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Adaptation to Leftward Shifting Prisms Alters Motor Interhemispheric Inhibition

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Abstract

Adaptation to rightward shifting prisms (rightward prism adaptation, RPA) ameliorates neglect symptoms in patients while adaptation to leftward shifting prisms (leftward prism adaptation, LPA) induces neglect-like behaviors in healthy subjects. It has been hypothesized that prism adaptation (PA) modulates interhemispheric balance between the parietal cortices by inhibiting the posterior parietal cortex (PPC) contralateral to the prismatic deviation, but PA's effects on interhemispheric inhibition (IHI) have not been directly investigated. Since there are hyper-excitability connections between the PPC and primary motor cortex (M1) in the left hemisphere of neglect patients, we reasoned that LPA might mimic right hemisphere lesions by reducing parietal IHI, hyper-exciting the left PPC and PPC-M1 connections, and in turn altering IHI at the motor level. Namely, we hypothesized that LPA would increase IHI from the left to the right M1. We examined changes in left-to-right and right-to-left IHI between the 2 M1s using the ipsilateral silent period (iSP) (Meyer et al. 1995) before and after either LPA or RPA. The iSP was significantly longer after LPA but only from left-to-right and it did not change at all after RPA. This is the first physiological demonstration that LPA alters IHI in the healthy brain.

Key words: ipsilateral silent period, prism adaptation, TMS, visuospatial neglect

Introduction

Visuospatial neglect manifests as a failure to attend, respond, or orient to stimuli in the contralesional hemispace and is most common after right hemisphere (RH) lesions (Vallar 1993). Prism adaptation (PA) is both a promising rehabilitation technique for this complex, multicomponent syndrome, and a research tool for investigating the mechanisms underlying neglect (Luauté et al. 2006; Redding and Wallace 2006; for reviews). Indeed, PA can ameliorate neglect symptoms when vision is shifted rightward (rightward prism adaptation, RPA) (Rossetti et al. 1998;

Farnè et al. 2002; Frassinetti et al. 2002; Pisella et al. 2002; Serino et al. 2006) and induce neglect-like behavior in healthy subjects when vision is shifted leftward (leftward prism adaptation, LPA) (Michel et al. 2003; Schintu et al. 2014).

Pisella et al. (2006; see also Striemer and Danckert 2010) have proposed that PA relies on the integrity of the cerebellum (Weiner et al. 1983; Pisella et al. 2005) and affects cognition by first inhibiting the posterior parietal cortex (PPC) contralateral to the prismatic deviation and, in turn, modulating interhemispheric balance. Converging support for this claim, albeit

indirect, comes from functional neuroimaging and electroencephalography studies showing bilateral changes in PPC functional activity after PA (Saj et al. 2013; Crottaz-Herbette et al. 2014; Martín-Arévalo et al. 2016).

Interhemispheric balance, or rather imbalance, has also been implicated in neglect following RH damage. Kinsbourne's theory of Hemispheric Rivalry (1977) postulates that each hemisphere contains a spatial attention processor for the opposite half of space but that there is "an imbalance in lateral orienting tendencies" (1977, p. 46) making these processors asymmetric such that the left hemisphere (LH) exerts a stronger rightward orienting tendency (1973, 1987). The theory posits that "opposing directional turning tendencies are in mutually inhibitory competition" (1977, p. 71) or "reciprocal inhibition" (1987, p. 76). As such, unilateral stroke in either hemisphere will weaken orienting to contralateral space and release the other hemisphere from interhemispheric inhibition (IHI). The consequences of RH stroke will be more severe because the initially weaker orienting to leftward space will not only be further weakened, but also because orienting to rightward space will be strengthened due to the release of the LH from inhibition (Kinsbourne 1970, 1977, 1987).

The Hemispheric Rivalry theory is one of the main theories in the neglect literature, and it is supported by data showing that recovery of neglect correlates with restoration of interhemispheric balance between the 2 PPCs (Corbetta et al. 2005; He et al. 2007), and more specifically with inhibition of the intact LH (Oliveri et al. 2001; Brighina et al. 2003; Nyffeler et al. 2009; Cazzoli et al. 2012; Salatino et al. 2014). Further support comes from the observation that neglect patients have hyper-excitability connections between the left PPC and left primary motor cortex (M1) (Koch et al. 2008) and that improvements observed after RPA are even greater when RPA is combined with excitation of the right (damaged) PPC by anodal transcranial direct current stimulation (tDCS) (Lädavas et al. 2015).

The Hemispheric Rivalry theory can be summarized by 2 main ideas: 1) hemispheric asymmetry for attention and 2) reciprocal inhibition between hemispheres. One implicit assumption of this theory (e.g., see Szczepanski and Kastner 2013) is that this reciprocal inhibition is of equal strength. Recent evidence suggests, however, that IHI between the parietal cortices is asymmetric. Using a triple pulse transcranial magnetic stimulation (TMS) paradigm, Koch et al. (2011) found that a single TMS pulse on the right PPC inhibited parietal-to-motor connections in the LH, but not the reverse. In light of this result we suggest that some phenomena explained by Hemispheric Rivalry in terms of asymmetries in attentional orienting e.g., alterations in visuospatial biases in healthy subjects by LPA but not RPA (Colent et al. 2000; Michel et al. 2003; Schintu et al. 2014), or by inhibition of the right (Fierro et al. 2000; Bjoertomt et al. 2002; Nyffeler et al. 2008; Giglia et al. 2011) but not the left PPC (Fierro et al. 2000; but see Szczepanski and Kastner 2013), or even the predominance of neglect after RH lesion (Jacobs et al. 2012; for a review), might also be partially explained by asymmetric IHI between the parietal cortices.

Here, we investigated whether PA affects IHI by examining changes in left-to-right and right-to-left IHI at the motor level using the ipsilateral silent period (iSP; Meyer et al. 1995, see Materials and Methods for more details). Studies in patients with abnormalities of the corpus callosum (Meyer et al. 1995, 1998; Schmierer et al. 2000; Wolters et al. 2004; Wittstock et al. 2007) suggest that the iSP results from activation of interhemispheric transcallosal inhibitory connections between the motor cortices (Meyer et al. 1998; Chen et al. 2003; Daskalakis et al. 2003; Giovannelli et al. 2009). We predicted that LPA—which induces neglect-like behaviors in the healthy brain—would

mimic the effect of RH lesions by inhibiting the right PPC. Then, via the reduction of right-to-left parietal IHI it would increase left PPC excitability. This, in turn, would increase the excitability of left PPC-M1 connections (Karabanov et al. 2012; Chao et al. 2013)—similar to what has been observed in neglect patients (Koch et al. 2008)—and it would consequently increase IHI from left-to-right M1 (see Fig. 1). In contrast, given that RPA would inhibit the left PPC, which according to Koch et al. (2011) does not inhibit its homolog, we predicted no subsequent increase of right PPC-M1 connectivity and thus no change in IHI between the 2 M1s after RPA. To test our predictions, we adapted healthy subjects to either LPA or RPA and recorded the left-to-right and right-to-left iSP before and after PA.

Materials and Methods

The iSP (Meyer et al. 1995, 1998) is the brief interruption of tonic voluntary muscle activity following stimulation of the M1 ipsilateral to the contracting muscle. It is assumed to reflect the function of transcallosal fibers that mediate an inhibitory effect from the stimulated M1 to the nonstimulated, voluntarily active, M1 in the opposite hemisphere (Chen et al. 2003; Daskalakis et al. 2003; Giovannelli et al. 2009). This assumption is based upon studies in patients with callosal lesions (Meyer et al. 1995, 1998) and neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, corticobasal degeneration or progressive supranuclear palsy (Schmierer et al. 2000; Wolters et al. 2004; Wittstock et al. 2007) all of which show a delayed or absent iSP, indicating that the iSP reflects interhemispheric cortico-cortical inhibitory mechanisms mediated by transcallosal fibers.

Figure 1. Figure displays hypothesized pathways of action of PA. "Red arrows" represent interhemispheric inhibitory connections both at baseline (left panel) and after PA (middle and right panels). "Black arrows" represent the action of PA as proposed by Pisella et al. (2006): PA (both LPA and RPA) critically depends on the cerebellum and exerts its subsequent after-effects by initially inhibiting the PPC contralateral to the prism deviation. The mechanism of action of LPA (middle panel) would be as follows: LPA would mimic the effect of RH lesions by reducing right-to-left parietal IHI (Koch et al. 2011) and increasing left PPC excitability (Kinsbourne 1977). Given the functional connections between PPC-M1 (Karabanov et al. 2012; Chao et al. 2013), their hyperexcitability in the LH of neglect patients (Koch et al. 2008), and the critical fact that anodal tDCS over PPC modifies intrahemispheric circuits within M1 (Rivera-Urbina et al. 2015), LPA would increase excitatory intrahemispheric connections in the LH ("white arrow") and subsequently increase IHI from left-to-right at the motor level (M1). We predict no change from right-to-left M1 because changes in IHI in one direction can occur without modifying the reverse (Murase et al. 2004; Stinear et al. 2015). In contrast, because RPA (right panel) inhibits the left PPC (black arrow), based on the recent finding by Koch et al. (2011) that left PPC does not seem to inhibit its homolog, we predicted no subsequent change in right PPC excitability and thus no change of IHI between the 2 M1s after RPA. Note that we did not predict a direct action of PA on the PPC-M1 contralateral to the prism deviation via a reduction of intrahemispheric PPC-M1 connectivity because cathodal tDCS over PPC has been shown not to alter intracortical motor circuits within the same hemisphere as measured by short-interval intracortical inhibition or facilitation (SICI or ICF) (Rivera-Urbina et al. 2015).

Participants

A total of 24 healthy volunteers (fourteen females, mean age = 21.0 years, standard deviation [SD] = 2.1) participated in the study; 12 participants per PA group (LPA—6 females, mean age = 21.0 years, SD = 2.1; RPA—8 females, mean age = 21.1 years, SD = 2.2). All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). They were undergraduate students, naive to the purpose of the experiment, had normal or corrected-to-normal vision, gave written informed consent and were paid for their participation. None of the participants had a history of neurological or psychiatric diseases. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (last update: Seoul, 2008).

General Procedure

The experiment consisted of 2 iSP measurement sessions, one before and one after a PA procedure; and in each session, iSP was measured from left-to-right and right-to-left with the order counterbalanced across participants. Half of the subjects were adapted using LPA and half using RPA. Throughout the experiment, participants were comfortably seated on an armchair and their head was positioned on a neck-rest during the iSP measurements and on a chin-rest during the PA procedure.

Prism Adaptation

Participants were adapted to prisms that deviated their vision by 15° (left or right) using a procedure, stimuli, and material that conformed to well-established protocols running in our laboratory (see e.g., Schintu et al. 2014). Participants were seated with their head positioned on a chin-rest at a distance of 57 cm in front of a white horizontal board on which 3 target dots (subtending 0.5° of visual angle) were positioned at 0°, -10°, and +10° from their body midline. All participants used their right index finger during the PA procedure.

At the start of the PA procedure, participants placed their right index finger on the starting position—just in front of their chest. Participants could not see their hand when it was in the starting position or during the first third of the pointing movement. First, they made 10 pointing movements to a position straight-ahead of their body's midline with their eyes closed to avoid visual feedback regarding their movements. They were told to look at the central target (0°), close their eyes, point to the target while keeping the eyes closed, and then return their hand to the starting position. The average of these 10 pointing movements gave the open-loop pointing measurement. During adaptation, participants were fitted with prism goggles that deviated their visual field by 15° either leftward (LPA group) or rightward (RPA group).

While wearing the goggles, participants performed a total of 150 verbally instructed pointing movements toward the right (+10°) and left (-10°) targets in a pseudorandom order. They were instructed to make a ballistic movement and to correct any errors on the subsequent movement. Following the adaptation phase, the goggles were removed and open-loop pointing was tested straight after adaptation (Post 1) as well as at the end of the experiment (Post 2; i.e., around 12 min after the end of adaptation) to assess whether the sensorimotor after-effects were still present. The difference between open-loop pointing

measures before and after adaptation was used to determine the size of the after-effect.

Electromyography Recording and TMS Procedure

Electromyography (EMG) and motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) of both hands using Ag-AgCl surface electrodes (Delsys). EMG signals were collected and digitized at a sampling rate of 1984 kHz using an analog-to-digital converter (Power 1401II, Cambridge Electronics Design). TMS over M1 (LH or RH) was performed with a figure-of-eight coil (outer diameter of each wing: 90 mm). The coil was connected to a Magstim 200² magnetic monophasic stimulator (The Magstim Company) and was held tangential to the scalp at an angle of approximately 45° from the midline (Di Lazzaro et al. 1998). Participants were comfortably seated on an armchair and their head was positioned on a neck-rest.

The session began by first determining the hotspots for both FDI, defined as the optimum site that evoked the largest contralateral MEP in the relaxed muscle. This site was then used to determine resting motor threshold (rMT)—the minimum stimulus intensity to elicit MEPs >50 μ V in at least 5 out of 10 consecutive trials (Triggs et al. 1994; Chen et al. 2003; Rossini et al. 2015). Hotspot and rMT measurements were both performed in one hemisphere and then the other, with the order counterbalanced across participants. Thresholds were similar for both the LPA and RPA groups (LPA: 38.2% of maximum stimulator output (MSO); RPA: 35.1% MSO).

iSP measurements were taken at the FDI hotspot, which was recorded in a neuronavigation system (Brainsight, Rogue Research) in order to monitor the coil position throughout the experiment and to return to the same coil position after PA.

Maximal Voluntary Contraction and iSP Measurements

Prior to performing the iSP measurements, participants were instructed to produce their maximal isometric voluntary contraction (MVC) force in FDI by squeezing a small memory-foam object as hard as possible between their thumb and index finger. They performed 6 consecutive 3- to 4-s trials with a break between each trial. Visual feedback of the EMG activity in the FDI was displayed on a monitor and MVC was calculated as the average of the maximum integrated EMG value from each of the 6 trials. This procedure was repeated for both hands, with the order counterbalanced across participants. MVC values were similar for both the LPA and RPA groups (LPA: 0.9 mV; RPA: 1.1 mV). After the hotspots, thresholds and MVCs were calculated for each hemisphere and each hand, iSP measurements were performed first in one hemisphere then in the other.

Throughout the experiment, participants were required to squeeze the memory-foam object and maintain a tonic FDI contraction of between 30 and 50% of MVC. Visual feedback was provided by a screen in front of the participants, which displayed the integrated EMG signal as well as horizontal cursors indicating 30 and 50% of MVC. Once the FDI contraction level was between the 2 horizontal cursors, 20 iSPs were recorded by stimulating at 120% of rMT (Giovannelli et al. 2009; Fling et al. 2013). The intertrial interval varied randomly between 6 and 10 s and participants were told that they could relax for a few seconds after each TMS pulse. Trials on which contraction level was too high or too low were discarded off-line (these represented less than 1% of all trials). EMG activity in the hand

contralateral to the TMS was monitored to ensure that this hand remained relaxed throughout the experiment.

Data Analysis

iSP onset latency and duration were calculated using the method described previously by Garvey et al. (2001) implemented in a custom-made MatLab program (MathWorks). A single iSP measurement was made from the 20 TMS trials from each participant by rectifying and averaging EMG activity in the hand ipsilateral to the TMS for 100 ms before (baseline) and 180 ms after the TMS pulse. The following equation was used to calculate 99.7% of possible prestimulus EMG data point values: (average baseline EMG $\pm$ [(maximum value of baseline EMG – minimum value of baseline EMG) $\times$ 2.66]). The onset and offset of the iSP were defined as the first of 5 consecutive data points that fell below the lower limit calculated from the equation above (onset) and the first data point that fell above the higher limit calculated by the equation above (offset) if more than 50% of the data points in the previous 5 ms were also above the lower limit (Garvey et al. 2001). Duration was then calculated from the onset and offset values. We also measured the depth of the iSP using the 2 different methods described by Jung and Ziemann (2006): 1) the minimum EMG level during the iSP (depth iSP-max) and 2) the average EMG level during the iSP (depth iSP). Both measures were expressed as a percentage of the average baseline EMG level.

All iSP measurements (iSP onset latency, iSP duration, depth iSP-max and depth iSP) were analyzed separately using mixed effects analysis of variance (ANOVA) with Hemisphere (LH vs. RH) and Time (pre-PA vs. post-PA) as within-participant factors and PA group (LPA vs. RPA) as a between-participant factor. Significant effects were further analyzed using Bonferroni post hoc tests and the critical α level was set at 0.05. All data are presented as mean $\pm$ SD.

Results

Prism Adaptation

The average landing position during open-loop pointing immediately before PA (baseline), immediately after PA (Post 1) and after all TMS measurements (Post 2) was used to assess whether participants adapted to prisms and whether they remained adapted until the end of the experiment (~12 min after PA). To do this, we calculated the difference between Post 1 and baseline and Post 2 and baseline. Since the sign of the shift depends upon the direction of the prisms, we submitted the absolute value of the shift to a mixed ANOVA with Time (Post 1 vs. Post 2) as a within-participant factor and PA group (LPA vs. RPA) as a between-participant factor. This analysis

revealed a significant effect of Time ($F_{1,22} = 95.25$, $P < 0.01$, $\eta_p^2 = 0.81$) with greater adaptation at Post 1 than Post 2 (7.0 vs. 4.2 cm from the central target). The main effect of Group was significant ($F_{1,22} = 7.92$, $P = 0.01$, $\eta_p^2 = 0.26$), with greater adaptation in the RPA than in the LPA group (6.4 vs. 4.7 cm). The interaction between Time and PA group was also significant ($F_{1,22} = 7.98$, $P < 0.01$, $\eta_p^2 = 0.26$). Bonferroni post hoc tests revealed a greater adaptation in the RPA than in the LPA group at Post 1 (8.3 vs. 5.7 cm, $P < 0.01$) but no difference between the groups at Post 2 (4.6 vs. 3.7 cm, $P = 0.70$), suggesting that in both groups participants remained significantly and equally adapted until the end of the iSP experimental session.

iSP Measurements

Table 1 shows the mean and SD for all 4 iSP parameters separated by PA group (LPA, RPA), Hemisphere (LH, RH) and Time (Pre-PA, Post-PA). Separate mixed ANOVAs were conducted on the iSP onset latency, iSP duration, depth iSP-max and depth iSP with the following factors: Hemisphere (LH vs. RH) and Time (Pre-PA vs. Post-PA) as within-participant factors and PA group (LPA vs. RPA) as a between-participant factor. Note that none of the iSP measurements differed between hemispheres or groups before the adaptation procedure (all P s > 0.14). Contralateral MEP amplitudes were also analyzed. This analysis revealed no significant main effects or interactions (all P s > 0.074).

"iSP duration" was longer in the LPA than in the RPA group ($F_{1,22} = 6.49$, $P = 0.02$, $\eta_p^2 = 0.22$) and the interaction between Time and PA group ($F_{1,22} = 9.46$, $P < 0.01$, $\eta_p^2 = 0.30$) was significant, with a longer iSP duration Post-PA in the LPA group and no change in the RPA group, but none of the Bonferroni post hoc tests were significant (all P s > 0.16). The interaction between Hemisphere and Time ($F_{1,22} = 4.32$, $P = 0.04$, $\eta_p^2 = 0.16$) was also significant, with a longer iSP duration after PA for the LH and a shorter iSP duration after PA for the RH, but none of the Bonferroni post hoc tests were significant (all P s > 0.13). Neither the main effects of Hemisphere and Time nor the 2-way interaction between PA group and Hemisphere was significant (all P s > 0.14) but the 3-way interaction between Hemisphere, Time and PA group ($F_{1,22} = 4.53$, $P = 0.04$, $\eta_p^2 = 0.17$) was significant. Bonferroni post hoc tests revealed only one significant effect: in the LH of the LPA group iSP duration was longer after PA ($P = 0.02$; all other post hoc t-tests, P s > 0.11).

In a complementary analysis, we separated the data from the LPA and RPA groups and performed separate 2-way repeated measures ANOVAs on the data from each group with the factors Hemisphere and Time. In the LPA group, the interaction between Hemisphere and Time was significant ($F_{1,11} = 8.17$, $P < 0.01$, $\eta_p^2 = 0.42$), with a significantly longer iSP duration after PA for the LH ($P = 0.02$) but no difference for the RH ($P = 0.16$). In the RPA group, neither the main effects nor the interaction was significant

Table 1. iSP measurements for each experimental condition

	LPA				RPA			
	LH (left FDI)		RH (right FDI)		LH (left FDI)		RH (right FDI)	
	Pre-PA	Post-PA	Pre-PA	Post-PA	Pre-PA	Post-PA	Pre-PA	Post-PA
iSP duration (in ms)	27.91 (4.84)	34.16 (6.50)	29.83 (4.08)	29.16 (4.49)	25.66 (3.33)	24.33 (3.10)	25.33 (3.05)	24.08 (2.26)
iSP onset latency (in ms)	46.41 (2.40)	45.41 (2.19)	44.33 (1.90)	45.41 (1.94)	49.83 (2.89)	52.33 (3.49)	47.41 (2.42)	48.01 (2.25)
Depth iSP-max (in %)	73.24 (5.55)	71.41 (5.32)	72.42 (3.02)	70.88 (5.34)	61.22 (5.15)	62.56 (4.74)	60.76 (6.61)	61.06 (3.89)
Depth iSP (in %)	52.39 (6.47)	52.92 (4.93)	53.81 (3.47)	53.56 (5.91)	64.10 (3.87)	63.30 (3.69)	60.17 (5.16)	60.31 (4.33)

All data presented are the mean with the SD in parentheses.

(all $P_s > 0.25$). The effect observed at the group level in the LPA group in both the 3-way and 2-way ANOVAs was observed in each of the 12 subjects and is illustrated in Figure 2, which shows the averaged, rectified EMG obtained from one representative subject in the LPA group. This figure shows that iSP duration was significantly longer after LPA for the LH (left FDI) whereas in the RH it did not change.

"iSP onset latency" was significantly later in the RPA than in the LPA group ($F_{1,22} = 6.64$, $P = 0.01$, $\eta_p^2 = 0.22$). The main effect of Hemisphere was also significant ($F_{1,22} = 4.99$, $P = 0.04$, $\eta_p^2 = 0.18$), as the onset latency was later for the LH. None of the other main effects or interactions reached significance (all $P_s > 0.07$).

For iSP "depth" measurements, the main effect of PA group was significant for both depth iSP-max and depth iSP ($F_{1,22} = 13.01$, $P < 0.01$, $\eta_p^2 = 0.37$ and $F_{1,22} = 7.56$, $P = 0.01$, $\eta_p^2 = 0.25$, respectively), as both the minimum and average EMG levels during the iSP were greater in the LPA group. For depth iSP, the interaction between Hemisphere and PA group was also significant ($F_{1,22} = 5.17$, $P = 0.03$, $\eta_p^2 = 0.19$), as in the RPA group the depth iSP was greater for the LH than for the RH, whereas in the LPA group there was no difference between hemispheres, but note that none of the Bonferroni post hoc tests were significant (all $P_s > 0.19$). None of the other main effects or interactions for either depth iSP-max or depth iSP reached significance (all $P_s > 0.23$).

Discussion

We examined changes in left-to-right and right-to-left IHI at the motor level before and after LPA or RPA in healthy subjects. We found that only LPA modulated IHI between the 2 motor cortices and only from the left to the right motor cortex. This is the first physiological demonstration that PA alters IHI.

Symmetric and Asymmetric After-Effects of PA

In healthy subjects, PA to a leftward or rightward deviation produces equal but opposite sensorimotor after-effects (Colent et al. 2000; Michel et al. 2003; Schintu et al. 2014). In contrast, only adaptation to a leftward deviation produces visuospatial after-effects (Colent et al. 2000; Michel et al. 2003; Striemer et al. 2006; Nijboer et al. 2010). The fact that we observed a change in IHI after LPA but not RPA suggests that increased IHI from the left-to-right motor cortex reflects changes in higher level cognitive processes rather than low-level sensory-motor processes. Higher level cognitive after-effects could be linked to direct connections from the cerebellum to the PPC, whereas low-level sensory-motor processes generated by both LPA and RPA could be linked to direct connections between the cerebellum and M1. This is supported by evidence from patients showing that bilateral lesions to PPC disrupt visuospatial after-effects (Striemer et al.

Figure 2. Examples of iSP measurements from one representative subject in the LPA group separated by Session (pre-PA and post-PA) and Hemisphere (LH (left FDI)—upper row, and RH (right FDI)—bottom row). All data are averages of 20 single-trial rectified sweeps with TMS applied at time 0. Horizontal lines indicate the upper and lower variation limits of the prestimulus EMG level. Vertical dashed lines indicate iSP onset and offset.

2008) without affecting sensorimotor after-effects (Pisella et al. 2004). Further support for this idea comes from evidence showing that the cerebellum plays a crucial role in sensorimotor adaptation (Weiner et al. 1983; Pisella et al. 2005), that cerebellar stimulation can modulate intracortical circuits within the contralateral M1 (Chen 2004; Daskalakis et al. 2004), and that RPA and LPA produce equal increases in intracortical-facilitation (ICF) but in opposite M1s (Magnani et al. 2014).

Before PA, we observed no differences between the right-to-left and left-to-right silent periods nor between silent periods in the LPA and RPA groups. This is in agreement with a previous study showing that motor IHI is symmetric both at rest and during sustained unimanual contraction (Nelson et al. 2009) and shows that our results cannot be explained by between-group differences before PA. They also cannot be ascribed to the use of the right arm during the adaptation procedure or to changes in corticospinal excitability, as subjects in both the LPA and RPA groups used their right arm and MEPs elicited in the contralateral hand were unchanged after PA (see also Magnani et al. 2014).

The origin of the asymmetrical effects of LPA and RPA on cognition has long been attributed to RH specialization for visuospatial cognition and attention (Fink et al. 2000; Corbetta and Shulman 2002). The present results suggest that the source of this asymmetry could, at least in part, also lie in differences in IHI between the parietal cortices, as only the right PPC seems to inhibit its homolog (Koch et al. 2011). The specificity of PA-induced changes in IHI (found only following LPA and only from the LH to the RH) would be predicted if LPA increased right-to-left parietal IHI and produced the follow-on effects of an increase in LH parietal-to-motor connectivity and internal circuits of left M1 (Rivera-Urbina et al. 2015). The direct action of PA on parietal-to-motor connectivity in the hemisphere contralateral to the prism deviation cannot explain the specificity of our effect for LPA as this pathway would predict a very different pattern of results from what we observed. Namely, opposite increases in motor IHI after “both” LPA and RPA, with the LPA increase occurring from right-to-left and not from left-to-right as in our data. Indeed, we did not predict this possibility because a previous study showed that inhibition of left PPC by cathodal (inhibitory) tDCS did not alter intracortical motor circuits in left M1 as measured by SICI or ICF (Rivera-Urbina et al. 2015). This, together with the fact that observing a change after LPA only is coherent with behavioral changes on visuospatial tasks after LPA but not RPA, leads us to suggest that the change in IHI we observed at the motor level is the result of a chain of LPA-induced modifications that include changes in parietal IHI.

Implications for Models of Neglect and Neglect-Like After-Effects of PA

Theoretical models of attention account for the fact that neglect occurs preferentially after RH damage by postulating hemispheric dominance in attentional allocation across space (either in the LH, Kinsbourne 1977, or in the RH, Heilman and Van Den Abell 1980; Mesulam 1981; Cohen et al. 1994). The recent finding by Koch et al. (2011) that the right (but not the left) PPC inhibits its homolog suggests that there might be another mechanism at play in the processes underlying neglect and PA. Asymmetrical IHI could contribute to the preferential occurrence of neglect after RH damage as well as observations that left PPC damage can produce subclinical attentional deficits without a diagnosis of clinical neglect (Karnath et al. 2002;

Beis et al. 2006). Indeed, when asymmetries in IHI are added to the Hemispheric Rivalry model, damage to both the right and left PPC would directly weaken attention toward the contralateral space, but only right PPC damage would alter IHI, resulting in hyper-activation of the left PPC and an exacerbation of the rightward attentional bias.

Asymmetric IHI could also explain why only LPA modifies spatial cognition in healthy subjects (Colent et al. 2000; Michel et al. 2003; Schintu et al. 2014). Similar to an RH lesion (Corbetta et al. 2005), LPA would inhibit the right PPC that would subsequently reduce right-to-left parietal IHI and then produce hyperactivity of the left PPC and follow-on effects in the motor cortex. In contrast, RPA would inhibit the left PPC but not alter parietal IHI and therefore produce no subsequent changes in right PPC. In neglect patients, however, the effectiveness of RPA might be due to a direct inhibitory effect on the left PPC which counteracts the left PPC hyperexcitability that is frequently observed after RH lesions (Brighina et al. 2003; Koch et al. 2008, 2012; Nyffeler et al. 2009; Cazzoli et al. 2012; Salatino et al. 2014), but which seems to depend upon the temporal epoch poststroke at which it is evaluated (acute/subacute vs. chronic; Corbetta et al. 2005; Cramer 2008; Bartolomeo and Thiebaut De Schotten 2016).

Importance of Interhemispheric Connections for Both Motor and Attentional Symptoms After RH Damage

Typically, the greater severity of motor impairments after RH than LH stroke (with or without a clinical diagnosis of neglect) has been attributed to attentional difficulties that are known to interfere with motor rehabilitation (Heilman et al. 1987; Buxbaum et al. 2004; Farnè et al. 2004; Di Monaco et al. 2011). When the lesion includes the right PPC we speculate that the severity of motor impairments might be due to alterations in both parietal and motor IHI. More precisely, we suggest that a decrease in right (but not left) PPC excitability (induced by a lesion, neurostimulation or LPA) has transcallosal consequences at the motor level. These consequences could lead to persistent modifications in frontal areas, even though left PPC hyperactivity seems to gradually decrease after the subacute phase (Corbetta et al. 2005; Cramer 2008).

In hemiparetic patients, no hemispheric asymmetry in the severity of motor impairments has been observed when stroke affects subcortical structures or M1 (Hendricks et al. 2002). When the lesion includes the right but not the left PPC, motor impairments might be more severe because of an exacerbation of the imbalance in motor IHI (Murase et al. 2004; Hummel and Cohen 2006). In nonhemiparetic patients, lesions including the right (but not left) PPC could have deleterious effects on motor control by inducing an asymmetry in IHI at the motor level. While speculative, it is plausible that an imbalance in motor IHI contributes to high-level motor deficits like underuse of the contralateral side of the body and/or bradykinesia and hypokinesia when moving an ipsilesional body part into contralesional hemisphere, both of which have been described in the context of neglect (Mattingley et al. 1992, 1998; but see Bisiach et al. 1990, 1995, 1998; Bartolomeo et al. 1998, for a discussion of the possible dissociation between perceptual and response biases in neglect).

Finally, the proposed importance of interhemispheric connections in the severity of motor symptoms in the acute/subacute phase of stroke (Traversa et al. 1997; Delvaux et al. 2003; Di Lazzaro et al. 2010) parallels that which has been confirmed for the severity and recovery of attentional symptoms in neglect patients. While “intra”hemispheric fronto-parietal

disconnection is a well-established factor in both the emergence and chronic persistence of neglect (Thiebaut de Schotten et al. 2005; Bartolomeo et al. 2007), recent data suggest that “inter”hemispheric disconnection is also important (Lunven et al. 2015). Lunven et al. (2015) highlight an important role of interhemispheric communication for neglect recovery but when they compared subacute patients with and without neglect, both intrahemispheric and interhemispheric integrity were decreased in the neglect group. Together with previous studies (Gaffan and Hornak 1997; Park et al. 2006; Tomaiuolo et al. 2010), this demonstrates the importance of interhemispheric disconnection, as well as RH damage, in the genesis of neglect. This idea is in accordance with studies showing that neglect severity correlates with microstructural damage to transcallosal fibers in the posterior portion of the corpus callosum (Bozzali et al. 2012; Umarova et al. 2014) and with interhemispheric resting-state functional connectivity (Corbetta et al. 2005; Carter et al. 2012).

Our model clearly emphasizes an important role of LH hyperactivity in neglect genesis and PA-induced amelioration. It is supported by several experimental and clinical observations (discussed above) and is appealing because of its simplicity. However, LH hyperactivity remains controversial (see Bartolomeo 2015 for a review). For example, behavioral markers of LH frontal hyperactivity do not always correlate with neglect severity (Bartolomeo and Chokron 1999), and some studies have even reported a link between neglect recovery and an increase in both LH and RH activity (Luauté et al. 2006; Saj et al. 2013). In addition, TMS studies in healthy subjects (Ricci et al. 2012; Bagattini et al. 2015) have shown that inhibition of the inferior (ventral) part of the right PPC decreases left PPC activity. Note, however, that Bagattini et al. (2015) put forward the idea that this left PPC decrease does not preclude alterations in IHI at the level of the superior (dorsal) part of the PPC. The origin of this controversy might indeed lie in where the LH hyperexcitability is measured. Finally, it is clearly an oversimplification to consider that processes perturbing or rebalancing spatial behavior express themselves exclusively as alterations in mutual IHI (see Corbetta et al. 2005; Martín-Arévalo et al. 2016). Rather, “callosal connections are likely to exert both excitatory and inhibitory effects (mostly through interneurons) on the opposite hemisphere” (Bartolomeo 2015, p. 311). Thus, a more sophisticated and dynamic model of visuospatial attention networks that integrates both intrahemispheric and interhemispheric interactions is needed to understand the action mechanisms of LPA in healthy individuals and of RPA in neglect patients, as well as the complex processes that lead to neglect’s attentional and motor symptoms.

In conclusion, the current results provide the first direct demonstration that PA affects IHI. They highlight the crucial role of interhemispheric interactions in visuospatial attention in general, and more specifically, in visuospatial and motor components of neglect.

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Notes

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