Frontoparietal regions may become hypoactive after intermittent theta burst stimulation over the contralateral homologous cortex in humans

Xiaofei He,1,2* Yue Lan,2* Guangqing Xu,1 Yurong Mao,1 Zhenghong Chen,1 Dongfeng Huang,1 and Zhong Pei2

1Department of Rehabilitation Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; 2Department of Rehabilitation Medicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;

Submitted 26 June 2013; accepted in final form 18 September 2013

He X, Lan Y, Xu G, Mao Y, Chen Z, Huang D, Pei Z. Frontoparietal regions may become hypoactive after intermittent theta burst stimulation over the contralateral homologous cortex in humans. J Neurophysiol 110: 2849–2856, 2013. First published September 18, 2013; doi:10.1152/jn.00369.2013.—Brain injury to the dorsal frontoparietal networks, including the posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (DLPFC), commonly cause spatial neglect. However, the interaction of these different regions in spatial attention is unclear. The aim of the present study was to investigate whether hyperexcitable neural networks can cause an abnormal interhemispheric inhibition. The Attention Network Test was used to test subjects following intermittent theta burst stimulation (iTBS) to the left or right frontoparietal networks. During the Attention Network Test task, all subjects tolerated each conditioning iTBS without any obvious iTBS-related side effects. Subjects receiving real-right-PPC iTBS showed significant enhancement in both alerting and orienting efficiency compared with those receiving either sham-right-PPC iTBS or real-left-PPC iTBS. Moreover, subjects exposed to the real-right-DLPFC iTBS exhibited significant improvement in both alerting and executive control efficiency, compared with those exposed to either the sham-right-DLPFC or real-left-DLPFC conditioning. Interestingly, compared with subjects exposed to the sham-left-DLPFC stimuli, subjects exposed to the real-left-PPC iTBS had a significant deficit in the orienting index. The present study indicates that iTBS over the contralateral homologous cortex may induce the hypoactivity of the right PPC through interhemispheric competition in spatial orienting attention.

Spatial attention; frontoparietal networks; theta burst stimulation; facilitation; competition

VISUOSPATIAL ATTENTION DEFICIT is one of the most common symptoms in patients with localized brain damage, especially those with right hemisphere lesions (Buxbaum et al. 2004; Pedersen et al. 1997; Ringman et al. 2004). Although the dorsal frontoparietal networks (FPNs), including the posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (DLPFC) regions, have been reported to participate in visuospatial attention (Appelros et al. 2002; Giesbrecht et al. 2003; Oliveri et al. 1999; Xu et al. 2010), the interaction of these different regions in visuospatial attention is unclear (Corbetta and Shulman 2011).

Visuospatial attention is generally distinguished among three relatively independent components, namely the alerting, orienting, and executive control networks (Fan et al. 2002; Posner and Petersen 1990; Wang et al. 2005). Each functional component activates distinct but overlapping areas (Fan et al. 2007, 2009). It is commonly believed that interhemispheric competing connectivity plays a key role in the efficient control of spatial attention by FPNs (Vuilleumier et al. 1996). There are several physiological indicators supporting the notion of hemispheric rivalry. For example, asymmetry of parietal interhemispheric connections between the PPC of the right hemisphere and left hemisphere has been demonstrated in healthy subjects (Koch 2011). In addition, right ventral FPN damage has been reported to cause spatial neglect, probably through affecting the normal functions of dorsal FPNs (Corbetta and Shulman 2002; Corbetta et al. 2005). Previously, our laboratory used a continuous theta burst stimulation protocol to examine the interactions among the FPNs in visuospatial attention. We found that both intrahemispheric and interhemispheric competitive inhibition in dorsal FPNs may be highly associated with the dysfunction of spatial attention (Xu et al. 2013), suggesting that hypoactivity in unilateral hemisphere lesions might evoke pathological hyperactivity in the contralateral homologous cortical regions via interhemispheric rivalry. Although the spatial neglect after unilateral hemispheric lesions was reported to lead to pathological hyperactivity of contralateral hemisphere circuits due to release from rivalry (Dambeck et al. 2006; Hilgetag et al. 2001; Sack 2009; Sack et al. 2005), it is not clear whether the hyperactivity of unilateral hemisphere can also lead to inhibition of the contralateral site. Given that intermittent theta burst stimulation (iTBS) is capable of producing a lasting increase in cortical excitability, we hypothesize that iTBS over the contralateral homologous cortex may induce the hypoactivity of the right PPC through interhemispheric competition in spatial orienting attention. The Attention Network Test (ANT) is also widely used to evaluate alerting, orienting, and executive attention. Within a single 30-min testing session, the ANT is able to examine the correlation between the three functional networks, and to produce reliable single-subject estimates of the network efficiencies (Fan et al. 2002). In the present study, we combined iTBS and the ANT paradigm to explore the different roles of FPNs and the competitive balance mechanisms during the spatial attention process.

METHODS

Participants

All protocols used in this study were approved by the Ethical Committee of the First Affiliated Hospital of Sun Yat-sen University. Sixty healthy subjects (30 men, 30 women; mean age 20.1 yr old;
range 19–23 yr old; undergraduate education: 2–4 yr, all right-handed) were recruited from Zhongshan Medical School of Sun Yat-sen University. All subjects provided written, informed consent to participate in this study. All subjects had normal or corrected-to-normal vision, and none of them had a history of previous drug abuse or psychotropic drug use, or a family history of mental illness. Exclusion criteria included history of seizures or a family history of epilepsy. Subjects were divided into two groups: a DLPFC group and a PPC group. There was no significant difference between the two groups in sex, age and education.

Experimental Design

Subjects in the experiment were tested for a total of four separate testing sessions, with an interval of 3–5 days between each session. Each session included 192-s iTBS followed by a 30-min ANT task (Fig. 1). Specifically, subjects in both the DLPFC and PPC groups received either sham or real iTBS on each hemisphere, successively, according to a random sequence. Session order by side (right or left) and type of iTBS (real or sham) were counterbalanced across subjects in the DLPFC and PPC groups. Therefore, there was one between-session factor (group of stimulus site), and two within-session factors (side and type of iTBS conditioning).

Experimental Task

Repetitive TMS. Stimulation was carried out to either right or left of the PPC (corresponding to the P3/P4 labels of the EEG system) or DLPFC (corresponding to the F3/F4 labels of the EEG system) using a magnetic stimulator (Yiruide CCY-I, Wuhan, China) with a liquid-nitrogen-cooled figure-eight coil (each loop diameter = 3.5 cm). Fixed by an unframed trestle, the coil was placed tangential to the scalp with real stimulation and vertical to the scalp with sham stimulation. Subjects laid comfortably in bed in the supine position with the handle pointing backwards, parallel to the midline, in the DLPFC group. Conversely, subjects were placed in a lateral position, with the handle pointing forwards, parallel to the midline, in the PPC group. The TBS protocol developed by Huang et al. (2005) can produce bidirectional changes in cortical excitability in healthy subjects. The continuous TBS usually induces a persistent decrease, whereas the iTBS produces a persistent increase in cortical excitability (Cárdenas-Morales et al. 2011; Mastroeni et al. 2013). The iTBS paradigm consisted of three continuous pulses delivered at a frequency of 50 Hz every 200 ms and lasted 2 s (total 10 bursts, 30 pulses) with an interval of 8 s. The stimuli intensity was set to 80% of rest motor threshold (Cazzoli et al. 2009; Wu et al. 2012). For iTBS, stimulation (total of 600 pulses) was applied for 192 s.

Participants sat comfortably in an armchair. We placed the surface recording electrode on the right abductor pollicis brevis muscle, and the reference electrode on the other side. The motor-evoked potential (MEP) recording was carefully measured during the stimulation. At resting state, the coil was positioned 4 cm left of center on the head. The stimulus intensity was initially subthreshold and then gradually increased until the right abductor pollicis brevis muscle was obviously induced. Next the coil was moved in 1-cm increments, until the optimal location that induced the greatest amplitude and shortest latency of MEP was defined. This point of maximum evoked motor response was generally located in the primary motor area. The rest motor threshold was defined as the minimal stimulation capable of inducing a MEP with amplitude greater than 50 μV peak to peak in at least 5 out of 10 trials.

Behavioral study. We used the ANT task to measure the effects of iTBS of the dorsal FPNs on reaction times (RTs) and spatial attention network efficiency (Fan et al. 2002). The ANT paradigm contained four cue conditions (none, center, double and spatial cues) and three target types (single, congruent and incongruent flankers). Throughout the entire experiment, a fixation cross was presented in the center of a black background. The cue was specified as an asterisk and was at the same location as the fixation cross in the center-cue condition. No asterisk appeared in the null-cue condition. Moreover, the asterisk was presented at 5° of vertical visual angle in the double and spatial-cue conditions. The spatial cues were always the valid-cue conditions, indicating that the target would appear at the same location. In addition, flanker stimuli consisted of one or a row of five horizontal white lines with arrowheads pointing to the left or right. A single arrow subtended 0.58° of visual angle, and the contours of adjacent arrows or lines were separated by 0.06° of visual angle. The stimuli subtended a total of 3.27°. The target was presented in one of two locations: 1.06° above or below the fixation cross. The three different target types were equally distributed in trials containing each of the different cue conditions.

Each train contained five events. A fixation cross was first presented for 400 ms at the onset of each trial, followed by a warning cue for 100 ms. Following a short fixation period of 400 ms, a target was presented alternatively either above or below the fixation cross. The target immediately disappeared after a response was recorded, but the time window for participants’ responses was no longer than 1,700 ms. Finally, the fixation cross was presented a third time to remind subjects of the next trial. Each trial persisted for 4,000 ms on average.

The ANT was carried out in a dimly lit, quiet room. Stimuli were presented using E-prime experimental software on a 17-in. Lenovo computer monitor. The participants were positioned 65 cm from the screen. They were asked to carefully identify the direction of the centrally presented flanker and to press the left button of a mouse for the left direction and the right button for the right direction as quickly and accurately as possible. It took ~30 min to finish four blocks of 312 trains, including one preliminary block of 24 trials (subjects received feedback about accuracy of responses after each trial) and 3 formal blocks of 288 trials (no feedback given). Moreover, each formal block contained 96 test trials (4 cue conditions × 2 target locations × 2 target directions × 3 flanker types, with 2 repetitions).

Subjects were given a rest for 3–5 min between each formal block. Trial with incorrect response, or with RTs longer than 1,500 ms (including missing responses) or shorter than 200 ms was deleted (Fan et al. 2009). Moreover, data from subjects with >20% total errors in any or all sessions were excluded from analysis (Rueda et al. 2005). Values for attention network efficiency were calculated from the raw RT data, as previously described (Fan et al. 2002). RTs were computed individually for the four cue × three target conditions. The average of these 12 conditions was the individual mean RT. The operational definitions of the effects of the three attention networks based on RT were as follows: alerting efficiency = RT (none cue) − RT (double cue) (neutral and congruent flanker types only); orienting efficiency = RT (central cue) − RT (spatial cue) (neutral and congruent flanker types only); executive control efficiency = RT (target incongruent) − RT (target congruent) (all cue conditions). Additionally, the efficiency ratio of each attention component is equal.
Table 1. Mean behavioral ratings in the left and right PPC

<table>
<thead>
<tr>
<th></th>
<th>Pre-iTBS</th>
<th>Sham-iTBS</th>
<th>Real-iTBS Over Left PPC</th>
<th>Real-iTBS Over Right PPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>Comfort: discomfort–comfort</td>
<td>0.43</td>
<td>1.63</td>
<td>0.7</td>
<td>1.42</td>
</tr>
<tr>
<td>Fatigue: fatigued–rested</td>
<td>0.83</td>
<td>1.599</td>
<td>0.73</td>
<td>1.552</td>
</tr>
<tr>
<td>Anxiety: anxious–calm</td>
<td>0.33</td>
<td>1.47</td>
<td>0.3</td>
<td>1.489</td>
</tr>
<tr>
<td>Mood: Sad–happy</td>
<td>0.93</td>
<td>1.413</td>
<td>0.97</td>
<td>1.299</td>
</tr>
<tr>
<td>Irritation: irritated–soothed</td>
<td>1.1</td>
<td>1.348</td>
<td>0.6</td>
<td>1.429</td>
</tr>
<tr>
<td>Pain: feel pain–do not feel pain</td>
<td>0.63</td>
<td>1.299</td>
<td>0.57</td>
<td>1.501</td>
</tr>
</tbody>
</table>

iTBS, intermittent theta burst stimulation; PPC, posterior parietal cortex.

Table 2. Mean behavioral ratings in the left and right DLPFC

<table>
<thead>
<tr>
<th></th>
<th>Pre-iTBS</th>
<th>Sham-iTBS</th>
<th>Real-iTBS Over Left DLPFC</th>
<th>Real-iTBS Over Right DLPFC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>Comfort: discomfort–comfort</td>
<td>0.83</td>
<td>1.416</td>
<td>0.7</td>
<td>1.579</td>
</tr>
<tr>
<td>Fatigue: fatigued–rested</td>
<td>0.93</td>
<td>1.311</td>
<td>0.53</td>
<td>1.408</td>
</tr>
<tr>
<td>Anxiety: anxious–calm</td>
<td>0.63</td>
<td>1.351</td>
<td>0.43</td>
<td>1.478</td>
</tr>
<tr>
<td>Mood: Sad–happy</td>
<td>1.13</td>
<td>1.252</td>
<td>0.63</td>
<td>1.45</td>
</tr>
<tr>
<td>Irritation: irritated–soothed</td>
<td>0.7</td>
<td>1.264</td>
<td>0.6</td>
<td>1.453</td>
</tr>
<tr>
<td>Pain: feel pain–do not feel pain</td>
<td>0.7</td>
<td>1.343</td>
<td>0.47</td>
<td>1.383</td>
</tr>
</tbody>
</table>

DLPFC, dorsolateral prefrontal cortex.

**RESULTS**

All subjects tolerated iTBS conditioning without side effects and performed the ANT task well.

**Neurobehavioral Results**

To eliminate the potential behavioral changes on the results induced by the iTBS delivery over PPC or DLPFC, behaviors including comfort, fatigue, anxiety, mood, irritation and pain were evaluated using a 7-point Likert scale. All subjects completed all iTBS condition trials. There were no significant differences in behavioral ratings among different conditions, both in the PPC group (Table 1) and in the DLPFC group (Table 2).

Comparison of the RT Under Different Cue Stimuli

A 2 × 2 × 4 × 2 mixed-model ANOVA was performed to analyze how stimulus type, conditioning side, cue condition, and site group affected the mean RTs. The statistical analysis revealed a significant interaction among the four factors (F = 3.62, P < 0.05). Moreover, there was significant main effect of cue condition (F = 1146.44, P < 0.001).

As shown in Fig. 2, there were significant differences in the mean RTs among none-, center-, double- and spatial-cue conditions in the SL (F = 210.11, P < 0.001), SR (F = 138.49, P < 0.001), RL (F = 85.98, P < 0.001) and RR (F = 226.46, P < 0.001) iTBS to PPC studies. The results were similar for the SL (F = 172.5, P < 0.001), SR (F = 124.87, P < 0.001), RL (F = 99.23, P < 0.001) and RR (F = 176.69, P < 0.001) iTBS to DLPFC studies. However, there were no significant interactions in the mean RTs under none- (F = 0.03, P = 0.86), center- (F = 0.08, P = 0.78), double- (F = 0.08, P =
0.78), and spatial-cue conditions ($F = 0.87, P = 0.36$) among stimuli type, and side and group factors. Furthermore, there was no significant main effect of either type of iTBS (none cue $F = 0.25, P = 0.61$; center cue $F = 0.36, P = 0.55$; double cue $F = 1.61, P = 0.21$; spatial cue $F = 0.28, P = 0.6$) or group (none cue $F = 0.51, P = 0.48$; center cue $F = 0.01, P = 0.91$; double cue $F = 0.01, P = 0.93$; spatial cue $F = 1.01, P = 0.32$). However, the side of iTBS had a significant main effect during none-cue condition ($F = 5.41, P < 0.05$), but no significant main effect under the center ($F = 2.35, P = 0.13$), double ($F = 1.15, P = 0.29$) and spatial-cue conditions ($F = 1.16, P = 0.29$).

Comparison of the RT Under the Various Types of Stimuli

A $2 \times 2 \times 3 \times 2$ mixed-model ANOVA was performed to analyze how stimulus type, conditioning side, flanker type, and site group affected the mean RTs. This analysis revealed no significant interaction between the four factors ($F = 2.68, P = 0.08$). Conversely, flanker type had a significant main effect ($F = 927.98, P < 0.001$).

As shown in Fig. 3, there were significant differences in the mean RTs among single, congruent and incongruent flankers types after SL ($F = 213.13, P < 0.001$), SR ($F = 255.74, P < 0.001$), RL ($F = 139.34, P < 0.001$) and RR ($F = 189.09, P < 0.001$) iTBS to the PPC. Similarly, the mean RTs were significantly different between SL ($F = 223.41, P < 0.001$), SR ($F = 303.78, P < 0.001$), RL ($F = 117.54, P < 0.001$) and RR ($F = 149.96, P < 0.001$) iTBS to the DLPFC. However, there were no significant interactions between stimuli type, and side and group factors in the mean RTs under neutral ($F = 0.09, P = 0.76$), congruent ($F = 0.78, P = 0.38$) and incongruent flanker types ($F = 0.003, P = 0.96$). Furthermore, there was no significant main effect due to type of iTBS (neutral flanker $F = 0.84, P = 0.36$; congruent flanker $F = 0.01, P = 0.96$).

![Fig. 2. Mean reaction times (in ms, with standard error) after delivery of the SL (sham left), SR (sham right), RL (real right) and RR (real right) iTBS over either PPC or DLPFC site during the ANT program with none-cue (A), center-cue (B), double-cue (C) and spatial-cue (D) conditions.](image1)

![Fig. 3. Mean reaction times (in ms, with standard error) after delivery of the SL, SR, RL and RR iTBS over either the PPC or DLPFC site during the ANT program with single flanker (A), congruent flanker (B) and incongruent flanker (C) types.](image2)
The efficiency of each visuospatial attention network component was analyzed using a mixed-model ANOVA with the group (DLPFC vs. PPC) as the between-subject factor, and the type (sham vs. real) and side (left vs. right) of stimulation as the within-subject factors. The statistical analysis revealed a significant interaction between these factors (F = 10.82, P < 0.01) in the orienting network, but no significant interaction in the alerting network (F = 0.05, P = 0.83) or in the executive network (F = 3.96, P = 0.05). However, there was significant interaction between the type and side of iTBS (F = 7.41, P < 0.01) in the alerting network. Furthermore, the type of iTBS significantly affected the alerting network (F = 46.8, P < 0.01) and the executive network (F = 9.06, P < 0.01), but did not have a significant main effect in the orienting network (F = 0.001, P = 0.98). In addition, the side of iTBS significantly affected the alerting network (F = 9.99, P < 0.01), but did not have a significant main effect in the orienting network (F = 1.51, P = 0.22) or the executive network (F = 0.39, P = 0.54). Similarly, there was a significant effect due to DLPFC vs. PPC group in the alerting network (F = 4.48, P < 0.05), but no significant main effect in the orienting network (F = 0.13, P = 0.72) or the executive network (F = 0.1, P = 0.76).

The results of the index calculations are presented in Fig. 4, A–C. Alerting, orienting, and executive efficiency in SL-PPC/SR-PPC/RL-PPC/RR-PPC were [means (SD)] 54(18)/53(20)/52(28)/69(27), 44(20)/40(16)/27(30)/46(21)/56(23)/47(44)/57(29) ms, respectively. In SL-DLPFC/SR-DLPFC/RL-DLPFC/RR-DLPFC, they were 47(22)/497(27)/463(23)/61(18), 42(19)/41(27)/46(21)/39(23), and 63(29)/63(22)/51(32)/40(33) ms, respectively. As shown in Fig. 4A, the efficiency was significantly improved after the RR-PPC iTBS compared with the SR-PPC iTBS (time t = 2.47, P < 0.05) in the alerting networks. Similarly, efficiency was significantly improved after the RR-DLPFC iTBS compared with the SR-DLPFC iTBS (t = 2.17, P < 0.05). Moreover, there was a significant difference between the RL iTBS and RR iTBS, both in the PPC group (t = 2.32, P < 0.05) and in the DLPFC group (t = 3.77, P < 0.01). In the orienting networks (Fig. 4B), the efficiency was significantly improved in the RR-PPC iTBS compared with the SR-PPC iTBS (t = 2.57, P < 0.05). In contrast, it was significantly impaired in the RL-PPC iTBS compared with the SL-PPC iTBS (t = 3.31, P < 0.01). However, there was no significant difference between the real DLPFC iTBS and the sham DLPFC iTBS (RL vs. SL t = 0.76, P = 0.45; RR vs. SR t = 0.32, P = 0.75). There was a significant difference between the RL-PPC iTBS and the RR-PPC iTBS (t = 4.45, P < 0.001), but no significant difference between the RL-DLPFC iTBS and the RR-DLPFC iTBS (t = 1.08, P = 0.28). In addition, the orienting effect index was significantly lower in the RL-PPC iTBS than in the RL-DLPFC iTBS (t = 2.81, P < 0.01), but significantly higher in the RR-PPC iTBS compared with the RR-DLPFC iTBS (t = 2.79, P < 0.01). Fig. 4C illustrates that the executive efficiency was significantly improved in the RR-DLPFC iTBS compared with the SR-DLPFC iTBS (t = 3.54, P < 0.01) and the RR-PPC iTBS (t = 2.16, P < 0.05). However, there was no significant difference between the real and sham iTBS to either the right PPC (t = 0.1, P = 0.94) or left PPC (t = 1.94, P = 0.06).

The Attention Network Efficiency After iTBS

The efficiency of each visuospatial attention network component was analyzed using a mixed-model ANOVA with the group (DLPFC vs. PPC) as the between-subject factor, and the type (sham vs. real) and side (left vs. right) of stimulation as the within-subject factors. The statistical analysis revealed a significant interaction between these factors, both in the orienting network (F = 12.31, P < 0.01) and in the executive network (F = 4.7, P < 0.05), but no significant interaction in the alerting network (F = 0.09, P = 0.76). However, there was significant interaction between the type and side of iTBS (F = 8.12, P < 0.01) in the alerting network. Furthermore, the type of iTBS had a significant main effect in both the alerting network (F = 7.38, P < 0.01) and the executive network (F = 6.98, P < 0.05), but not the orienting network (F = 0.00, P = 0.99). In addition, the side of iTBS had a significant main effect in the alerting network (F = 9.74, P < 0.01), but not in the orienting network (F = 1.25, P = 0.27) or the executive network (F = 0.52, P = 0.47). Similarly, stimulation group (DLPFC vs. PPC) had a significant main effect in the alerting network (F = 4.8, P < 0.05), but not in the orienting network (F = 0.54, P = 0.46) or the executive network (F = 0.02, P = 0.89).

As shown in Fig. 5, A–C, the alerting, orienting, and executive efficiency ratios (SL-PPC/SR-PPC/RL-PPC/RR-PPC/SL-DLPFC/SR-DLPFC/RL-DLPFC/RR-DLPFC) were as follows [means(SD)]: 0.107(0.037)/0.104(0.042)/0.135(0.05)/0.089(0.041)/0.093(0.044)/0.088(0.047)/0.123(0.038), 0.087(0.04)/0.076(0.033)/0.051(0.057)/0.107(0.037)/0.084(0.041)/0.082(0.059)/0.094(0.041)/0.078(0.04), and 0.123(0.043)/0.107(0.047)/

Fig. 4. Alerting (A), orienting (B), and executive efficiency (C) (in ms, with standard error) results for the SL, SR, RL and RR iTBS over either PPC or DLPFC site during the ANT program. *P < 0.05, **P < 0.01, ***P < 0.001.
The RL-DLPFC iTBS (t ratio was significantly lower in the RL-PPC iTBS compared with SR-PPC iTBS (t ratios were significantly improved in the RR-PPC iTBS compared with the RR-DLPFC iTBS (t/H11005/P = (higher in the RR-PPC iTBS compared with the RR-DLPFC iTBS.

However, there was no significant difference between the RL iTBS and RR iTBS both in the PPC group (t = 2.45, P = 0.05) and in the DLPFC group (t = 3.36, P < 0.01). In the orienting network (see Fig. 5B), the efficiency ratio was significantly improved in the RR-PPC iTBS compared with in the SR-PPC iTBS (t = 2.56, P < 0.05). In contrast, it was significantly reduced in the RL-PPC iTBS compared with the SL-PPC iTBS (t = 3.48, P < 0.01). However, there was no significant difference between the real iTBS DLPCF and the sham iTBS DLPCF (RL vs. SL, t = 0.91, P = 0.37; RR vs. SR, t = 0.35, P = 0.73). There was a significant difference between the RL-PPC iTBS and the RR-PPC iTBS (t = 4.92, P < 0.001), but no significant difference between the RL-DLPFC iTBS and the RR-PPC (t = 1.37, P = 0.18). In addition, the orienting efficiency ratio was significantly lower in the RL-PPC iTBS compared with the RL-DLPFC iTBS (t = 3.33, P < 0.01), but significantly higher in the RR-PPC iTBS compared with the RR-DLPFC iTBS (t = 2.95, P < 0.01). Fig. 5C illustrates that the efficiency ratio was significantly improved in the RR-DLPFC iTBS compared with the SR-DLPFC iTBS (t = 3.1, P < 0.01) in the executive control network. However, there was no significant difference between the real and sham iTBS to either the right PPC (t = 0.39, P = 0.7) or left PPC (t = 1.89, P = 0.06).

Right PPC and right DLPFC iTBS significantly increased the efficiency of the alerting network, but left PPC and left DLPFC iTBS did not (Fig. 6). Moreover, right PPC iTBS significantly improved, while left PPC iTBS significantly weakened the efficiency of the orienting network. Similarly, right DLPFC iTBS, but not left DLPFC, drastically increased the efficiency of the executive network.

DISCUSSION

In the present study, we found that the PPC and DLPFC areas of the right dorsal FPNs were distinctly and predominantly involved in spatial attention components. Moreover, iTBS over contralateral homologous areas significantly suppressed the function of the right dorsal FPNs, suggesting the interhemispheric competition between the visuospatial attention regions of the two hemispheres. All subjects tolerated conditioning stimuli without any obvious iTBS-related side effects, such as headache, pain, discomfort, or irritation. Thus such potential confounding factors to our findings can be ruled out.

The interhemispheric competition is a normal neurophysiological property. Therefore, spatial attention dysfunction might result from the imbalance of competitive inhibition between the homologous regions of two hemispheres (Dambeck et al. 2006; Kirton et al. 2008; Sack et al. 2005). Consistent with this idea, we previously showed that the interhemispheric competition effect is highly associated with the dysfunction of spatial attention (Xu et al. 2013). Recently, hyperactivity in the cerebral cortex was reported to be associated with the brain dysfunction in attention deficit hyperactivity disorder and epilepsy (McDonald et al. 2013; Walcott and Landau 2004; Wu et al. 2012). However, it is not clear whether the hyperactivity in one hemisphere can suppress the activity in the other hemisphere through transcallosal competition. Furthermore, it is still controversial whether the recovery of attention deficit is due to the powerful neural compensatory ability or the restoration of the interhemispheric balance (Naeser et al. 2005). The data on interhemispheric competition are largely based on a hypoactive model in healthy humans with a “virtual lesion” induced by noninvasive suppressive stimulation (Sparing et al. 2009). The facilitatory iTBS, a novel noninvasive stimulation, has been widely applied to modulate the motor cortical activity through alteration of the brain excitability. Consistent with previous studies showing that the right dorsal FPNs were preferentially associated with spatial attention in right-handed subjects (Gitelman et al. 1999; Karnath et al. 2004; Mesulam 1999; Shimozaki et al. 2006; Xu et al. 2010), we found that this right PPC iTBS significantly improved the efficiency of spatial orienting. However, contrary to the general notion that facilitating the excitability of targeted brain regions would be commonly associated with brain function enhancement, facilitation of the left PPC by iTBS significantly reduced the spatial

![Fig. 5. Alerting (A), orienting (B), and executive efficiency ratio (C) (standard error) results for the SL, SR, RL and RR iTBS over either the PPC or DLPFC site during the ANT program. *P < 0.05, ***P < 0.01, ****P < 0.001.](http://jn.physiology.org/)
orienting efficiency. This paradoxical phenomenon could be due to the competitive inhibition between two hemispheres (Kinsbourne 1994; Lomber et al. 2002; Sprague 1966). Based on the competitive theory, hyperactivity of left PPC induced by iTBS will lead to the interhemispheric imbalance between two hemispheres, which in turn results in hypactivity of the right PPC. Alternatively, the transcallosal effects of TMS may explain this paradoxical phenomenon. However, it seems unlikely that the effects were due to the distant spread of cortical excitability induced by iTBS, as the localized iTBS effects could not be matched to remote effects. By combining the inhibitory research and excitatory studies, we conclude that the transcallosal competitive balance might be a fundamental component to sustain or restore normal spatial attention. In our previous study, we found that there is interhemispheric competition between different FPN regions, not only in the orienting network, but also in the alerting and executive networks (Xu et al. 2013). However, the present study did not reveal a similar interhemispheric inhibition either in the DLPFC for the executive network or in the DLPFC/PPC for the alerting network. One possibility could be that iTBS-induced facilitation may be less efficient than continuous theta burst stimulation-induced inhibition. Alternatively, this could be due to the difference in interhemispheric connectivity between the DLPFC and the PPC. Additionally, the interpretation of the present data should be cautious, because the present study only presented indirect evidence of competitive interaction between brain regions. Therefore, further studies are needed to systematically clarify this issue.

In conclusion, deficits of spatial attention function after unilateral brain damage were not only associated with decreased cortical excitability of the affected hemisphere, but also associated with increased cortical excitability of the unaffected hemisphere (Dambeck et al. 2006; Oliveri et al. 1999). It has been reported that the improvement of function in stroke patients can be achieved either by the upregulation of excitability of the lesioned cortex, or the downregulation of the homologue area in the intact hemisphere (Hummel and Cohen 2006). Thus iTBS shows great potential as a potential treat-

ACKNOWLEDGMENTS

We thank the volunteers who participated in this study and Dr. Fan Jin. We thank Dr. Jinxin Zhang for contributions and technical support.

REFERENCES


Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, Theoret H, Fregni F, Maria-Tormos J, Kurland J, Loron KW, Pascual-


