

Reshaping the brain after stroke: The effect of prismatic adaptation in patients with right brain damage[☆]



Sonia Crottaz-Herbette^{a,*}, Eleonora Fornari^{b,c}, Michael P. Notter^{d,e}, Claire Bindschadler^a, Laura Manzoni^a, Stephanie Clarke^a

^a Neuropsychology and Neurorehabilitation Service, Department of Clinical Neurosciences, University Hospital Center (CHUV) and University of Lausanne, 1011 Lausanne, Switzerland

^b Department of Radiology, University Hospital Center (CHUV) and University of Lausanne, 1011 Lausanne, Switzerland

^c MR Core, Centre for Biomedical Imaging (CIBM), 1011 Lausanne, Switzerland

^d Laboratory for Investigative Neurophysiology (The LINE), Department of Radiology and Department of Clinical Neurosciences, University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland

^e EEG Brain Mapping Core, Centre for Biomedical Imaging (CIBM), 1011 Lausanne, Switzerland

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ABSTRACT

Prismatic adaptation has been repeatedly reported to alleviate neglect symptoms; in normal subjects, it was shown to enhance the representation of the left visual space within the left inferior parietal cortex. Our study aimed to determine in humans whether similar compensatory mechanisms underlie the beneficial effect of prismatic adaptation in neglect. Fifteen patients with right hemispheric lesions and 11 age-matched controls underwent a prismatic adaptation session which was preceded and followed by fMRI using a visual detection task. In patients, the prismatic adaptation session improved the accuracy of target detection in the left and central space and enhanced the representation of this visual space within the left hemisphere in parts of the temporal convexity, inferior parietal lobule and prefrontal cortex. Across patients, the increase in neuronal activation within the temporal regions correlated with performance improvements in this visual space. In control subjects, prismatic adaptation enhanced the representation of the left visual space within the left inferior parietal lobule and decreased it within the left temporal cortex. Thus, a brief exposure to prismatic adaptation enhances, both in patients and in control subjects, the competence of the left hemisphere for the left space, but the regions extended beyond the inferior parietal lobule to the temporal convexity in patients. These results suggest that the left hemisphere provides compensatory mechanisms in neglect by assuming the representation of the whole space within the ventral attentional system. The rapidity of the change suggests that the underlying mechanism relies on uncovering pre-existing synaptic connections.

1. Introduction

Prismatic adaptation (PA) was shown to alleviate left neglect in patients with right hemispheric damage (Rossetti et al., 1998). Single and multiple cases studies have demonstrated positive PA effects on various neuropsychological tests or daily life activities (Berberovic and Mattingley, 2003; Maravita et al., 2003; McIntosh et al., 2002; Rode et al., 1998, 2001; Rode et al., 2006a, 2006b; Saevarsson et al., 2009; Tilikete et al., 2001). Although the beneficial effect of PA was confirmed in several group studies (Fortis et al., 2010; Frassinetti et al., 2002; Hatada et al., 2006; Keane et al., 2006; Mizuno et al., 2011; Serino et al., 2007; Shiraishi et al., 2008, 2010; Vangkilde and

Habekost, 2010), individual studies have reported interesting discrepancies: short-term but no long-term effects (Nijboer et al., 2008); effects in straight-ahead pointing, partially in-line bisection, but not in visual search (Morris et al., 2004); efficacy in only a subgroup of patients with mild neglect (Mizuno et al., 2011); no effect with only one weekly session (Rode et al., 2015); or the absence of effect (Rousseaux et al., 2006; Turton et al., 2010). These conflicting results across studies may be due to the heterogeneity of neglect syndrome; a better understanding of the mechanisms underlying PA may help identify neglect profiles that respond to PA treatment (Clarke et al., 2015).

Several neuroimaging studies have investigated brain activation while normal subjects were exposed to PA (Chapman et al., 2010;

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* Correspondence to: Neuropsychology and Neurorehabilitation Service, University Hospital Center (CHUV), Av. Pierre-Decker 5, 1011 Lausanne, Switzerland.
E-mail address: sonia.crottaz-herbette@chuv.ch (S. Crottaz-Herbette).

Table 1
Demographic and clinical characteristics of the patients.

Patient	Age	Sex	Delay since stroke onset (months)	Etiology	Lesion territory	Visual extinction	Bells test (1st column)
1	43	M	3.1	hemorrhagic	deep and superficial sylvian	yes	7
2	55	F	48.7	hemorrhagic	deep and superficial sylvian	yes	2
3	54	M	2.3	ischemic	superficial sylvian	yes	4
4	65	M	46.7	ischemic	deep and superficial sylvian	yes	2
5	50	M	0.9	ischemic	superficial sylvian	yes	4
6	63	F	11.6	ischemic	deep sylvian	no	1
7	59	F	21.3	ischemic	superficial sylvian	yes	7
8	56	M	27.0	hemorrhagic	deep sylvian	no	1
9	48	F	2.8	hemorrhagic	deep sylvian	yes	7
10	67	F	22.4	ischemic	deep and superficial sylvian	no	1
11	52	F	0.8	ischemic	superficial sylvian	no	1
12	52	M	14.4	ischemic	superficial sylvian	no	7
13	67	F	6.1	ischemic	deep sylvian	yes	2
14	49	M	4.8	ischemic	deep and superficial sylvian	yes	1
15	44	F	7.7	ischemic	deep and superficial sylvian	no	1

Clower et al., 1996; Danckert et al., 2008; Küper et al., 2014; Luauté et al., 2009). They revealed the involvement of the right cerebellum and the right posterior parietal cortex during the stages of visuo-motor adaptation. In a recent study, we showed that a single, brief PA exposure modulated neuronal activity yielded by a visual detection task by increasing the activation in the left inferior parietal lobule (IPL) and decreasing it in the right inferior parietal region for the whole visual field in a group of normal subjects (Crottaz-Herbette et al., 2014). However, the increased activation in the left IPL following PA was greater when the stimuli to be detected were presented in the left rather than in the central or right visual field, suggesting a reversal of the right hemispheric dominance for visual space processing after PA. Taking into account that PA-related modulation involved regions in the left IPL typically spared in neglect patients and that modulation increased the competence of the left hemisphere for the left visual space, one could expect that the left IPL, or more generally the left homologue of the right-lateralized ventral attentional network, underlies the beneficial effect of PA in neglect.

The beneficial effects of PA in neglect have been investigated in two neuroimaging studies. A PET study highlighted a significant correlation between PA-induced improvement in the performance on the Behavioural Inattention Test and increase in regional cerebral blood flow in the right cerebellum, the left thalamus, the left temporo-occipital cortex, the left medial temporal cortex and the right posterior parietal cortex (Luauté et al., 2006). Although the significant contribution of the left hemisphere, which was revealed in this study, could be interpreted as a result of PA-induced shift of the ventral attentional system from the right to the left hemisphere, this study does not provide any direct evidence. An fMRI study reported PA-induced changes in activation patterns to visuo-spatial tasks; line bisection and visual search, but not visual short-term memory. These changes corresponded to an increased neural activity bilaterally within the occipito-parieto-frontal cortex, predominantly within the superior parietal lobules (Saj et al., 2013). Line bisection and visual search are known to depend on the dorsal attentional network in normal subjects (Baumgartner et al., 2013; Leonards et al., 2000) and in neglect PA has indeed enhanced the involvement of the dorsal attentional system in these two tasks (Saj et al., 2013). The PA-induced involvement of the dorsal attentional system may be the result of the shift of the ventral attentional system to the left hemisphere (as discussed in Clarke and Crottaz-Herbette, 2016), but the study of Saj et al. did not address this issue.

Taken together, the above discussed evidence suggests that the effect of PA in neglect is accompanied by a change in the representation of the left visual space, in particular its enhancement within the left homologue of the right-lateralized ventral attentional system (Crottaz-Herbette et al., 2014; Clarke and Crottaz-Herbette, 2016). The issue has not been addressed in previous studies of PA effect in neglect (Luauté

et al., 2006; Saj et al., 2013). The present study is based on the hypothesis that the effect of PA in neglect is accompanied by a change in the representation of the left visual space, in particular its enhancement within the left homologue of the right-lateralized ventral attentional system. To test this hypothesis, we conducted an event-related fMRI study with a target detection paradigm in neglect patients and compared them to age-matched controls.

2. Materials and methods

To assess the effect of PA in neglect patients and age-matched controls, we used the same experimental approach from our previous study (Crottaz-Herbette et al., 2014). A brief PA session was preceded and followed by event-related fMRI sessions using a detection task of targets within the right, central or left visual space. The activation patterns before and after PA were compared across groups. We have used rightward deviating prisms, as used in neglect rehabilitation. In this context, PA requires subjects to point towards visual targets with one hand while wearing prismatic lenses that deviate the visual field to the right (Pisella et al., 2006). After prism removal, pointing errors occur with overshoot to the left; this after-effect reflects prism-induced sensorimotor realignment (Weiner et al., 1983).

2.1. Participants

Twenty-six participants were included in this study: 15 patients with right hemispheric damage (8 women; mean \pm SEM age: 55 \pm 8 years) and 11 control subjects without history of neurological or psychiatric illness (7 women; mean age: 53 \pm 7 years). Both groups were age-matched ($t = 0.77$; $p = 0.45$). All participants were right handed (Oldfield, 1971), and all had normal visual fields and normal or corrected-to-normal visual acuity. The participants provided written informed consent according to procedures approved by the Ethics Committees of the Faculty of Biology and Medicine, University of Lausanne and Canton de Vaud. Patients were recruited among the inpatients or outpatients treated by the Neuropsychology and Neurorehabilitation Service at the CHUV or the Lavigny Institution. Inclusion criterion included a first unilateral right hemispheric stroke (Table 1). Exclusion criteria included age outside the 20–70-year bracket; visual field defect; and/or major behavioural deficits which would preclude participation in the experimental paradigm. All patients underwent standard multidisciplinary rehabilitation during their hospitalization. A detailed neuropsychological evaluation was carried out at the time of the fMRI investigation, including neglect assessment with a full, standardized battery (Azouvi et al., 2006) and activities of daily living (Azouvi et al., 2003). The extent and location of lesions were analysed on structural MRI scans (Fig. 1).

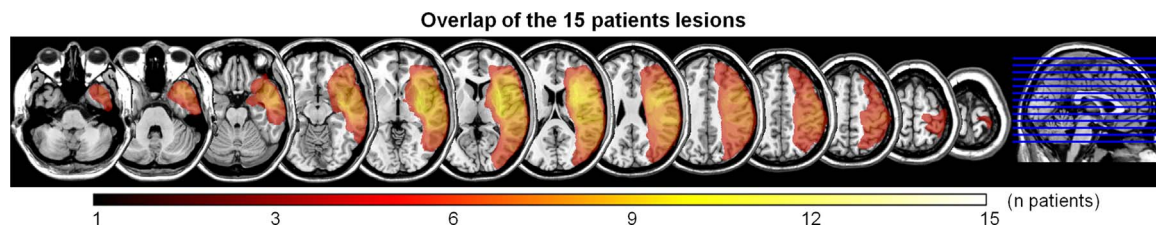


Fig. 1. The overlap of lesions in 15 patients who participated in this study on axial slices of a normalized MRI template (MNI coordinates of the slices in blue). The red to yellow scale indicates the number of patients with a lesion in each given voxel. The overlap is maximal in the right subcortical and cortical portions of the temporal and parietal regions.

2.2. Experimental design

Both groups followed the same procedure: the first MRI block was followed by an exposure to PA outside the scanner and then a second MRI block. Each MRI block consisted of anatomical sequences and an event-related fMRI acquisition during a visual detection task. Additional acquisitions were conducted as described in Crottaz-Herbette et al. (2014). Patients performed the Bells test (Azouvi et al., 2006) after the first fMRI acquisition but just before the PA session. They repeated the Bells test just after the PA session. The performance on the Bells test was assessed in terms of total omissions, left omissions, time, and column of the first cancelled item. Further analyses were carried on this latter index as this parameter was previously shown to be the most sensitive index of neglect severity (Azouvi et al., 2002, 2006); the difference in performances obtained before and after the PA session was assessed by a Wilcoxon test.

2.2.1. Prismatic adaptation

PA was performed outside the scanner following the same procedure in our previous study (Crottaz-Herbette et al., 2014). Participants were asked to point with the right index finger to visual targets presented 14° to the left or to the right of the midsagittal plane while they were wearing prisms (www.optiquepeter.com) that deviated their visual field 10° to the right (Jacquin-Courtois et al., 2013; Pisella et al., 2006; Redding et al., 2005; Rode et al., 2006a, 2006b; Rossetti et al., 1998). A head rest was used to immobilize the participant's head. The initial two-thirds of the pointing trajectories were hidden from their view. The participants were asked to point to the targets with the right hand during 3 min (~150 movements). During the first pointing movements, participants showed a pointing error in the direction of the prism deviation; they corrected their movement during subsequent trials; then all participants finished the PA session by pointing correctly to both targets. Immediately after the prisms were removed, the after-effect was assessed by asking the participants to look (without the prisms) at the visual target, then to close their eyes and to point with their right index finger to where they have seen the target. This procedure was used twice for the left target and twice for the right target in a randomized order across participants. For each pointing movements during the after-effect test, the pointing deviation was recorded and expressed in mm, with negative values representing a deviation to the left of the targets and positive values representing a deviation to the right of the targets. For each separate target, the deviations of both pointings were averaged together, which provided a value for the deviation of the left target and another value for the deviation of the right target. These values were analysed in two-way mixed-design ANOVA with Group (Pat, Ctl) as a between-subjects factor and Target location (left target, right target) as a within-subject factor.

2.2.2. Visual detection task

Participants were asked to detect large white stars presented on a black background in 3 different locations: in the midsagittal plane at 20° to the right or 20° to the left (Crottaz-Herbette et al., 2014). The stars were presented for 500 ms, 20 different intervals between stimuli were used, all between 1 and 20 s, with a step of 1 s of duration

between intervals. A pseudo-random presentation of these intervals was used. Stimuli locations were randomized, and each location was presented 20 times. Participants were asked to press the response button when they detected a star. The duration of the task was 6 min 44 s. Central fixation was maintained by asking the participants to keep their gaze fixed on a central red cross. The participants responded by pressing a button with their right hands. The tasks were programmed using E-Prime (Psychology Software Tools, Inc). The normality of the accuracy and response times data was assessed by a Shapiro-Wilk test. These data were then analysed using non-parametric tests as they did not follow a normal distribution. Non-parametric repeated-measures Fisher tests (F-tests) were conducted on accuracy and reaction time data. This non parametric analysis includes a bootstrapping of the subjects and a permutation of the within subjects factors (as in Knebel et al., 2011). On each cycle an F-value was calculated. Repeating that 10,000 times generated a distribution of F-values, from which the F-value of the real data (no bootstrapping or permutation) can be compared and a p-value obtained. The factors included were Group (Pat, Ctl) as a between-subject factor and Stimulus position (Left, Center, Right) and Session (Pre-PA, Post-PA) as within-subject factors.

In this study participants performed both PA and the detection task with their right hand. This choice was motivated by the fact that most neglect patients present a left hemisindrome, which compromises the use of the left hand. The consistent use of the right hand in patients and in control subjects facilitated the comparison of the two groups. The pre- and post-PA fMRI sessions used the same protocol and thus the motor act of pressing the button was the same in both. We cannot formally exclude that the implication of the right hand in PA and in the response during the fMRI detection task did not contribute to favouring left hemispheric involvement in the effect. This is, however, unlikely since we observed a spatial gradient for the effect, i. e. PA enhanced the representation of the left and central and not right space in the left hemisphere. A separate study in normal subjects needs to address the putative influence of right vs. left hand.

2.3. Imaging data acquisition

Imaging acquisitions were recorded at the Lemanic Biomedical Imaging Center (CIBM) in the CHUV, Lausanne. A single-shot echo-planar imaging gradient echo sequence was used for the event-related functional acquisitions (Siemens 3T Magnetom Trio, 32-channels head-coil, repetition time = 2 s; flip angle = 90° ; echo time = 30 ms; number of slices = 32; voxel size = $3 \times 3 \times 3$ mm; 10% gap). The 32 slices were acquired in the AC-PC plane in a sequential ascending order and covered the whole head volume. For each participant, a high-resolution T1-weighted 3D gradient-echo sequence was acquired (160 slices, voxel size = $1 \times 1 \times 1$ mm). These scanning parameters, especially the repetition time and the field of view, preclude complete coverage of the cerebellum. Considering that the cerebellum has been reported in previous studies, a further study should be conducted to address specifically the role of this region in PA. To prevent head movements in the coil, we placed padding around the participant's head.

2.4. Imaging data analysis

Brain lesions for each patient were manually drawn on axial slices on the patient unnormalized structural image using MITK 3 M3 software (<http://www.mint-medical.de/>) with a method similar to one previously described (Manuel et al., 2013). Anatomical and functional imaging data were processed using the software SPM12 (Wellcome Department of Cognitive Neurology, London, UK) and the Clinical Toolbox for SPM (Brett et al., 2001; Rorden et al., 2012) that we adapted to work with SPM12.

Functional acquisitions were corrected for motion correction using a 6 parameter rigid-body transformation to minimize the difference between each image and the first scan. Then, slice timing correction was performed on these realigned images. The participant's anatomical image and these realigned functional acquisitions were co-registered and then normalized to the MNI template using the deformation field calculated by SPM12. During the normalization process, the lesion and the surrounding area were masked from the anatomical image using the Clinical Toolbox for SPM (Brett et al., 2001; Rorden et al., 2012). This step should allow for acquisition of a normalization not distorted by the lesion. The normalized functional images were finally resliced to obtain a $2 \times 2 \times 2$ mm voxel size and spatially smoothed using an isotropic Gaussian kernel of 8 mm FWHM to increase the signal-to-noise ratio.

The lesion images were normalized to the MNI template for each patient using the deformation parameters obtained by the normalization of the patient's anatomical images in SPM12 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). The volumes of the lesions were calculated by MITK 3 M3 software. MRIcroN software (Rorden et al., 2007) was used to calculate and display the average image of all lesions in the patients.

First level statistics were performed for each participant using the general linear model as implemented in SPM12 software. For each patient, a mask based on the lesion image obtained by the Clinical toolbox for SPM (Brett et al., 2001; Rorden et al., 2012) was used to remove damaged areas in our patients from the statistical analyses. Those steps allowed us to prevent the contamination of the results by artefacts that are often observed in patients with brain lesions (Strigelin et al., 2005). The realignment parameters were included in the model as regressors and contrasts of interest were specified for both sessions in the same design. The highpass filter cut-off was set to 128 s. Maps were created from these contrasts and were then used as input values for the second-level (group-level) statistics based on the random field theory. Finally, a mask image was created from the a priori template available in SPM and used at the step of the results display to exclude voxels belonging to white matter. This masking does not change the statistical results, only the display.

General mixed-design ANOVA including the factors Group (Pat, Ctl) as between-subjects factor and Stimulus position (Left, Center, Right) and Session (Pre-PA, Post-PA) as within-subjects factors was used on the activation maps. All activation maps included in the statistical analyses of this study were thresholded at $p < 0.05$ and cluster extent of $k > 115$ (always above the expected number of voxels per cluster provided automatically by SPM12). The prismatic adaptation effect was analysed more precisely with region of interest analyses using 3 mm diameter spheres located on the peak of the main clusters of this ANOVA. Two additional ANOVAs including the factors Stimulus position and Session were then used on the activations maps of each group separately.

Furthermore, for the group of patients, the effect of the prismatic adaptation on the activation related to the left, center and right stimuli was analysed in more detail. For each stimulus position, post hoc T-tests comparing session 1 and session 2 were conducted. The statistical maps of activation for these T-tests were thresholded at $p < 0.05$ and cluster extent of $k > 250$ (above the expected number of voxels per cluster provided automatically by SPM12).

Correlation analyses were conducted to determine the relationships between modulations of the BOLD signal induced by PA and 3 indices:

(1) the neglect severity, as measured by performance on the Bells test (column of the first detected bell); (2) the change between sessions 1 and 2 of the detection of the left and central targets; and (3) the volume of the lesions. Two regions of interest were selected for the measures of the BOLD modulations, and they corresponded to the peak of the clusters of the activation in the anterior STG-MTG and posterior STG observed in ANOVA Stimulus position \times Session for the patient group. The column of the first detected target in the Bells test was chosen to represent the neglect severity as this parameter is the most sensitive index of neglect severity (Azouvi et al., 2002, 2006). In the results of these analyses, we have further indicated which patients were good performers for the left and central targets before PA exposure.

3. Results

3.1. Behavioural results

Both the patient and the control groups presented a consistent PA after-effect. The pointing error which occurred after the prisms were removed was always towards the left of the targets; in patients, it was -61 ± 7 mm (mean \pm SEM) for the left and -47 ± 6 mm for the right target; for control subjects, it was -56 ± 4 mm for the left and -50 ± 4 mm for the right target. Two-way mixed-design ANOVA with Group (Pat, Ctl) as a between-subjects factor and Target location (left, right) as a within-subjects factor did not reveal a significant effect.

The effect of PA on neglect symptomatology was assessed with the Bells test. The Wilcoxon test showed that the first cancelled item was significantly (Wilcoxon test: $z = -2.39$, $p = 0.017$) more to the right side of the page for the test conducted before ($m = 3.08 \pm 0.68$, mean \pm SEM) the PA session compared to after the PA session ($m = 1.92 \pm 0.42$).

The performance on the detection task, which was administered during each of the fMRI acquisitions, was analysed with non-parametric repeated-measures F tests (as in Knebel et al., 2011) with Group (Pat, Ctl) as a between-subjects factor and Stimulus position (Left, Center, Right) and Session (Pre-PA, Post-PA) as within-subjects factors.

For accuracy (Fig. 2), there was a significant main effect of Group ($p = 0.038$), which was driven by better performance in controls than patients. A significant main effect of Session ($p = 0.013$) was driven by better performances after PA than before PA. A trend was observed for the main effect of the factor Stimulus position ($p = 0.0507$), driven by globally higher accuracy when targets were in the right than in the center or left positions. This effect tended to be larger for the patients than for control group as shown by the trend observed for the interaction between the factors Group and Stimulus position ($p = 0.066$). The interaction between the factors Group and Session showed also a trend ($p = 0.060$), driven by larger differences between sessions for the patients compared to the controls.

For response times (Fig. 2), this non-parametric repeated-measures F test showed significant main effects of the factors Group ($p = 0.0002$) and Stimulus position ($p = 0.0001$), as well as a significant interaction between these two factors ($p = 0.006$). Patients are slower than controls, and more so when targets are in the left, compared to the center and right positions. Finally, the interaction between the factors Group and Session showed a trend ($p = 0.08$), the patients tended to be faster after the PA session whereas controls then to be slower.

3.2. fMRI results

The activation patterns were assessed in successive steps, from more global analyses including both groups and all conditions to local analyses detailing the effects in each group. Three-way mixed-design ANOVA with Group (Pat, Ctl) as a between-subjects factor and Stimulus position (Left, Center, Right) and Session (Pre-PA, Post-PA) as within-subjects factors (Fig. 3 top, Table 2) revealed large significant interactions between Group, Session and Stimulus position in the left temporal

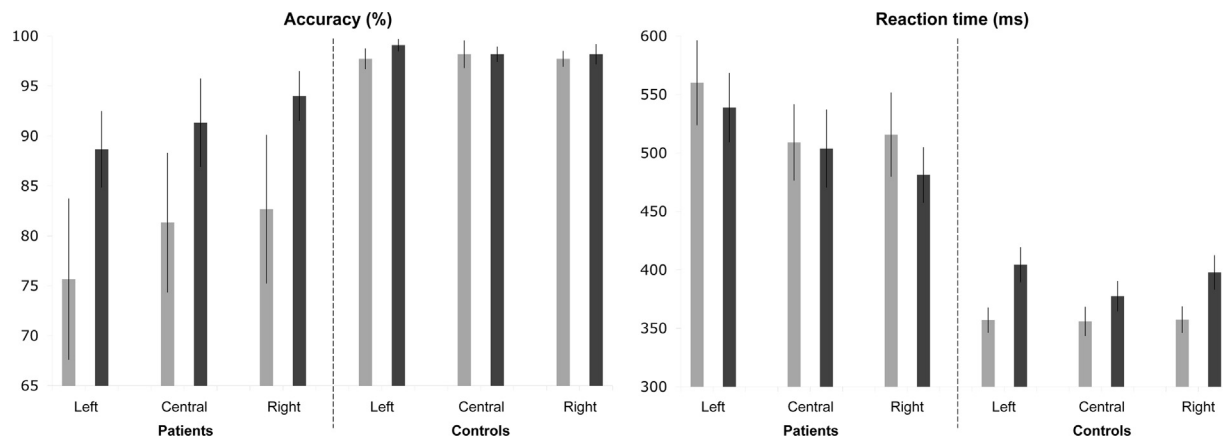


Fig. 2. Mean (± SEM) accuracy (% of correct response) and reaction time (of the correct responses) for the patients and controls as a function of the stimulus position and session (session 1 in light grey and session 2 in dark grey).

regions, including an area (region 1) in the anterior region of the superior temporal gyrus (STG) and middle temporal gyrus (MTG) and a large region in the posterior part of the superior (region 2) and middle (region 3) temporal gyri just below the temporo-parietal junction. Additional interactions were significant in the left IPL (region 4), as well as in frontal regions, in the inferior (region 5) and middle frontal gyri. The significant interaction within these five regions was mostly driven by differential modulation of activation by left vs central vs right stimuli in patients and controls, as shown by the analysis of regions of interest (Fig. 3 middle portion). In the temporal regions (regions 1–3), patients tended, after PA, to show increased activation related to the left and central stimuli and decreased activation induced by right stimuli, whereas in the same regions control subjects tended to show decreased activation related to all stimuli after PA (except for the region 3 right stimuli). In the IPL (region 4), patients showed the same effect (increased activation for left and central stimuli and decreased for right

stimuli after PA), whereas controls showed decreased activation for central stimuli and increased activation for left and right stimuli. Modulations related to these stimuli are similar to our findings in a group of young controls (Crottaz-Herbette et al., 2014). In IFG (region 5), patients showed increased activation for the left stimuli and, to a smaller extent, to central stimuli and decreased activation for right stimuli. For this region, controls showed decreased activation for left and central stimuli and an increase for right stimuli. Thus, neuronal activity increased in response to left and right targets within the left IPL in controls, whereas the increase in the IPL was observed for left and central targets in patients. More importantly, PA increased activation in patients in the left temporal regions.

Two-way ANOVA with the factors Stimulus position (Left, Center, Right) and Session (Pre-PA, Post-PA) were carried out separately in patients and controls (Fig. 3 bottom, Table 2). Significant interactions between the factors Session and Stimulus position highlighted the

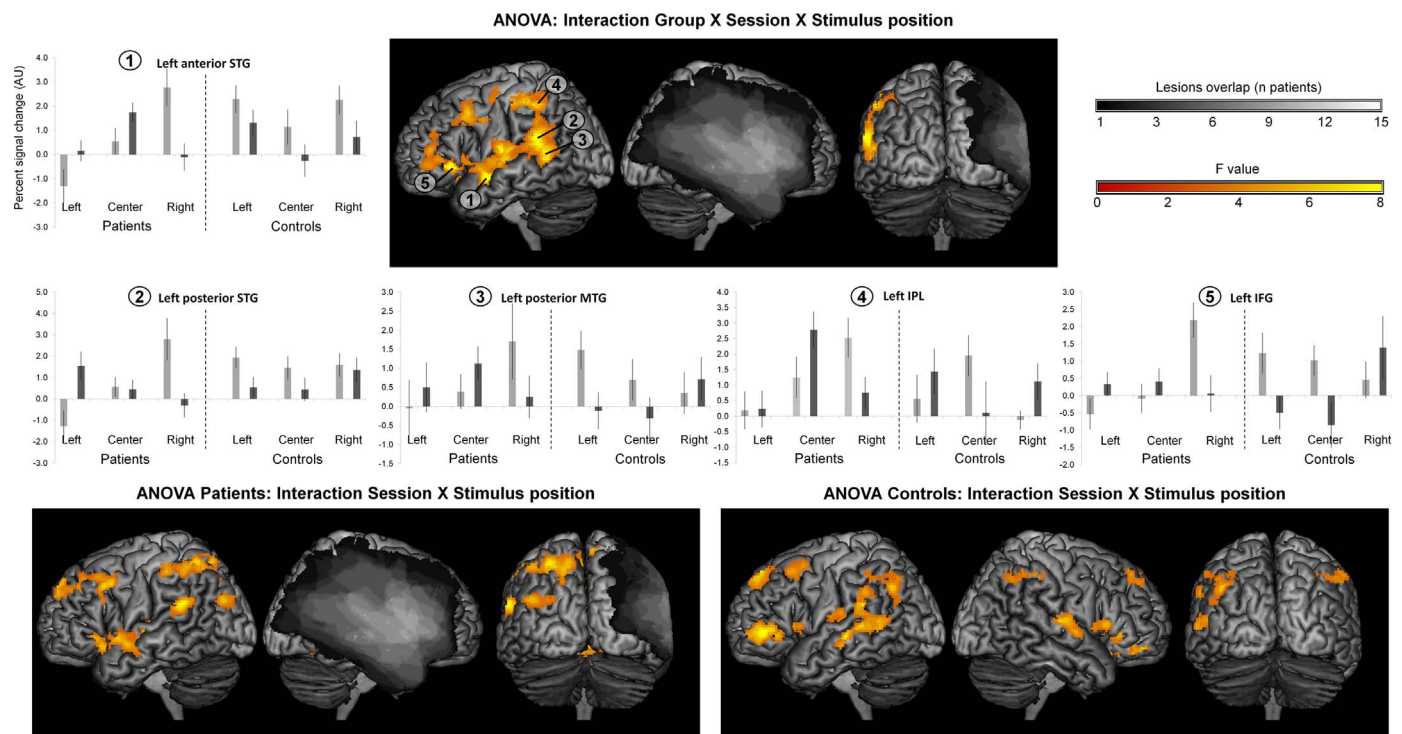


Fig. 3. Surface renderings of the brain activation showing significant interaction in 3-way ANOVA between the factors Group x Stimulus position x Session (top, middle) and in 2-way ANOVAs between the factors Stimulus position x Session for the patients (bottom, left) and controls (bottom, right). The lesion overlap across the 15 patients is displayed with a greyscale on the surface renderings (top middle and bottom left). Numbers 1–5: Graphs (mean ± SEM) of the percent BOLD signal changes in session 1 (in light grey) and session 2 (in dark grey) as a function of the position of the visual stimuli in region 1 top 5. All activation maps are thresholded at $p < 0.05$ and cluster extent of $k > 70$. AU: arbitrary unit.

Table 2

(A) Brain regions showing significant effects in the 3-way ANOVA (Group x Stimulus position x Session); and in the 2-way ANOVAs (Stimulus position x Session) for (B) the patients and (C) the controls. BA; Brodmann area; MNI: Montreal neurological institute.

Area	BA	Number of voxels	Peak intensity	Peak MNI Coordinates
A 3-way ANOVA (Group x Stimulus position x Session)				
Left STG, MTG, IPL, supramarginal gyrus	21, 22, 40, 42	2574	10.2	-46 -2 -10
Left inferior and middle frontal gyri, insula	10, 13, 44, 45, 47	769	9.7	-36 28 -2
Left and right anterior cerebellum		349	7.4	-14 -44 -16
Left middle frontal gyrus	8, 9	263	6.4	-46 14 42
Left and right anterior cingulate, medial frontal gyrus	8, 9, 32	259	6.8	-2 34 28
Left precentral gyrus	6	143	6.0	-26 -8 48
B Patients 2-way ANOVA (Stimulus position x Session)				
Left and right hippocampus, thalamus, parahippocampal, fusiform, precuneus and lingual gyri, calcarine, anterior cerebellum, vermis	18, 19, 30, 35,36, 37	3314	13.3	-18 -38 4
Left superior and inferior parietal lobules	7, 40	849	8.5	-30 -56 56
Left superior temporal gyrus and inferior frontal gyri	22, 47	791	6.4	-36 26 -6
Left and right middle cingulate and precuneus gyri, paracentral lobule	5, 6, 31	552	8.7	4 -24 50
Left superior and middle frontal gyri	8, 9	387	6.8	-12 52 42
Left middle and inferior frontal gyri	8, 9	292	7.1	-40 12 40
Left angular gyrus	39	201	6.0	-46 -78 28
Left supramarginal and superior temporal gyri	40, 42	181	7.9	-62 -46 24
C Controls 2-way ANOVA (Stimulus position x Session)				
Left MTG, STG, IPL, supramarginal gyrus, insula	13, 21, 22, 40, 42	1031	8.6	-56 -26 0
Left inferior frontal gyrus, insula	13, 44, 45, 47	701	8.6	-42 42 2
Right inferior frontal gyrus, insula	13, 44, 45, 47	339	5.8	50 20 8
Left angular gyrus, IPL	39, 40	282	6.6	-42 -62 38
Right STG	22, 42	243	6.7	66 -16 10
Left superior frontal gyrus	8, 9	217	7.5	-14 44 50
Left middle frontal gyrus	8	194	5.5	-38 18 50
Right middle and inferior frontal gyrus	11, 47	175	6.7	32 42 -14
Right IPL, supramarginal and angular gyri	39, 40	168	5.0	40 -52 42
Right superior frontal gyrus	8, 9	139	5.1	24 40 48

regions which were partially co-extensive with the regions revealed by the triple Group x Session x Stimulus position interaction. In patients, a significant interaction of Session and Stimulus position was found within the left hemisphere in clusters on the anterior and posterior parts of the temporal convexity, in the IPL and on the prefrontal cortex. In the control group, a significant interaction of Session and Stimulus position was found within the left hemisphere in clusters at the temporo-parieto-occipital junctions, within the right hemisphere in temporal areas and bilaterally in the prefrontal cortices.

Post hoc T-tests for the patient group, comparing activation before and after PA for each stimulus position, confirmed extended modulation in the temporo-parieto-occipital cortex (Fig. 4). The activation increased significantly after PA for left targets in the left STG, insula and precentral gyrus; these left targets induced decreased activation after PA in the superior parietal lobule. For central targets, increased activation was mainly observed in the left STG, MTG, IPL, precuneus, middle and superior frontal gyri, posterior cingulate and extrastriate occipital cortices and in the right superior and medial frontal gyri, occipital and calcarine gyri. For right targets, PA increased activation in the left middle occipital and inferior temporal gyri and in the right superior frontal and middle cingulate gyri, while PA decreased activation in the left supramarginal gyrus in the IPL (Fig. 4).

In summary, a brief exposure to prismatic adaptation enhances, in both patients and control subjects, the competence of the left hemisphere for the left space, but the regions extended beyond the inferior parietal lobule to the temporal convexity in patients.

3.3. Correlations

The change in activation in the left anterior STG-MTG (region 1 Fig. 3, MNI coordinates: -52 6 -4) correlated significantly with neglect severity, as measured by the first bell detected on the Bells test before PA ($r = 0.553$; $p = 0.04$); the more severe the neglect, the greater the PA-induced increase in this region (Fig. 5A).

In patients, PA significantly improved the detection accuracy of the left and central targets (Fig. 2); we tested if this improvement was correlated with the increase in the representation of these targets within the left hemisphere. The PA-induced change in the performance of target detection correlated significantly with the change in activation in the anterior STG-MTG (region 1 Fig. 3, $r = 0.533$; $p = 0.05$); the greater the PA-induced increase in activation, the greater the performance improvement (Fig. 5B). The PA-induced change in performance also correlated positively with the posterior STG change in activation (region 2 Fig. 3, MNI coordinates: -64 -46 14, $r = 0.551$; $p = 0.033$,

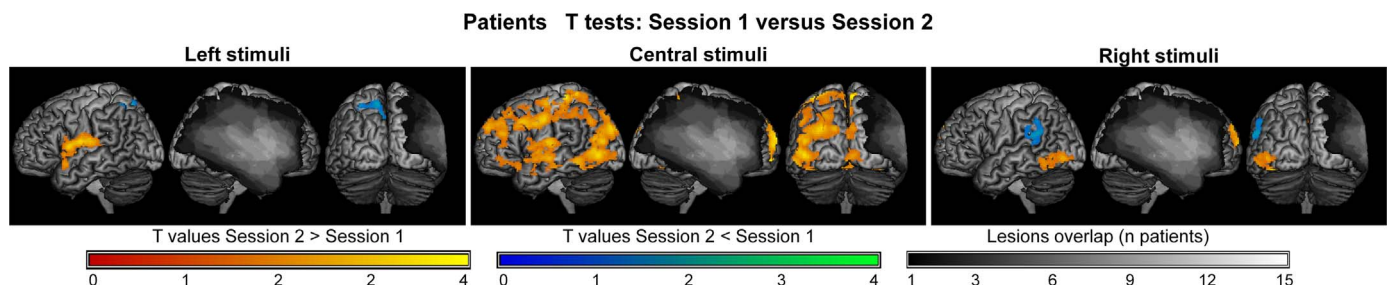


Fig. 4. Surface renderings of the brain activation of the patient group showing significant differences between Session 1 and Session 2 (T-test; red to yellow scale: Session 2 > Session 1, blue to green scale: Session 2 < Session 1) for each stimulus position separately. The lesion overlap across the 15 patients is displayed with a greyscale on the surface renderings. All maps are thresholded at $p < 0.05$ and cluster extent of $k > 70$.

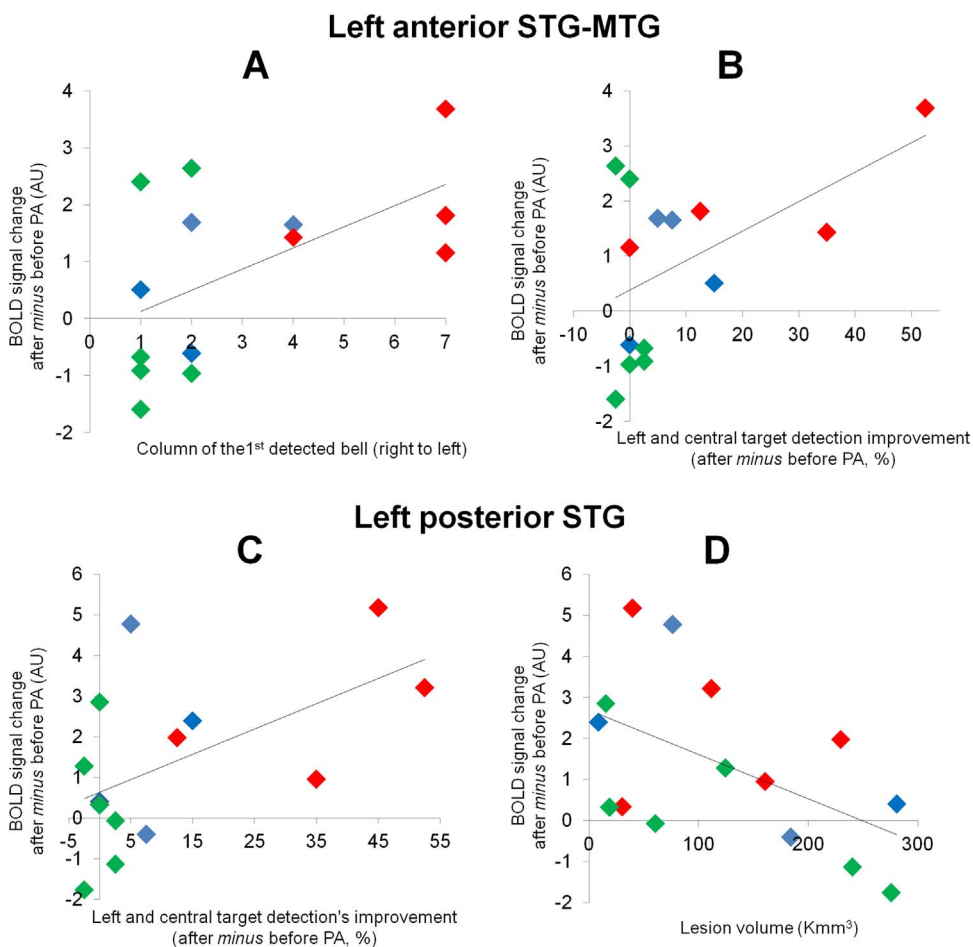


Fig. 5. Graphs of the relation between the changes in BOLD signal modulation after a comparison with the signal prior to PA in the left anterior STG-MTG region and (A) the column of the first detected item in the Bells test; and (B) improvement of the left and central stimuli detection. Graphs of the relationship between the changes in BOLD signal modulation after a comparison with the signal prior to PA in the left posterior STG and (C) the improvement of the left and central stimuli detection; and (D) the volume of the lesion reconstructions. In all graphs, patients with the lowest average accuracy (< 80%) for left and central targets during the task conducted before PA exposure are indicated in red, while patients with the highest average accuracy (> 98%) for these stimuli are indicated in green. Patients with an average accuracy for these stimuli between 85% and 95% are indicated in blue. Both correlations including the left anterior STG-MTG ROIs (A and B) were calculated on 14 patients, as one patient showing an outlier BOLD signal change was removed from these analyses.

Fig. 5C).

In addition, the PA-induced increase of activation in the left posterior STG was negatively correlated with lesion volume ($r = -0.523$; $p = 0.045$); a greater increase in activity was found in cases with smaller lesions (Fig. 5D).

The correlation between the time since stroke and the PA-related changes in BOLD activation did not yield any significant effect for the anterior STG-MTG region or the posterior STG region. In summary, the effect of PA appears to be particularly beneficial for patients with severe neglect and is very likely to depend on the recruitment of the left temporal regions.

4. Discussion

In neglect patients, a brief exposure to PA improved the accuracy of target detection in the left and central visual field and enhanced the neuronal response to left and central stimuli within the left hemisphere, in the STG, IPL and prefrontal cortex. This effect did not correspond to a general increase in left hemispheric activity, since neuronal activation elicited by stimuli presented within the right visual field tended to decrease after PA. Across patients, performance improvement within the left and central field correlated significantly with the increase in neuronal activation within the clusters on the anterior and posterior portions of the STG. These findings demonstrate that the left hemisphere, particularly the STG, provide compensatory mechanisms in neglect. The implication of the left STG in the representation of the left and central space very likely has a causal relationship with the behavioural improvement in target detection. The left hemispheric involvement which we observed is not a mere effect of (very) large right hemispheric lesions or a transient phenomenon. In fact, the effect of PA

on the recruitment of the left STG tended to be greater in patients with small lesions and it did not depend on time since stroke.

4.1. Contribution of the left hemisphere to recovery from neglect

A series of seminal fMRI studies investigated the role of the left hemisphere in the recovery from neglect. Using the Posner task, Corbetta and colleagues have shown that four weeks after stroke, the deficits in target detection could be related to abnormally low activation in the dorsal parietal and occipital cortices on the right side and in the prefrontal and occipital cortices on the left side; at the same time, there was strong activation within the left parietal and motor cortices (Corbetta et al., 2005). The positive correlation Corbetta et al. found between activation in the left STG and response times to invalid cued trials suggested that the involvement of this region may be indicative of bad performance. In the chronic stage (39 weeks post-stroke), the authors described strong reactivation in both hemispheres, while the left superior parietal lobule, which exhibited overactivation at four weeks, was back to normal. These observations were interpreted in the context of the hemispheric rivalry model; according to this model, a right hemispheric lesion creates an imbalance between the hemispheres and results in hyperresponsiveness of the left superior parietal lobule, which creates a right-ward attentional bias (Corbetta et al., 2005; Corbetta and Shulman, 2011; Kinsbourne, 1987, 1993). The postulated hyperexcitability of the parieto-motor circuitry has been demonstrated very elegantly by transcranial magnetic stimulation or transcranial direct current stimulation experiments (Koch et al., 2008; Müri et al., 2013; Nyffeler et al., 2009; Sparing et al., 2009).

The conclusion that neglect is mainly due to deleterious hyperactivation of the left hemisphere has been questioned (Karnath, 2015).

Indeed, a recent study challenged the assertion that the relative hyperactivation of the left parietal cortex is characteristic of neglect (and not generally of a right hemispheric lesion; Umarova et al., 2011). The authors compared the activation yielded by a Posner task in normal subjects and in patients with acute right hemispheric lesions. Not only the patients with neglect but also patients with only extinction and control patients (normal visuo-spatial performance) showed an imbalance in left-right parietal activation, which was proposed to represent “an epiphenomenon of the acute structural lesion in the right hemisphere”. Furthermore, the more the left parietal and prefrontal cortices were activated in patients with neglect or extinction, the better was their performance in the detection of left targets. The authors concluded that the parieto-frontal attentional network within the left hemisphere may provide compensatory mechanisms in neglect. Our results further confirm that the left hemisphere, particularly the superior temporal cortex, is likely to provide compensatory mechanisms in neglect.

4.2. The superior temporal gyrus

Several lesion studies highlighted the critical role of right superior temporal lesions in visuo-spatial neglect. Overlap of lesions (Karnath et al., 2001) and voxel-wise mapping in a large number of cases (Karnath et al., 2004) identified the right superior temporal cortex as one of the key damaged structures in both the acute and chronic stages of neglect (Karnath et al., 2011). The relationship is particularly strong for subtypes of neglect, such as extrapersonal space (Committeri et al., 2007) or for allocentric frames of reference.

There is concurring evidence from studies in normal subjects that the superior temporal region is involved in visual attention. In both hemispheres, this region was shown to be activated when attending to contralateral targets (Macaluso and Frith, 2000). The superior temporal region is part of the network that is involved in reorienting attention (Thiel et al., 2004). In addition, the left and right STG were reported to be activated during the exploration of a dense stimulus (Himmelbach et al., 2006) and to be modulated during a task in an allocentric frame of reference (Neggens et al., 2006).

What is particularly interesting for our study is that the superior temporal region encodes visual information in the context of multisensory representations. The superior temporal sulcus has been shown to receive visual, auditory and somatosensory input, partially segregated in separate clusters and partially overlapping (Beauchamp et al., 2004a). This region was specifically explored for the combination of visual and auditory stimuli, which yielded greater responses when combined (Beauchamp et al., 2004b), with fine tuning to temporal overlap between the two modalities (Noesselt et al., 2007). The effect was contralateral to visual stimulation (the auditory stimulation being not lateralized; Noesselt et al., 2007).

Thus, current evidence strongly supports a role for the superior temporal region in visual representations, including attentional tasks and multisensory context. However, there is no prior report of the involvement of the left superior temporal region in the representation of the ipsilateral, left visual field.

4.3. Effects of therapeutic interventions in normal subjects and neglect patients

A brief therapeutic intervention, PA, led to a change in hemispheric competence in both normal subjects (Crottaz-Herbette et al., 2014; here) and neglect patients. The left hemisphere exhibited increased competence for the ipsilateral, left visual hemifield. In patients, the change in visual representation correlated with the improvement of target detection in the left and central visual space. However, there was a difference between normal subjects and patients which concerned the regions where activity was modulated by PA. In normal subjects, the effect mostly concerned the angular gyrus, whereas the effect mostly

concerned the temporal areas in the patients.

The left temporal region, together with the posterior parietal cortex, was proposed to be involved in recovery from neglect, as they are functionally homologous to those areas involved in spatial cognition in the damaged hemisphere (Pisella et al., 2006; Rode et al., 2006a, 2006b). A behavioural improvement in target detection between the acute and early chronic stage was indeed shown to be associated with a gain in activity on the left side in the STG, the angular gyrus and the anterior cingulate cortex, along with an increase on the right side in the IPL, the middle frontal gyrus, the inferior temporal gyrus and the fusiform gyrus (Thimm et al., 2008).

Two previous neuroimaging studies investigated different types of PA-induced changes in neglect. Their results are compatible with our observations, but they do not address the issue of a shift within the ventral attentional system. Luauté et al. reported a significant correlation between PA-induced improvement in performance in the Behavioural Inattention Test and increase in regional cerebral blood flow in the left temporo-occipital and medial temporal cortex, the left thalamus, the right posterior parietal cortex and the right cerebellum (Luauté et al., 2006). Their observation stresses the role of the left temporal cortex in the effect of PA and is compatible with our results. Saj et al. used two tasks known to involve the dorsal attentional system, line bisection and visual search, and reported a PA-induced increase within a bilateral occipito-parieto-frontal network, predominantly within the superior parietal lobules (Saj et al., 2013). This study did not address the issues of PA-induced modulation within the ventral attentional system; furthermore, it did not analyse separately activation patterns to stimuli presented in the right or left hemifield.

The striking similarity in the overall effect of PA in normal subjects and neglect patients, as demonstrated in our study, suggests that the left hemisphere has the potential to take over dominance for the representation of the whole visual space. The precise mechanisms by which PA facilitates this change are currently unknown. The rapidity of the effect suggests that it relies on uncovering pre-existing synaptic contacts rather than creating new ones. Why PA involves mostly the left superior temporal region in neglect patients and the angular gyrus in normal, young subjects requires further investigation.

The PA-induced modulation of the ventral attentional system is very likely to have widespread effects. The ventral attentional system is densely interconnected with the dorsal system, and there are close interactions between top-down attentional control by the dorsal system and stimulus-driven, bottom-up control by the ventral system (Corbetta and Shulman, 2002). The finely-tuned, reciprocal inhibitory connections between the left and right dorsal regions, which are disrupted by right hemispheric lesions, were proposed to create a rightward attentional bias (Corbetta and Shulman, 2011; Koch et al., 2008, 2011). The PA-induced involvement of the left IPL and temporal regions in the detection of salient targets is likely to provide alerting visual input to dorsal networks on either side and to restore their inhibitory balance. This would predict restoration of dorsal system function, as indeed demonstrated in previous behavioural and fMRI studies in patients with right hemispheric lesions. In behavioural studies using covert orienting of attention (Striemer and Danckert, 2010), PA was indeed shown to reduce the rightward attentional bias and the reorienting deficit (Nijboer et al., 2008; Schindler et al., 2009; Striemer and Danckert, 2007). In a fMRI study, which used two tasks known to activate the dorsal attentional system in normal subjects (e.g., Baumgartner et al., 2013; Leonards et al., 2000), PA induced greater activation by these tasks within regions known to belong to the dorsal system (Saj et al., 2013).

5. Conclusions

In this study, PA was shown to enhance left hemispheric competence for left visual space in neglect patients, as it was previously demonstrated for normal subjects (Crottaz-Herbette et al., 2014). In

patients, the change in visual representation correlated with improvement of target detection and concerned not only the left but also the central visual space. The PA-induced increase of the left visual field representation in neglect predominately involved the left superior temporal region, which is known for its involvement in visuo-attentional and multisensory representations. Our results suggest that the left hemisphere, particularly the superior temporal region, contribute to the compensatory mechanisms which lead to the alleviation of neglect.

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