and not due to a more 'general-domain' modulation of attention, which, in turn, should have also affected measures of participant's performance. The non-significant modulation of *response bias* (Bisiach, Ricci, Lualdi, & Colombo, 1998; Brighina et al., 2002; Ricci et al., 2012) and RTs in the landmark task further confirms this speculation (see Supplementary Materials). It has to be noted that a control task could have been implemented to better disentangle the contribution of general attentional processes in our results; however, in the present study, this choice was discarded to maximize the detection of visuospatial bias modulations due to the unknown duration of our ccPAS aftereffects (see next paragraphs).

Crucially, our results showed that ccPAS was not effective when (*a*) the pulse order was reversed (i.e., first pulse over the right IPL and second pulse over the right FEF – PF$_{10ms}$, *Main experiment*) and (*b*) the ISI between the paired pulses was too long (i.e., 100 ms – FP$_{100ms}$, *Control experiment*). This evidence proved the direction specificity and the timing dependency of our ccPAS, two crucial features of this class of non-invasive brain stimulation protocols (Guidali et al., 2021a).

Results from the *Main experiment* showed that the direction of ccPAS paired pulses was crucial for increasing the leftward bias in the landmark task's PSE, pointing out how frontal-to-parietal connectivity – specifically, FEF-to-IPL connectivity – might play a central role in the modulation of visuospatial biases.

We can speculate that an increased attentive top-down control mediated this effect – likely through the DAN. Indeed, previous literature using concurrent TMS and fMRI or dynamic causal modeling suggested that both the FEF and the IPS – which also encompass part of the superior region of the IPL that was targeted in our study (see 2.1.3) – modulated visual cortices activity through backward connections, likely reflecting anticipatory attentional deployment (e.g., Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Ruff, Blankenburg, et al., 2009; Ruff et al., 2008; Vossel, Geng, & Fink, 2014; Vossel, Weidner, Driver, Friston, & Fink, 2012). For instance, in an fMRI study exploiting a visual spatial attention paradigm and using Granger causality measures on blood oxygen level-dependent time series, Bressler et al. (2008)

found that FEF modulated IPS far more than the contrary, suggesting that frontal-to-parietal connectivity plays a significant role in orienting visuospatial attention (Bressler et al., 2008). In support of the influence of top-down attentional control on visuospatial biases, clinical studies on patients with spatial neglect showed that when voluntary attention is oriented to the contralesional (i.e., left) side of space, stimulus detection in that side of space can be facilitated, suggesting compensatory effects of their pathological rightward bias (for a review, see: Corbetta & Shulman, 2011). Moreover, after a stroke, recovery of attentional functions has been found to be accompanied by a restoration of interhemispheric connectivity within the DAN – where FEF-to-IPS connectivity plays a crucial role (He et al., 2007).

Taken together, this evidence suggests that the FP_{10ms} protocol might have acted by potentiating top-down attention allocation toward the left side of space, leading to a more significant leftward bias, as evidenced by the shift of the landmark task's PSE. This effect might be induced through PAS-related associative plasticity between the frontal and parietal regions of the DAN, likely through the mediation of the SLF (de Schotten et al., 2011; Kocsis et al., 2019). In this frame, the evidence that the stimulation of parietal-to-frontal connectivity (i.e., PF_{10ms} cc-PAS) did not induce any shift in the bisection judgment might suggest that the sensorimotor integration accompanying visuospatial processing does not exert a central role in the modulation of pseudoneglect.

The present results do not allow us to state whether top-down attention – and, in a broader perspective, the DAN – is the sole responsible for the genesis of pseudoneglect. We can only speculate that top-down attention is, at least in part, responsible for the increase of such visuospatial bias found in the landmark task. Further research has to be conducted to better disentangle the neurophysiological underpinnings of FP_{10ms} protocol effects. For instance, future ccPAS studies might deepen the role of connectivity between the right PPC and the contralateral homologous regions or with low-level visual areas by targeting these cortical nodes instead of the FEF. Indeed, besides frontal-to-parietal connectivity, the literature suggests that these inter- and intra-hemispheric cortico-cortical pathways might also play a crucial role in visuospatial processing and attention (e.g., Mengotti et al., 2020; Ricci et al., 2012; Salatino et al., 2014; Vossel et al., 2014).

An alternative hypothesis – which does not exclude the one described before – could be that the FP_{10ms} cc-PAS might have primarily boosted right IPL functioning, which is known to play a core role in the spatial neglect phenomenon, being a crucial anatomical correlate of conscious visual space representation (e.g., Driver & Mattingley, 1998; Mort et al., 2003; Pisella & Mattingley, 2004; Salvato et al., 2021). Previous electrophysiological studies tracking the temporal evolution of visuospatial bias during line bisection and landmark tasks have found an early locus for the genesis of pseudoneglect in the right parietal cortex, where the integration of visual information from both hemispheres would take place (Benwell et al., 2014; Foxe et al., 2003). Typically, perceptual tasks used to investigate pseudoneglect – like the landmark task – require that visual information from the left and right visual fields are integrated into representations that preserve input topography before a perceptual decision can be made. This critical memory buffer might rely on the PPC – more precisely, on areas of the IPL (Chen, Lee, O'Neil, Abdul-Nabi, & Niemeier, 2020). For instance, according to the 'space anisometry' hypothesis (Bisiach, Ricci, & Mòdona, 1998), neglect may depend on the alteration of the representational medium along the horizontal dimension, appearing progressively 'relaxed' towards the contralesional side of space and progressively 'compressed' towards the ipsilesional one (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Savazzi, Posteraro, Veronesi, & Mancini, 2007). The almost balanced representation characterizing the healthy brain (e.g., slight distortions giving rise to the pseudoneglect phenomenon) is mainly achieved thanks to the contribution of parietal areas like IPL. The modulation of cortico-cortical connectivity targeting the parietal cortex might have led to a transient 'contraction' of the left – contralateral (to stimulation) – side of space representation and a 'relaxation' of the right – ipsilateral (to stimulation) – one. This effect could be attributable to the modulation of IPL functioning, which in turn generated the leftward visuospatial bias observed in our results. By targeting parietal-to-frontal areas connectivity, as in the $PF_{10\ msec}$ protocol, parietal areas might not have been effectively modulated, then no shifting in the visuospatial bias was detectable.

The *Control experiment* showed that the ISI between the two paired pulses is a key factor for the success of the fronto-parietal ccPAS. Indeed, the (longer) ISI of 100 ms exploited in the second experiment of our study should not reflect the timing of the cortico-cortical pathway between frontal and parietal areas (e.g., Nord et al., 2019). In the FP_{100ms} protocol, the contingency between pre- and post-synaptic activation driven by the TMS pulses – crucial for the induction of PAS plastic effects – was not achieved, and associative plasticity was not induced, making the FP_{100ms} cc-PAS ineffective in modulating participants' performance in the landmark task.

It has to be noted that, from the results of this experiment, we cannot *a-priori* exclude that other ISIs are effective in modulating frontal-to-parietal connectivity and, hence, pseudoneglect. For instance, Suppa, Li Voti, Rocchi, Papazachariadis, and Berardelli (2015) found that a PAS protocol targeting visuo-motor connectivity was effective in enhancing MEPs with both ISIs corresponding to visual-evoked potentials' P1 component latency *plus* 100 ms and *plus* 120 ms (Suppa et al., 2015). Thus, it may be possible that the adequate time windows able to induce plasticity within long-range connections are wider (i.e., in the order of tens of ms) than in PAS protocols targeting primary cortical systems, where differences of a few ms are crucial for plasticity induction (Guidali et al., 2021b). In the future, other ISIs could be exploited to investigate the existence of more efficient ones or whether the 'direction' of the visuospatial bias (i.e., induction of rightward instead of leftward bias) can be modulated in a timing-dependent manner.

Previous literature reporting pseudoneglect modulations after repetitive TMS (rTMS) of the right PPC found the so-called 'neglect-like induction,' i.e., a pattern of results mimicking the rightward bias of unilateral spatial neglect (Bagattini, Mele, Brignani, & Savazzi, 2015; Bjoertomt, Cowey, & Walsh, 2002; Fierro, Brighina, & Bisiach, 2006; Jin & Hilgetag, 2008; Nyffeler et al., 2008; Oliveri, Bisiach, & Brighina, 2001; Ricci et al., 2012). Namely, this is the opposite direction of the one found in the present study. This result is not so unexpected considering that we used a TMS protocol which, differently from rTMS, took advantage of a higher spatial focality by stimulating two nodes of a cortico-cortical pathway and, in a broader perspective, of a cortical network (Guidali et al., 2021a). Nowadays, the effects of rTMS are considered in a 'network framework' rather than a 'virtual lesion' one; i.e., rTMS effects are known to be widespread to regions directly and indirectly connected to the target one (e.g., Bestmann et al., 2008; Mengotti, Käsbauer, Fink, & Vossel, 2022; Ruff, Driver, & Bestmann, 2009; Sack et al., 2007). Thus the 'neglect-like induction' found in previous literature could be caused by inter and intra-hemispheric effects spreading from the stimulated area (e.g., IPL) to other areas of the network responsible for spatial processing and attention. Studies on this topic combining fMRI and TMS confirmed such a view (Ricci et al., 2012; Sack et al., 2007). Hence, the increased 'spatial focality' of ccPAS (i.e., its ability to target specific cortico-cortical connections and modulate connectivity between two cortical nodes of the same network) could be a further advantage for the exploitation of these protocols in the investigation of high-order cognitive networks or pathologies relying on the activation of different interconnected brain areas, like visuospatial processing or neglect (Baldassarre et al., 2014; Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016; Corbetta & Shulman, 2011).

The ineffectiveness of all tested ccPAS versions in modulating performance in the manual line bisection task is thought-provoking, but not unexpected. A possible explanation is that this task is less sensitive to pseudoneglect modulation *per se*. This task is widely used for the clinical assessment of hemispatial neglect, but its efficacy in assessing pseudoneglect in healthy individuals is more controversial (Jewell & McCourt, 2000; Mitchell, Harris, Benstock, & Ales, 2020). Furthermore, different studies have highlighted how participants' performance and cortical networks' activation might differ between landmark and bisection tasks (e.g., García-Pérez & Peli, 2014; Harvey, Krämer-McCaffery, Dow, Murphy, & Gilchrist, 2002; Harvey & Olk, 2004). The manual line bisection task adopted in the present study is a basic version, comprising a few trials (only ten lines) and presenting lines with the same length. In addition, it has always been administered *after* the landmark task, and thus in a time window where ccPAS' aftereffects might already be over. This choice was made considering that the primary aim of our experiments was to maximize the detection of possible ccPAS effects on the landmark task rather than the manual line bisection task. Different ccPAS studies (e.g., Buch et al., 2011; Chao et al., 2015; Romei et al., 2016) showed that ccPAS aftereffects are detectable for almost double the time of the protocol's duration (i.e., with an administration time of ~8 min, we can hypothesize that our protocol-induced plasticity lasts for ~16 min after its administration). Future studies should investigate whether administering a more complex version of the line bisection task – or its administration as soon as the ccPAS ends – leads to a similar pattern of results found for the landmark task.

Finally, a possible limitation of our study is that neuronavigation procedures were based on a standard MRI template rather than on the participants' own MRI, reducing the precision of individualized FEF and IPL stimulation. However, the adopted neuronavigation procedure has been successfully used in previous studies to localize (and stimulate) focal areas with precision within a few mm (e.g., Carducci & Brusco, 2012; Collins & Jacquet, 2018; Guidali, Roncoroni, Papagno, & Bolognini, 2020) and thus we can assume to have targeted the correct brain regions. Another limitation is that our sample was not balanced for gender (namely, we have tested more females than males): inter-hemispheric differences – as well as the right hemisphere dominance for attentional processes – could be attenuated in females and this could have slightly impacted the pattern of our results (e.g., Agcaoglu, Miller, Mayer, Hugdahl, & Calhoun, 2015; Ricci et al., 2012).

In conclusion, our ccPAS proves that this class of non-invasive brain stimulation protocols can be used to modulate pseudoneglect, likely through the induction of associative plasticity and exploiting frontal-to-parietal connectivity. In the future, this protocol could represent a promising tool, not only to investigate connectivity properties within visuospatial and attentive networks in the healthy, but also as a potential rehabilitation protocol in patients suffering from severe visuospatial pathologies (e.g., unilateral spatial neglect) – which are known to be among the most common outcomes after right hemisphere's stroke (Esposito, Shekhtman, & Chen, 2021). Again, it could also be used to investigate connectivity abnormalities and plastic reorganization in these patients, considering that visuospatial neglect is often associated with damages at the SLF and/or disconnection with the interconnected regions (Gammeri, Iacono, Ricci, & Salatino, 2020; Karnath & Rorden, 2012). Furthermore, investigating the relationship between cortico-cortical connectivity alterations and ccPAS effects may lay the foundation for developing prognostic markers of ccPAS efficacy. From a broader perspective, ccPAS protocols could become the elected non-invasive brain stimulation protocol for all the pathologies where cortico-cortical connectivity or cerebral network impairments are crucial in the observed symptomatology.

CRediT authorship

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Matteo De Matola: investigation, software, manuscript – review and editing.

Debora Brignani: conceptualization, methodology, supervision, project administration, resources, manuscript – original draft.

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Open practices

The study in this article earned Open Data and Open Material badges for transparent practices. The data and materials used in this study are available at: https://osf.io/6mypr/.

Declaration of interest

The authors declare no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.08.012.

REFERENCES

Agcaoglu, O., Miller, R., Mayer, A. R., Hugdahl, K., & Calhoun, V. D. (2015). Lateralization of resting state networks and relationship to age and gender. *Neuroimage, 104*, 310–325. https://doi.org/10.1016/j.neuroimage.2014.09.001

Arai, N., Muller-Dahlhaus, F., Murakami, T., Bliem, B., Lu, M.-K., Ugawa, Y., et al. (2011). State-dependent and timing-dependent bidirectional associative plasticity in the human SMA-M1 network. *Journal of Neuroscience, 31*(43), 15376–15383. https://doi.org/10.1523/JNEUROSCI.2271-11.2011

Awiszus, F. (2003). TMS and threshold hunting. *Supplements to Clinical Neurophysiology, 56*(C), 13–23. https://doi.org/10.1016/S1567-424X(09)70205-3

Bagattini, C., Esposito, M., Ferrari, C., Mazza, V., & Brignani, D. (2022). Connectivity alterations underlying the breakdown of pseudoneglect: New insights from healthy and pathological aging. *Frontiers in Aging Neuroscience, 14*, 977. https://doi.org/10.3389/FNAGI.2022.930877/BIBTEX

Bagattini, C., Mele, S., Brignani, D., & Savazzi, S. (2015). No causal effect of left hemisphere hyperactivity in the genesis of neglect-like behavior. *Neuropsychologia, 72*, 12–21. https://doi.org/10.1016/j.neuropsychologia.2015.04.010

Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., et al. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain, 137*(12), 3267–3283. https://doi.org/10.1093/brain/awu297

Baldassarre, A., Ramsey, L. E., Siegel, J. S., Shulman, G. L., & Corbetta, M. (2016). Brain connectivity and neurological disorders after stroke. *Neurology, 29*(6). https://doi.org/10.1097/WCO.0000000000000396

Bartolomeo, P., de Schotten, M. T., & Chica, A. B. (2010). Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience, 0*(MAY 2012), 110. https://doi.org/10.3389/FNHUM.2012.00110/BIBTEX

Benwell, C. S. Y., Harvey, M., & Thut, G. (2014). On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length. *Neuroimage, 86*, 370–380. https://doi.org/10.1016/j.neuroimage.2013.10.014

Benwell, C. S. Y., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex, 69*, 152–165. https://doi.org/10.1016/J.CORTEX.2015.05.007

Benwell, C. S. Y., Thut, G., Learmonth, G., & Harvey, M. (2013). Spatial attention: Differential shifts in pseudoneglect direction with time-on-task and initial bias support the idea of observer subtypes. *Neuropsychologia, 51*(13), 2747–2756. https://doi.org/10.1016/j.neuropsychologia.2013.09.030

Bestmann, S., Ruff, C. C., Blankenburg, F., Weiskopf, N., Driver, J., & Rothwell, J. C. (2008). Mapping causal interregional influences with concurrent TMS–fMRI. *Experimental Brain Research, 191*(4), 383–402. https://doi.org/10.1007/s00221-008-1601-8

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119*(3), 851–857. https://doi.org/10.1093/brain/119.3.851

Bisiach, E., Ricci, R., Lualdi, M., & Colombo, M. R. (1998a). Perceptual and response bias in unilateral neglect: Two modified versions of the Milner Landmark task. *Brain and Cognition, 37*(3), 369–386. https://doi.org/10.1006/brcg.1998.1003

Bisiach, E., Ricci, R., & Mòdona, M. N. (1998b). Visual awareness and anisometry of space representation in unilateral neglect: A panoramic investigation by means of a line extension task. *Consciousness and Cognition, 7*(3), 327–355. https://doi.org/10.1006/ccog.1998.0361

Bjoertomt, O., Cowey, A., & Walsh, V. (2002). Spatial neglect in near and far space investigated by repetitive transcranial magnetic stimulation. *Brain, 125*(9), 2012–2022. https://doi.org/10.1093/brain/awf211

Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: Effects of hemispace on a tactile line bisection task. *Neuropsychologia, 18*(4–5), 491–498. https://doi.org/10.1016/0028-3932(80)90151-7

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision, 10*(4), 433–436. https://doi.org/10.1163/156856897X00357

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *Journal of Neuroscience, 28*(40), 10056–10061. https://doi.org/10.1523/JNEUROSCI.1776-08.2008

Brighina, F., Bisiach, E., Piazza, A., Oliveri, M., La Bua, V., Daniele, O., et al. (2002). Perceptual and response bias in visuospatial neglect due to frontal and parietal repetitive transcranial magnetic stimulation in normal subjects. *NeuroReport, 13*(18), 2571–2575. https://doi.org/10.1097/00001756-200212200-00038

Brooks, J. L., Sala, S. Della, & Darling, S. (2014). Representational pseudoneglect: A review. *Neuropsychology Review, 24*(2), 148–165. https://doi.org/10.1007/s11065-013-9245-2

Buch, E. R., Johnen, V. M., Nelissen, N., O'Shea, J., & Rushworth, M. F. S. (2011). Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. *Journal of Neuroscience, 31*(48), 17669–17679. https://doi.org/10.1523/JNEUROSCI.1513-11.2011

Caporale, N., & Dan, Y. (2008). Spike timing–dependent plasticity: A hebbian learning rule. *Annual Review of Neuroscience, 31*(1), 25–46. https://doi.org/10.1146/annurev.neuro.31.060407.125639

Carducci, F., & Brusco, R. (2012). Accuracy of an individualized MR-based head model for navigated brain stimulation. *Psychiatry Research: Neuroimaging, 203*(1), 105–108. https://doi.org/10.1016/j.pscychresns.2011.12.013

Casarotto, A., Dolfini, E., Cardellicchio, P., Fadiga, L., D'Ausilio, A., & Koch, G. (2023). Mechanisms of Hebbian-like plasticity in the ventral premotor – primary motor network. *The Journal of Physiology, 601*(1), 211–226. https://doi.org/10.1113/JP283560

Casula, E. P., Pellicciari, M. C., Picazio, S., Caltagirone, C., & Koch, G. (2016). Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. *Neuroimage, 143*, 204–213. https://doi.org/10.1016/j.neuroimage.2016.08.060

Cazzoli, D., & Chechlacz, M. (2017). 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. *Cortex, 86*, 230–246. https://doi.org/10.1016/j.cortex.2016.06.015

Chao, C. C., Karabanov, A. N., Paine, R., Carolina De Campos, A., Kukke, S. N., Wu, T., et al. (2015). Induction of motor associative plasticity in the posterior parietal cortex-primary motor network. *Cerebral Cortex, 25*(2), 365–373. https://doi.org/10.1093/cercor/bht230

Chechlacz, M., Humphreys, G. W., Sotiropoulos, S. N., Kennard, C., & Cazzoli, D. (2015). Structural organization of the corpus callosum predicts attentional shifts after continuous theta burst stimulation. *Journal of Neuroscience, 35*(46), 15353–15368. https://doi.org/10.1523/JNEUROSCI.2610-15.2015

Chen, J., Lee, A. C. H., O'Neil, E. B., Abdul-Nabi, M., & Niemeier, M. (2020). Mapping the anatomy of perceptual pseudoneglect. A multivariate approach. *Neuroimage, 207*(July 2019), 1–10. https://doi.org/10.1016/j.neuroimage.2019.116402

Çiçek, M., Deouell, L. Y., & Knight, R. T. (2009). Brain activity during landmark and line bisection tasks. *Frontiers in Human Neuroscience, 3*(MAY), 7. https://doi.org/10.3389/NEURO.09.007.2009/BIBTEX

Collins, T., & Jacquet, P. O. (2018). TMS over posterior parietal cortex disrupts trans-saccadic visual stability. *Brain Stimulation, 11*(2), 390–399. https://doi.org/10.1016/j.brs.2017.11.019

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201–215. https://doi.org/10.1038/nrn755

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attentional networks. *Annual Review of Neuroscience, 34*, 569. https://doi.org/10.1146/ANNUREV-NEURO-061010-113731

Dan, Y., & Poo, M. M. (2004). Spike timing-dependent plasticity of neural circuits. *Neuron, 44*(1), 23–30. https://doi.org/10.1016/j.neuron.2004.09.007

de Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G. M., et al. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience, 14*(10), 1245–1246. https://doi.org/10.1038/nn.2905

de Schotten, M. T., & Forkel, S. J. (2022). The emergent properties of the connected brain. *Science, 378*(6619), 505–510. https://doi.org/10.1126/SCIENCE.ABQ2591

Di Luzio, P., Tarasi, L., Silvanto, J., Avenanti, A., & Romei, V. (2022). Human perceptual and metacognitive decision-making rely on distinct brain networks. *Plos Biology, 20*(8), 1–19. https://doi.org/10.1371/journal.pbio.3001750

Dissanayaka, T., Zoghi, M., Farrell, M., Egan, G., & Jaberzadeh, S. (2018). Comparison of Rossini–Rothwell and adaptive threshold-hunting methods on the stability of TMS induced motor evoked potentials amplitudes. *Journal of Neuroscience Research, 96*(11), 1758–1765. https://doi.org/10.1002/jnr.24319

Doricchi, F., & Tomaiuolo, F. (2003). The anatomy of neglect without hemianopia: A key role for parietal-frontal disconnection? *NeuroReport, 14*(17), 26–36. https://doi.org/10.1097/00001756-200312020-00021

Driver, J., & Mattingley, J. B. (1998). Parietal neglect and visual awareness. *Nature Neuroscience, 1*(1), 17–22. https://doi.org/10.1038/217

Esposito, E., Shekhtman, G., & Chen, P. (2021). Prevalence of spatial neglect post-stroke: A systematic review. *Annals of Physical and Rehabilitation Medicine, 64*(5), 101459. https://doi.org/10.1016/J.REHAB.2020.10.010

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Fierro, B., Brighina, F., & Bisiach, E. (2006). Improving neglect by TMS. *Behavioural Neurology, 17*(3–4), 169–176. https://doi.org/10.1155/2006/465323

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., et al. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *NeuroReport, 11*(7), 1519–1521. https://doi.org/10.1097/00001756-200005150-00031

Fink, G. R., Marshall, J. C., Shah, N. J., Weiss, P. H., Halligan, P. W., Grosse-Ruyken, M., et al. (2000). Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology, 54*(6), 1324–1331. https://doi.org/10.1212/WNL.54.6.1324

Foxe, J. J., McCourt, M. E., & Javitt, D. C. (2003). Right hemisphere control of visuospatial attention: Line-bisection judgments evaluated with high-density electrical mapping and source analysis. *Neuroimage, 19*(3), 710–726. https://doi.org/10.1016/S1053-8119(03)00057-0

Gammeri, R., Iacono, C., Ricci, R., & Salatino, A. (2020). Unilateral spatial neglect after stroke: Current insights. *Neuropsychiatric Disease and Treatment, 16*, 131–152. https://doi.org/10.2147/NDT.S171461

García-Pérez, M. A., & Peli, E. (2014). The bisection point across variants of the task. *Attention, Perception, and Psychophysics, 76*(6), 1671–1697. https://doi.org/10.3758/s13414-014-0672-9

Guidali, G., Roncoroni, C., & Bolognini, N. (2021a). Modulating frontal networks' timing-dependent-like plasticity with paired associative stimulation protocols: Recent advances and future perspectives. *Frontiers in Human Neuroscience, 15*(April), 658723. https://doi.org/10.3389/fnhum.2021.658723

Guidali, G., Roncoroni, C., & Bolognini, N. (2021b). Paired associative stimulations: Novel tools for interacting with sensory and motor cortical plasticity. *Behavioural Brain Research, 414*(September), 113484. https://doi.org/10.1016/j.bbr.2021.113484

Guidali, G., Roncoroni, C., Papagno, C., & Bolognini, N. (2020). Cross-modal involvement of the primary somatosensory cortex in visual working memory: A repetitive TMS study. *Neurobiology of Learning and Memory, 175*(October), Article 107325. https://doi.org/10.1016/j.nlm.2020.107325

Halligan, P. W., Fink, G. R., Marshall, J. C., & Vallar, G. (2003). Spatial cognition: Evidence from visual neglect. *Trends in Cognitive Sciences, 7*(3), 125–133. https://doi.org/10.1016/S1364-6613(03)00032-9

Harvey, M., Krämer-McCaffery, T., Dow, L., Murphy, P. J. S., & Gilchrist, I. D. (2002). Categorisation of "perceptual" and "premotor" neglect patients across different tasks: Is there strong evidence for a dichotomy? *Neuropsychologia, 40*(8), 1387–1395. https://doi.org/10.1016/S0028-3932(01)00202-0

Harvey, M., & Olk, B. (2004). Comparison of the milner and Bisiach landmark tasks: Can neglect patients be classified consistently? *Cortex, 40*(4–5), 659–665. https://doi.org/10.1016/S0010-9452(08)70162-X

Heekeren, H. R., Marrett, S., & Ungerleider, L. G. (2008). The neural systems that mediate human perceptual decision making. *Nature Reviews Neuroscience, 9*, 467–479. https://doi.org/10.1038/nrn2374

Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Annals of Neurology, 5*(2), 166–170. https://doi.org/10.1002/ANA.410050210

Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention. *Neurology, 30*(3). https://doi.org/10.1212/WNL.30.3.327, 327–327.

Heinen, K., Feredoes, E., Ruff, C. C., & Driver, J. (2017). Functional connectivity between prefrontal and parietal cortex drives visuo-spatial attention shifts. *Neuropsychologia, 99*(December 2016), 81–91. https://doi.org/10.1016/j.neuropsychologia.2017.02.024

Heinen, K., Ruff, C. C., Bjoertomt, O., Schenkluhn, B., Bestmann, S., Blankenburg, F., et al. (2011). Concurrent TMS–fMRI reveals dynamic interhemispheric influences of the right parietal cortex during exogenously cued visuospatial attention. *European Journal of Neuroscience, 33*(5), 991–1000. https://doi.org/10.1111/J.1460-9568.2010.07580.X

Hernandez-Pavon, J., San Agustín, A., Wang, M. C., Veniero, D., & Pons, J. L. (2023). Can we manipulate brain connectivity? A systematic review of cortico-cortical paired associative stimulation effects. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2023.06.016

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron, 53*(6), 905–918. https://doi.org/10.1016/j.neuron.2007.02.013

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: A review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia, 38*(1), 93–110. https://doi.org/10.1016/S0028-3932(99)00045-7

Jin, Y., & Hilgetag, C. C. (2008). Perturbation of visuospatial attention by high-frequency offline rTMS. *Experimental Brain Research, 189*(1), 121–128. https://doi.org/10.1007/s00221-008-1449-y

Karnath, H. O., & Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia, 50*(6), 1010–1017. https://doi.org/10.1016/j.neuropsychologia.2011.06.027

Kocsis, K., Csete, G., Erdei, Z., Király, A., Szabó, N., Vécsei, L., et al. (2019). Lateralisation of the white matter microstructure associated with the hemispheric spatial attention dominance. *Plos One, 14*(4), 1–15. https://doi.org/10.1371/journal.pone.0216032

Kohl, S., Hannah, R., Rocchi, L., Nord, C. L., Rothwell, J., & Voon, V. (2019). Cortical paired associative stimulation influences response inhibition: Cortico-cortical and cortico-subcortical networks. *Biological Psychiatry, 85*(4), 355–363. https://doi.org/10.1016/j.biopsych.2018.03.009

Lunven, M., De Schotten, M. T., Bourlon, C., Duret, C., Migliaccio, R., Rode, G., et al. (2015). White matter lesional predictors of chronic visual neglect: A longitudinal study. *Brain, 138*(3), 746–760. https://doi.org/10.1093/BRAIN/AWU389

Makris, N., Kennedy, D. N., McInerney, S., Sorensen, A. G., Wang, R., Caviness, V. S., et al. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: A quantitative, in vivo, DT-MRI study. *Cerebral Cortex, 15*(6), 854–869. https://doi.org/10.1093/cercor/bhh186

Mengotti, P., Käsbauer, A. S., Fink, G. R., & Vossel, S. (2020). Lateralization, functional specialization, and dysfunction of attentional networks. *Cortex, 132*, 206–222. https://doi.org/10.1016/j.cortex.2020.08.022

Mengotti, P., Käsbauer, A.-S., Fink, G. R., & Vossel, S. (2022). Combined TMS-fMRI reveals behavior-dependent network effects of right temporoparietal junction neurostimulation in an attentional belief updating task. *Cerebral Cortex, 32*(21), 4698–4714. https://doi.org/10.1093/cercor/bhab511

Mesulam, M. M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology, 10*(4), 309–325. https://doi.org/10.1002/ANA.410100402

Mitchell, A. G., Harris, J. M., Benstock, S. E., & Ales, J. M. (2020). The reliability of pseudoneglect is task dependent. *Neuropsychologia, 148*, 107618. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2020.107618

Momi, D., Neri, F., Coiro, G., Smeralda, C., Veniero, D., Sprugnoli, G., et al. (2019). Cognitive enhancement via network-targeted cortico-cortical associative brain stimulation. *Cerebral Cortex*, 1–12. https://doi.org/10.1093/cercor/bhz182

Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain, 126*(9), 1986–1997. https://doi.org/10.1093/brain/awg200

Nord, C. L., Popa, T., Smith, E., Hannah, R., Doñamayor, N., Weidacker, K., et al. (2019). The effect of frontoparietal paired associative stimulation on decision-making and working memory. *Cortex, 117*, 266–276. https://doi.org/10.1016/j.cortex.2019.03.015

Nyffeler, T., Cazzoli, D., Wurtz, P., Lüthi, M., Von Wartburg, R., Chaves, S., et al. (2008). Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. *European Journal of Neuroscience, 27*(7), 1809–1813. https://doi.org/10.1111/j.1460-9568.2008.06154.x

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Oliveri, M., Bisiach, E., & Brighina, F. (2001). rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology, 0–3*. https://doi.org/10.1212/WNL.57.7.1338

Parlatini, V., Radua, J., Dell'Acqua, F., Leslie, A., Simmons, A., Murphy, D. G., et al. (2017). Functional segregation and integration within fronto-parietal networks. *Neuroimage, 146*(September 2016), 367–375. https://doi.org/10.1016/j.neuroimage.2016.08.031

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology, 10*(2), 232–237. https://doi.org/10.1016/S0959-4388(00)00081-7

Pisella, L., & Mattingley, J. B. (2004). The contribution of spatial remapping impairments to unilateral visual neglect. *Neuroscience and Biobehavioral Reviews, 28*(2), 181–200. https://doi.org/10.1016/j.neubiorev.2004.03.003

Ricci, R., Salatino, A., Li, X., Funk, A. P., Logan, S. L., Mu, Q., et al. (2012). Imaging the neural mechanisms of TMS neglect-like bias in healthy volunteers with the interleaved TMS/fMRI technique: Preliminary evidence. *Frontiers in Human Neuroscience, 6*(NOVEMBER 2012), 1–13. https://doi.org/10.3389/fnhum.2012.00326

Rizzo, V., Siebner, H. S., Morgante, F., Mastroeni, C., Girlanda, P., & Quartarone, A. (2009). Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian mechanism. *Cerebral Cortex*, (19), 907–915. https://doi.org/10.1093/cercor/bhn144

Romei, V., Chiappini, E., Hibbard, P. B., & Avenanti, A. (2016). Empowering reentrant projections from V5 to V1 boosts sensitivity to motion. *Current Biology, 26*(16), 2155–2160. https://doi.org/10.1016/j.cub.2016.06.009

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., et al. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology, 132*(1), 269–306. https://doi.org/10.1016/J.CLINPH.2020.10.003

Ruff, C. C., Bestmann, S., Blankenburg, F., Bjoertomt, O., Josephs, O., Weiskopf, N., et al. (2008). Distinct causal influences of parietal versus frontal areas on human visual cortex: Evidence from concurrent TMS-fMRI. *Cerebral Cortex, 18*(4), 817–827. https://doi.org/10.1093/cercor/bhm128

Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J. D., et al. (2006). Concurrent TMS-fMRI and Psychophysics reveal frontal influences on human retinotopic visual cortex. *Current Biology, 16*(15), 1479–1488. https://doi.org/10.1016/J.CUB.2006.06.057

Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Weiskopf, N., & Driver, J. (2009a). Hemispheric differences in frontal and parietal influences on human occipital cortex: Direct confirmation with concurrent TMS-fMRI. *Journal of Cognitive Neuroscience, 21*(6), 1146–1161. https://doi.org/10.1162/jocn.2009.21097

Ruff, C. C., Driver, J., & Bestmann, S. (2009b). Combining TMS and fMRI: From "virtual lesions" to functional-network accounts of cognition. *Cortex, 45*(9), 1043–1049. https://doi.org/10.1016/j.cortex.2008.10.012

Sack, A. T., Kohler, A., Bestmann, S., Linden, D. E. J., Dechent, P., Goebel, R., et al. (2007). Imaging the brain activity changes underlying impaired visuospatial judgments: Simultaneous fMRI, TMS, and behavioral studies. *Cerebral Cortex, 17*(12), 2841–2852. https://doi.org/10.1093/cercor/bhm013

Salatino, A., Chillemi, G., Gontero, F., Poncini, M., Pyasik, M., Berti, A., et al. (2019). Transcranial magnetic stimulation of posterior parietal cortex modulates line-length estimation but not illusory depth perception. *Frontiers in Psychology, 10*(MAY), 1–8. https://doi.org/10.3389/fpsyg.2019.01169

Salatino, A., Poncini, M., George, M. S., & Ricci, R. (2014). Hunting for right and left parietal hot spots using single-pulse TMS: Modulation of visuospatial perception during line bisection judgment in the healthy brain. *Frontiers in Psychology, 5*(OCT), 1–7. https://doi.org/10.3389/fpsyg.2014.01238

Sale, M. V., Ridding, M. C., & Nordstrom, M.a. (2007). Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. *Experimental Brain Research, 181*(4), 615–626. https://doi.org/10.1007/s00221-007-0960-x

Salvato, G., Peviani, V., Scarpa, P., Francione, S., Castana, L., Gallace, A., et al. (2021). Investigating visuo-spatial neglect and visual extinction during intracranial electrical stimulations: The role of the right inferior parietal cortex. *Neuropsychologia, 162*(August), Article 108049. https://doi.org/10.1016/j.neuropsychologia.2021.108049

Santarnecchi, E., Momi, D., Sprugnoli, G., Neri, F., Pascual-Leone, A., Rossi, A., et al. (2018). Modulation of network-to-network connectivity via spike-timing-dependent noninvasive brain stimulation. *Human Brain Mapping, 39*(12), 4870–4883. https://doi.org/10.1002/hbm.24329

Savazzi, S., Posteraro, L., Veronesi, G., & Mancini, F. (2007). Rightward and leftward bisection biases in spatial neglect: Two sides of the same coin? *Brain, 130*(8), 2070–2084. https://doi.org/10.1093/brain/awm143

Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2005). Striate cortex (V1) activity gates awareness of motion. *Nature Neuroscience, 8*(2), 143–144. https://doi.org/10.1038/nn1379

Silvanto, J., Lavie, N., & Walsh, V. (2006). Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *Journal of Neurophysiology, 96*(2), 941–945. https://doi.org/10.1152/jn.00015.2006

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain: a Journal of Neurology, 123*, 572–584. https://doi.org/10.1093/brain/123.3.572

Suppa, A., Li Voti, P., Rocchi, L., Papazachariadis, O., & Berardelli, A. (2015). Early visuomotor integration processes induce LTP/LTD-like plasticity in the human motor cortex. *Cerebral Cortex, 25*(3), 703–712. https://doi.org/10.1093/cercor/bht264

Suppa, A., Quartarone, A., Siebner, H., Chen, R., Di Lazzaro, V., Del Giudice, P., et al. (2017). The associative brain at work: Evidence from paired associative stimulation studies in humans. *Clinical Neurophysiology, 128*(11), 2140–2164. https://doi.org/10.1016/j.clinph.2017.08.003

Szczepanski, S. M., & Kastner, S. (2013). Shifting attentional priorities: Control of spatial attention through hemispheric competition. *Annals of Internal Medicine, 158*(6), 5411–5421. https://doi.org/10.1523/JNEUROSCI.4089-12.2013

Taylor, P. C. J., Nobre, A. C., & Rushworth, M. F. S. (2007). FEF TMS affects visual cortical activity. *Cerebral Cortex, 17*(2), 391–399. https://doi.org/10.1093/CERCOR/BHJ156

Thiebaut De Schotten, M., Tomaiuolo, F., Aiello, M., Merola, S., Silvetti, M., Lecce, F., et al. (2014). Damage to white matter pathways in subacute and chronic spatial neglect: A group study and 2 single-case studies with complete virtual "in vivo" tractography dissection. *Cerebral Cortex, 24*(3), 691–706. https://doi.org/10.1093/cercor/bhs351

Turrini, S., Bevacqua, N., Cataneo, A., Chiappini, E., Fiori, F., Battaglia, S., et al. (2023). Neurophysiological markers of premotor – motor network plasticity predict motor performance in young and older adults. *Biomedicines, 11*(5), 1464. https://doi.org/10.3390/biomedicines11051464

Vallar, G., & Calzolari, E. (2018). Unilateral spatial neglect after posterior parietal damage. *Handbook of Clinical Neurology, 151*, 287–312. https://doi.org/10.1016/B978-0-444-63622-5.00014-0

Varnava, A., Dervinis, M., & Chambers, C. D. (2013). The predictive nature of pseudoneglect for visual neglect: Evidence from parietal theta burst stimulation. *Plos One, 8*(6), 1–11. https://doi.org/10.1371/journal.pone.0065851

Veniero, D., Ponzo, V., & Koch, G. (2013). Paired associative stimulation enforces the communication between interconnected areas. *Journal of Neuroscience, 33*(34), 13773–13783. https://doi.org/10.1523/JNEUROSCI.1777-13.2013

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *Neuroscientist, 20*(2), 150–159. https://doi.org/10.1177/1073858413494269

Vossel, S., Weidner, R., Driver, J., Friston, K. J., & Fink, G. R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *Journal of Neuroscience, 32*(31), 10637–10648. https://doi.org/10.1523/JNEUROSCI.0414-12.2012

Wang, X., Pathak, S., Stefaneanu, L., Yeh, F. C., Li, S., & Fernandez-Miranda, J. C. (2016). Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. *Brain Structure & Function, 221*(4), 2075–2092. https://doi.org/10.1007/S00429-015-1028-5

Wolters, A., Sandbrink, F., Schlottmann, A., Kunesch, E., Stefan, K., Cohen, L. G., et al. (2003). A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *Journal of Neurophysiology, 89*(5), 2339–2345. https://doi.org/10.1152/jn.00900.2002