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ORIGINAL RESEARCH

A lateralized top-down network for visuospatial attention and neglect

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Abstract The lateralization of visuospatial attention has been well investigated and demonstrated to be primarily resulting from unbalanced interaction between interhemispheric fronto-parietal networks in previous studies. Many recent studies of top-down attention have reported the neural signatures of its effects within visual cortex and identified its causal basis. However, the relationship between top-down networks and asymmetric visuospatial attention has not been well studied. In the current study, we aimed to explore the relationship between top-down connectivity and asymmetric visuospatial ability by using repetitive transcranial magnetic stimulation (rTMS) and resting-state functional connectivity (RSFC) analyses. We used rTMS and RSFC to model the virtual lesion to assess the behavioral performances in visuospatial attention shifting and to identify the behavior-related top-down functional connectivities, respectively. Furthermore, we also investigated the top-down connectivity in neglect patients to validate the RSFC findings. RSFC analyses in healthy subjects and neglect patients consistently revealed that asymmetric visuospatial ability and visuospatial neglect were closely related to the bias of top-down functional connectivity between posterior superior parietal lobule (SPL) and V1. Our findings indicate that stronger top-down connectivity has stronger dominance on its corresponding visual field. We argue that an asymmetric top-down network may represent a possible neurophysiological substrate for the ongoing functional asymmetry of visuospatial attention, and its interhemispheric unbalanced interaction could contribute to the clinical manifestations of visuospatial neglect.

Keywords Visuospatial attention · Neglect · Superior parietal lobule · Visual cortex · TMS

Introduction

The lateralization of visuospatial attention was established with studies in visuospatial neglect which is a complex syndrome following stroke and is characterized by a failure to attend and respond to contralesional stimuli (Vallar et al. 2003; Corbetta and Shulman 2011). Emerging evidence from human neuroimaging and lesion mapping has revealed that visuospatial neglect is primarily caused by disruption of fronto-parietal network (Corbetta et al. 2005; He et al. 2007; Thiebaut de Schotten et al. 2005; Ptak and Schnider 2010; Verdon et al. 2010). The imbalanced interaction of interhemispheric fronto-parietal network is also related to lateralization of visuospatial attention in healthy subjects (Thiebaut de Schotten et al. 2011; Koch et al. 2011; Bartolomeo et al. 2012). Recently, task-dependent functional magnetic resonance imaging (fMRI) studies in human and physiology

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studies in monkey have also found the attentional top-down effects in visual cortex (Kastner and Ungerleider 2000; Luck et al. 1997; Reynolds and Chelazzi 2004; Serences and Yantis 2006). The top-down biasing attentional signals can modulate the activity of visual cortex via feedback to the visual system to improve perception of behaviorally relevant stimuli (Corbetta and Shulman 2002; Gilbert and Li 2013; Hopfinger et al. 2000; Kastner et al. 1999; Miller and Cohen 2001; Moore and Armstrong 2003; Noudoost et al. 2010; Silver et al. 2007; Pessoa et al. 2003; Yantis et al. 2002; Yantis and Serences 2003). The accumulated evidence suggests that the superior parietal lobule (SPL) in the parietal cortex may provide a top-down biasing signal to the visual cortex that affects on-going processing to favor the attended location or object when it is transiently engaged during a switch event (Pessoa et al. 2003; Yantis et al. 2002; Yantis and Serences 2003). However, the relationship between the bias of top-down control and asymmetry of visuospatial attention remains unclear.

Models of visuospatial attention control were proposed mainly based on behavioral studies of patients with visuospatial hemineglect (Corbetta and Shulman 2011). In neglect patients, only right hemisphere lesions cause severe and persistent deficits (Driver and Mattingley 1998; Stone et al. 1993). Two prevalent models have been proposed to account for this hemispherical asymmetry. One is the hemispatial dominant theory which proposed that the right hemisphere directs attention to both visual fields, whereas the left hemisphere only directs attention to the right field space (Heilman and Van Den Abell 1980; Mesulam 1981). The other is the interhemispheric rivalry theory which proposed that each hemisphere directs attention toward the contralateral visual field and is balanced through reciprocal inhibition (Kinsbourne 1977, 1993). The interhemispheric competition theory has been widely demonstrated in recent studies by using transcranial magnetic stimulation (TMS) and functional MRI methods (Koch et al. 2008, 2011; Szczepanski et al. 2010). Therefore, the asymmetric visuospatial attention and visuospatial hemineglect may be resulting from the unbalanced dynamic interactions of the interhemispheric top-down networks between posterior parietal cortex and visual cortex.

In the current study, we aimed to uncover the possible neurophysiological basis of lateralization of visuospatial attention in healthy subjects and behavioral deficits in neglect by establishing the relationship between the top-down connectivities and behavioral performances using resting-state functional MRI and TMS techniques. The resting-state functional MRI predominantly reflects the spontaneous brain functional activities related to self-initiated behavior (Fox and Raichle 2007; Eickhoff and Grefkes 2011). Therefore, resting-state functional connectivity (RSFC) analyses could better characterize the intrinsic functional connectivity patterns of visuospatial function in healthy subjects and neglect patients. Additionally, TMS could temporally deactivate the brain cortex to model the virtual lesion to assess the behavioral performances in healthy subjects (Boroojerdi et al. 2000; Chen et al. 1997; Hilgetag et al. 2001). Thus, in our study, we first recorded behavioral performance during an experiment when TMS is applied in normal healthy subjects. Then, we calculated the RSFC in each subject and performed the correlation analysis to determine which top-down functional connectivities were correlated with behavioral performances. Finally, we further validated the findings in neglect patients to collectively reveal the relation between asymmetry of visuospatial attention and bias of top-down attention control.

Materials and methods

Participants

TMS experiments participants

Sixteen male, healthy, right-handed participants (mean age = 18.8 years, range: 18–21 years) were recruited via advertisement for TMS study. All the participants had never suffered from any neurological or psychiatric disease. None of the participants had previous experience with participating in TMS measurements and any contraindications for MRI scanning. All participants signed an informed consent form approved by the Local Research Ethics Committee of the University of Electronic Science and Technology of China.

Neglect patients

Twelve patients, four female, right-handed, mean age 57.83 years (SD 14.03; range 38–78 years), with right temporoparietal or inferior parietal lesion who initially demonstrated neglect participated in this study. All the patients underwent neglect tests including a line bisection test, Albert cancel test, clock drawing, and follower drawing tasks and neglect was found in the left visual field (contralesional neglect). All the patients signed an informed consent form approved by the Local Research Ethics Committee of the First Hospital of Anhui Medical University.

MRI data acquisition

TMS participants' MRI data

Before the TMS experiment, all participants were scanned using a 3.0 Tesla GE MR Scanner. For each participant, we also collected the resting-state functional images and structural T1 images. During resting-state fMRI scanning, subjects were instructed to close their eyes and lie still. Cushions were used to reduce head motion. 255 volumes of echo planar images were acquired (repetition time = 2000 ms, echo time =

30 ms; no gap; 40 axial slices, voxel size, 3.75×3.75×4 mm^3). Sagittal 3D T1-weighted images were also acquired (TR/TE = 8.16/3.18 ms; inversion time = 800 ms; FA = 7°; FOV = 256 mm×256 mm; matrix = 256×256; slice thickness = 1 mm, no gap; 188 sagittal slices).

Neglect patients' MRI data

All twelve neglect patients' resting-state fMRI data were obtained using 3.0 Tesla GE medical systems MR Scanner. During the resting-state fMRI scanning, subjects were instructed to close their eyes and lie still. Cushions were used to reduce head motion. 240 volumes of echo planar images were acquired (repetition time = 2000 ms, echo time = 30 ms; no gap; 34 axial slices, voxel size, 3.75×3.75×3.8 mm^3). Sagittal 3D T1-weighted (TR/TE = 7.012/2.876 ms; inversion time = 900 ms; FA = 8°; FOV = 256 mm×256 mm; matrix = 256×256; slice thickness = 1.2 mm, no gap; 149 sagittal slices) and T2-weighted images were also acquired to identify the location of lesion.

Resting-state fMRI data preprocessing

The preprocessing of the resting state fMRI data was carried out using SPM8 software. To allow for magnetization equilibrium, the first 10 volumes were discarded. The slice timing for the remaining images was corrected, and the images were realigned to the first volume for head motion correction. All the subjects with a maximum displacement of less than 1.5 mm and an angular motion of less than 1.5^o were used in this study. All of the fMRI images were further normalized to the Montreal Neurological Institute (MNI) EPI template and resampled to a 3 mm cubic voxel. Then, all of the functional images were smoothed using a Gaussian kernel of 6 mm full-width at half maximum (FWHM). Finally, six motion parameters, white matter, and cerebrospinal fluid signals were regressed out and filtered with a temporal band-path of 0.01~0.1Hz.

Definition of top-down networks

Previous studies have demonstrated that the top-down modulatory signal produced in posterior SPL (Kastner et al. 1999; Kastner and Ungerleider 2000). This area was also been demonstrated to primarily participate in attention shifting/switching (Mars et al. 2011; Rushworth et al. 2001; Schluppeck et al. 2006; Szczepanski et al. 2010). Therefore, in our current study, we primarily mapped the functional connectivities of top-down networks between posterior SPL and visual areas including V1, V2, V3, and V4 in both healthy subjects and neglect patients. However, because of lacking of the accurate anatomical boundary of posterior SPL, we defined the posterior SPL according to the SPL atlas constructed by connectivity-based parcellation in our previous study (Wang et al. 2015). The left and right SPL were each parcellated into five different subregions based on different anatomical connectivity patterns and the population maximum probability map were created. The most posterior subregion of the maximum probability map of SPL was used to map the top-down functional connectivity analyses and to guide localization for TMS in our current study.

Four visual areas were defined to investigate the top-down connectivity. The four visual areas included one striate cortical area (primary visual cortex: V1) and three extrastriate cortical areas (V2, V3, and V4). These visual target masks were delineated using the SPM Anatomy Toolbox by calculating the maximum probability map of each area (Eickhoff et al. 2005).

Top-down functional connections mapping in healthy subjects

Visuospatial attention task

The visuospatial attention task used in our study has been described in a previous study (Corbetta et al. 1995). The stimuli were displayed during a target-present color task trial. The participants searched the target dots defined by a conjunction of color and motion. Four square windows were used in our experiment and each window contained 10 dots (red or orange) which moved at two speeds (fast or slow). A speed and color were randomly assigned to each window and the "target" condition occurred when red dots moving at a fast speed appeared in a window; the other conditions were "non-target". When the target dots appeared, the participants were instructed to press the right hand button, and when the non-target condition appeared, the participants were instructed to press the left hand button. The duration of the dots was 500 ms and followed by a 1500 ms fixation. The CIE-xy chromaticity coordinates of the dots were: red (CIE values of x=0.73, y=0.27), orange (CIE values of x=0.49, y=0.50), background (CIE values of x=0.33, y=0.33) (Fig. 1a). The experiment was a block design containing three conditions: sham stimulus which was defined that the TMS stimulation was applied but the electricity is turned off, stimulus to the right SPL, and stimulus to the left SPL. Four blocks of stimuli were in each condition. The magnetic stimulations were synchronized with the visual stimulus, so when moving dots were presented at the computer display, the magnetic stimulation was simultaneously applied on the skull.

TMS on right and left posterior SPL

A Magstim Rapid stimulator (The Magstim Company Limited, Whitland, UK), figure-of-8, coil was used to generate the magnetic pulses in our study. The intensity

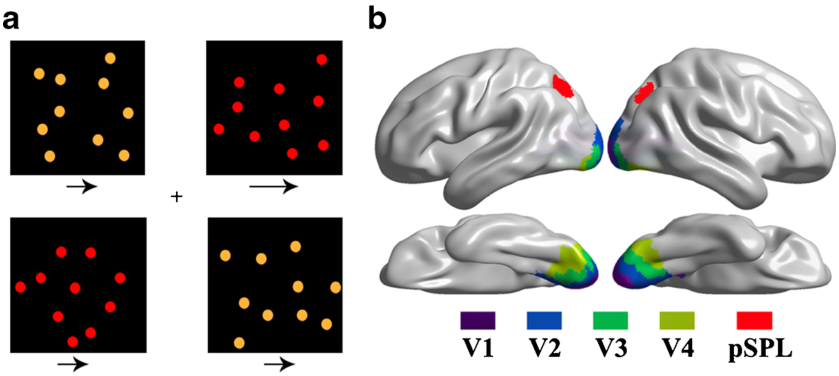

Fig. 1 The visuospatial attention shifting task and definition of the top-down networks. **a**, The visual stimuli were defined by a conjunction of color and motion. The screen was divided into four square windows, and each window contained 10 dots (*orange* or *red*) which moved at two speeds (fast or slow). The *arrows* under each window specify the two speeds at which the dots could move. The *long arrow* refers to fast speed and the *short arrow* the slow one. **b**, Posterior superior parietal lobule (SPL) was defined from the SPL atlas yielded by connectivity-based parcellation in our previous study. The target brain areas V1, V2, V3, and V4 were defined using the SPM Anatomy toolbox by calculating the maximum probability map of each area

of the magnetic stimulation was set separately for each individual at their motor threshold, as detected by a peripheral motor response, in other words a visually detectable twitch, in the contralateral hand when a stimulus was applied to the motor region. Stimulation frequency was 1 Hz which has been shown to reduce cortical excitability in the brain regions targeted by rTMS. Frameless stereotaxy was applied to identify the exact target brain area, and individual MRI-based TMS neuronavigation allowed for a precise localization of the target sites. The TMS coil was placed over the target brain area and fixed by a custom coil holder. During the TMS stimulation, we asked the participants to perform a visuospatial attention test. Before performing the TMS stimulation, we transformed the posterior SPL subregion's mask into each individual T1 space and marked the subregion as the target sites. The participants underwent two event-related TMS sessions, one on the right and the other on the left posterior SPL, separated by an interval of 1 week. The spatial attention task was executed by simultaneously applying TMS to the posterior SPL of each participant in all stimulus conditions (sham, stimulation on left posterior SPL, stimulation on right posterior SPL). The reaction time which was used to characterize the behavioral performance was recorded for further analysis.

Laterality index

We used laterality index (LI) which has been defined in the previous study to describe the asymmetry of posterior SPL in visuospatial functions and functional connections in our study (Steinmetz 1996; Tomasi and Volkow 2012). Laterality index was defined as follows. Positive LI values indicate rightward asymmetry and negative LI values indicate leftward asymmetry. Subsequently, paired two-sided t-test was performed on reaction times recorded when TMS was separately applied in left and right posterior SPL, and threshold was set at $p<0.05$ for significance.

$$\mathrm{LI} = (\mathrm{R}-\mathrm{L})/(\mathrm{R}+\mathrm{L})$$

Top-down functional connections mapping

We investigated the relationship between the top-down functional connectivities and behavioral performances of visuospatial attention in healthy subjects to explore the possible neurophysiological basis of asymmetric visuospatial attention of which the damage will cause visuospatial neglect. We calculated the functional connectivity between posterior SPL and ipsilateral each visual cortical area. We first sample the left and right posterior SPL masks and all the visual area masks to 3 mm cubic. Then, we obtained the mean time series of each area and computed the functional connections between posterior SPL and ipsilateral visual areas, respectively. Finally, Paired two-sided t-tests on top-down functional connectivity values of corresponding left and right SPL was performed, and a threshold value was set at $p<0.05$ for significance.

Correlation analyses

In order to determine which top-down functional connectivity was related to behavioral measurements, correlation analyses between laterality index of functional connection and laterality index of reaction time were performed. Results were considered to be significant at a threshold value $p<0.05$.

Top-down functional connections mapping in neglect patients

In order to validate the findings in healthy subjects in the previous part of this study, we computed functional connections between posterior SPL and ipsilateral visual cortical areas in neglect data. The functional connectivity was measured using Pearson linear correlation. First, the left and right posterior SPL masks and all the visual area masks were sampled to 3 mm cubic. Subsequently, the mean time series of each area were obtained and functional connections between posterior SPL and ipsilateral visual areas were calculated, respectively. Finally, Paired two-sided *t*-tests on top-down functional connectivity values of corresponding left and right SPL was performed, and a threshold value was set at $p<0.05$ for significance.

Results

Definition of top-down networks

The posterior SPL was defined according to our previous study which identified the SPL subregions by using anatomical connectivity-based parcellation. The most posterior SPL subregion which was demonstrated to produce the bias modulatory signals to visual system was selected for top-down functional connectivity analyses and TMS study. The MNI coordinates of left or right posterior SPL are: left posterior SPL [−20, −70, 56] and right posterior SPL [20, −71, 50]. Furthermore, four visual cortical target areas were defined using SPM Anatomy toolbox including V1, V2, V3, and V4 to map the top-down functional connectivities (Fig. 1b).

Top-down functional connectivity analyses in healthy patients

We mapped top-down functional connectivities between posterior SPL and each ipsilateral visual area (V1, V2, V3 and V4) and found right hemispheric top-down connectivities were significantly stronger than left hemispheric corresponding top-down connectivities with V1, V2, and V3 in healthy subjects (V1: $p< 0.05$; V2: $p< 0.05$; V3: $p=< 0.05$) (Fig. 2).

TMS-based behavioral test results

The reaction times were used to evaluate the lateralization of visuospatial attention using TMS method in the current study. Behavioral test results showed that the reaction times were obviously longer when the stimuli were applied in the right SPL than when they were applied in the left SPL. The paired *t-test* also revealed that significantly longer reaction times were observed when the stimuli were applied to the right SPL (0.02 ±0.01s; $p< 0.05$) (Fig. 3a).

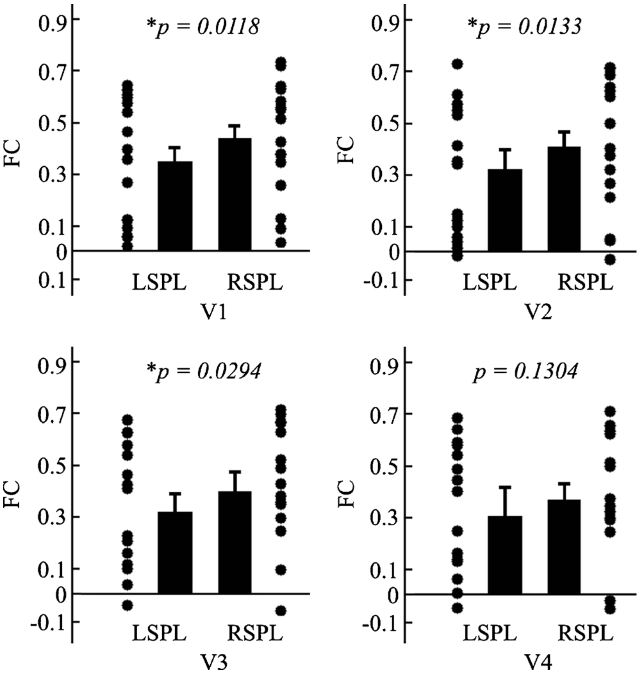

Fig. 2 The individual, mean, and standard error of mean of top-down functional connectivity between posterior superior parietal lobule (SPL) and each visual target area in healthy subjects. The top-down connectivity between posterior SPL and ipsilateral visual areas were computed and paired two-sided *t*-tests were performed. And a threshold value was set at $p<0.05$ for significance

Correlation analyses

In order to identify the behavior-related top-down connectivity between posterior SPL and ipsilateral visual areas, correlation analyses of laterality index of top-down functional connectivity and laterality index of reaction time were performed to reveal whether the asymmetrical functional connections were related to lateralization of visuospatial attention. Correlation analyses unraveled that asymmetrical functional connection between posterior SPL and V1 was significantly correlated to behavioral performances of lateralization of visuospatial attention (V1: $r=0.50$, $p< 0.05$) (Fig. 3b).

Top-down functional connectivity analyses in neglect patients

In our current study, we also investigated the changes of top-down functional connectivities in neglect patients to further validate the findings in normal subjects. The functional connectivity between posterior SPL and each ipsilateral visual area (V1, V2, V3 and V4) was separately calculated. Paired *t*-tests revealed that the contralesional top-down connectivity was stronger than ipsilesional top-down connectivity in V1 and V2 in neglect patients (V1: $p=0.03$; V2: $p< 0.05$) (Fig. 4).

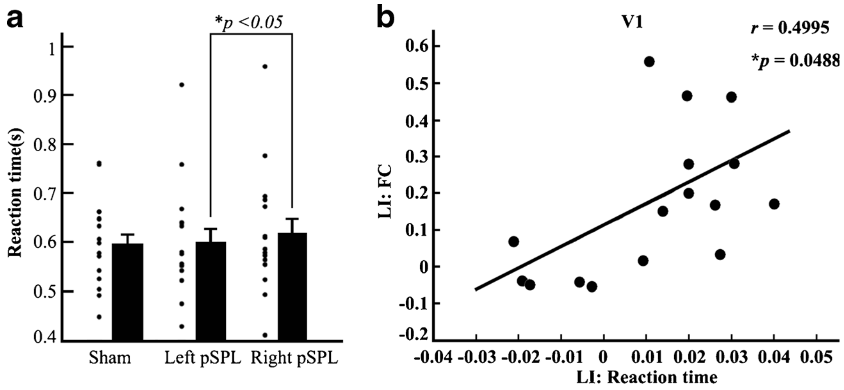

Fig. 3 TMS-based behavioral measurements and correlation analyses. A, The individual, mean, and standard error of mean of reaction time were shown in the three experiment conditions. Significant behavioral differences were found when TMS was separately applied on the left and right posterior SPL. B, Correlation analyses between laterality index (LI) of top-down connectivity between posterior SPL and V1 and LI of reaction time was performed and a threshold was set at $p<0.05$ for significance

Discussion

The goal of this study was to explore the possible neurophysiological basis of the lateralization of visuospatial attention and visuospatial neglect by establishing the relationship between the top-down functional connectivities and behavioral performances in healthy subjects and neglect patients by using RSFC analyses and TMS methods. The TMS-based behavioral tests and subsequent RSFC analyses revealed that the asymmetry of top-down functional connectivity with V1 was closely correlated with the behavioral performances of lateralization of visuospatial attention in normal subjects. Furthermore, RSFC analyses in neglect patients identified that contralesional top-down functional connectivities between posterior SPL and V1, V2 were significantly stronger than that of ipsilesional top-down functional connectivities. These findings consistently indicated that unbalanced interaction between interhemispheric top-down network of posterior SPL and V1 underlies the lateralization of visuospatial attention in healthy subjects and behavioral deficits in neglect disorder. In addition, our findings might provide the supporting evidence for top-down attention signals directly modulating the activity of V1 in the human brain.

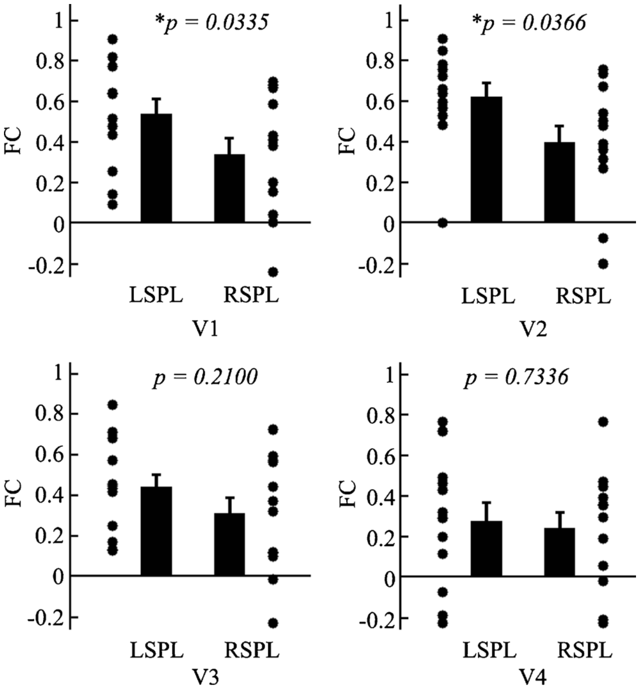

Fig. 4 The individual, mean, and standard error of mean of top-down functional connectivity in neglect patients. The top-down connectivity between posterior superior parietal lobule (SPL) and each visual target brain areas was calculated in neglect patients. The paired two-sided t-tests were performed and threshold was set at $p<0.05$ for significance

Posterior SPL has been widely demonstrated to be mainly involved in attention shifting/switching in previous studies using task-based neuroimaging approaches (Corbetta et al. 1995; Rushworth et al. 2001; Vandenberghe et al. 2001; Yantis et al. 2002; Kelley et al. 2008). During attention shifting, stronger activity in the right SPL was observed than that in the left SPL (Corbetta et al. 1993; Vandenberghe et al. 1997). However, the neural basis of the functional asymmetry has not been well investigated. Recent studies revealed that top-down feedback bias signals to visual cortex through direct cortico-cortical connections was produced by higher order cortex areas involving posterior SPL and was related to strong selection biases (Buffalo et al. 2010; Kastner and Ungerleider 2000). And this top-down bias could facilitate information processing of stimuli at attended locations or of attributes of attended stimuli (Baluch and Itti 2011; Gilbert and Li 2013; Noudoost et al. 2010; Ramalingam et al. 2013), which might imply that stronger activity in right SPL might better improve perception of behaviorally relevant stimulus in visual space. The top-down bias signal might result in lateralization of visuospatial attention. In our study, we found the top-down connectivity between posterior SPL and ipsilateral V1 was correlated with the behavioral performances in healthy subjects, which showed that the top-down bias signal was closely related to asymmetric visuospatial ability. This finding was also supported by our analyses in neglect patients. In neglect patients caused by right hemispheric lesion, the hemispheric dominance was reversed to left hemisphere. In the current study, we also found reversed top-down functional connectivities in neglect patients. The contralesional top-down functional connectivities were stronger than ipsilesional top-down functional connectivities. The cross-validation results in our study collectively demonstrated that bias of top-down connectivity underlies the behavioral deficits in neglect patients and the functional lateralization of visuospatial attention. And right or left hemispheric dominance for visuospatial attention in healthy subjects or neglect patients results from stronger top-down connectivity to control the corresponding visual field. Our findings were supported by previous low or high frequency TMS-based studies. Low frequency TMS-based studies revealed that the disruption of right posterior parietal cortex impaired visuospatial attention (Hilgetag et al. 2001; Ashbridge et al. 1997). Subsequently, Jin and Hilgetag (2008) used high frequency TMS to further demonstrate that excitation of the right posterior parietal cortex facilitated visuospatial attention processing. All these findings, together with our current study, consistently indicate that unbalanced interhemispherical interaction underlies asymmetric visuospatial ability. Recently, although Du and colleagues identified that right anterior SPL was involved in arousal and/or vigilance (Du et al. 2012), the role of posterior SPL in visuospatial attention is still unclear. A diffusion MRI based study in chronic neglect patients indicated that damaged the fibers connected the occipital cortex and SPL causing visual neglect (Lunven et al. 2015), and this finding was demonstrated in acute stroke patients with uncovered neglect (Umarova et al. 2014). Our current study using functional connectivity revealed how posterior SPL controls the lateralization of visuospatial attention and visuospatial neglect.

Whether attention modulates the activity of the primary visual cortex (V1) is controversial. Electrophysiological studies found that attention mainly modulated the activity of extrastriate visual areas and only small attentional effects found in V1 (Buffalo et al. 2010; Moore and Armstrong 2003; Moran and Desimone 1985; Motter 1993). However, emerging evidence from functional neuroimaging studies has revealed that attention could directly modulate the activity in V1 (Silver et al. 2007; Fang et al. 2008; Zhang et al. 2012; Kastner et al. 1998). The discrepancies between electrophysiological studies and functional neuroimaging studies were due to a variety of reasons (Boynton 2011). First, a long latency of attentional effects in V1 was accompanied with short stimulus presentations. Contrarily, the signal of functional MRI averaging activity changes over long intervals could easily include the late attentional effects (Buffalo et al. 2010). Second, the blood oxygen level-dependent (BOLD) signal is mainly driven by synchronized inputs that are more strongly affected by feedback than electrophysiological signals. Third, functional MRI could more easily detect the relatively small top-down influences due to the large amount of pooling associated with the hemodynamic coupling process than electrophysiological measure. Last, the discrepancies might result from differences in experimental design and interpretation of results. In our current study, we found that the most relevant top-down functional connectivity to behavioral performances is the connectivity between posterior SPL and V1, which further demonstrated that attention could directly modulate the activity of V1 to affect the perception or search efficiency of targets.

The origin of the top-down attention signals is still under debate. Some studies proposed that the top-down attention signals were produced by prefrontal cortex (PFC), especially the frontal eye field (FEF) (Moore and Armstrong 2003; Rossi et al. 2007), whereas the other studies using microstimulation, lesion, and inactivation methods showed top-down attention signals were also produced by parietal cortex (Mesulam 1981; Cutrell and Marrocco 2002; Wardak et al. 2004). A recent lesion-based study in macaque by removing the lateral PFC, including FEF and all of the lateral PFC areas and cutting the corpus callosum and anterior commissure to eliminate cross-hemisphere PFC feedback revealed that the top-down attentional effects on neuronal responses and synchrony in V4 were substantially reduced but not completely eliminated (Gregoriou et al. 2014). This finding indicated that attention top-down signals were produced by distributed brain regions. In our TMS-based study, we found that the hypoactivity of the posterior SPLs induced by using TMS will affect behavioral performance in visuospatial attention task. Our finding indicated that SPL plays a pivotal role in top-down attentional effects and suggested a possible role in origin of top-down attention signals.

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Compliance with ethical standards

Conflict of interest Jiaojian Wang, Yanghua Tian, Mengzhu Wang, Long Cao, Huawang Wu, Kai Wang, and Tianzi Jiang declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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