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Remodelling the attentional system after left hemispheric stroke: Effect of leftward prismatic adaptation

Sonia Crottaz-Herbette [a,*], Isabel Tissieres [a], Eleonora Fornari [b], Pierre-André Rapin [a,c] and Stephanie Clarke [a]

[a] Neuropsychology and Neurorehabilitation Service, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Lausanne, Switzerland

[b] CIBM (Centre d'Imagerie Biomédicale), Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Lausanne, Switzerland

[c] Institution de Lavigny, Lavigny, Switzerland

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ABSTRACT

Left hemispheric stroke is known to be associated with right neglect and/or not lateralized attentional deficits. The former appears to respond favourably to leftward prismatic adaptation (L-PA), as reported in a case of a large left stroke. In normal subjects, brief exposure to L-PA was shown to enhance the representation of the right visual field within the right inferior parietal lobule, emphasizing thus right hemispheric dominance within the ventral attentional system. We have investigated whether L-PA does the same in left hemispheric stroke by comparing neural responses to left, central and right stimuli before and after a brief exposure to L-PA. Neural responses to visual stimuli were significantly modulated within a large part of the occipito-temporal cortex and in smaller clusters in the angular gyrus, the anterior temporal lobe and the insula, corresponding to decrease in activity. Within the occipito-temporal region the decrease concerned predominantly neural activity elicited by left stimuli, downregulating thus the representation of the contralateral visual field, which is characteristic of the higher-order visual areas in this region.

Abbreviations: IPL, inferior parietal lobule; L-PA, prismatic adaptation induced by leftward deviating prisms; LHD, left hemispheric damage; PA, prismatic adaptation; R-PA, prismatic adaptation induced by rightward deviating prisms; RHD, right hemispheric damage.

* *Corresponding author.* Neuropsychology and Neurorehabilitation Service, Lausanne University Hospital (CHUV), Av. Pierre-Decker 5, 1011, Lausanne, Switzerland.

E-mail address: Sonia.Crottaz-Herbette@chuv.ch (S. Crottaz-Herbette).

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1. Introduction

A series of influential studies reported the occurrence of right visuo-spatial neglect following left hemispheric damage (LHD; e.g., Becker & Karnath, 2007; Beis, et al., 2004; Kleinman et al., 2007). Beyond the acute and postacute stages, right neglect tends to occur less frequently than left neglect after right hemispheric lesions and to recover more rapidly (Bowen, McKenna, & Tallis, 1999; Gainotti, Messerli, & Tissot, 1972; Ringman, Saver, Woolson, & Adams, 2005; Stone, Patel, Greenwood, & Halligan, 1992; Suchan, Rorden, & Karnath, 2012), suggesting that different neural mechanisms may be at play. Furthermore, attentional deficits associated with LHD appear to be less lateralized to the contralesional space and/or less severe (Ten Brink et al., 2017; Timpert, Weiss, Vossel, Dovern, & Fink, 2015). However, increasing the attentional load with multitasking paradigms was shown to reveal lateralized attentional deficits, which did not appear otherwise in classical neuropsychological testing (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Blini et al., 2016), illustrating well the discrepancy between performance at paper-pencil and computerized tasks (Bonato & Deouell, 2013). Together these studies suggest that right neglect in LHD is most likely underestimated.

The anatomical correlates of right neglect were investigated during the acute stage (Beume et al., 2017; Malherbe et al., 2018). Signs of visual neglect were associated with damage to the left superior and middle temporal gyri, including their anterior parts, the inferior ventral premotor cortex, the frontal operculum, the angular gyrus, and the insula. The severity of the visuo-spatial attentional shift correlated with damage to the anterior part of the left temporal lobe and the left frontal operculum. The persistence of neglect symptoms until the discharge of the patients (at approximately 7–17 days post stroke, i.e., during the subacute stage) correlated with damage to the posterior part of the middle temporal gyrus. As pointed out by the authors, the neural substrate of right neglect involved in the left hemisphere the same set of regions as does left neglect in the right hemisphere (Beume et al., 2017). The latter, i.e., left neglect in patients with right hemispheric damages (RHD) was found to be associated with lesions in the right superior temporal gyrus (Karnath, Mandler, & Clavagnier, 2011), the frontal convexity (Farnè et al., 2004; Maguire & Ogden, 2002), and/or damage to white matter fiber tracts (e.g., de Schotten et al., 2005; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008).

Right neglect, which persists into the chronic stage, can be severe, with major impact on activities of daily living (Beume et al., 2017; Malherbe et al., 2018). A pioneering study has reported a beneficial effect of leftward prismatic adaptation (L-PA) in a case of a large left fronto-parietal lesion (Bultitude & Rafal, 2010). This intriguing observation brings up interesting conceptual and clinical issues.

L-PA consists of a brief session, during which the subject wears left-deviating prisms while pointing to targets under visual control. In normal subjects the exposure to L-PA was found to induce neglect-like performance in specific tests of visuo-spatial attention, including right-ward bias in the line bisection task (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Michel, 2003, 2016), which can be long-lasting (Schintu et al., 2014). No behavioural effects were observed in the endogenous variant of the Posner paradigm (Bultitude, Van der Stigchel, & Nijboer, 2013; Morris et al., 2004). A series of activation studies investigated in normal subjects neural processes underlying ongoing L-PA and highlighted a key role of the parieto-temporal cortex and the cerebellum during the stages of visual and proprioceptive spatial realignement (Chapman et al., 2010; Clower et al., 1996; Luauté et al., 2009). The changes in brain organization, which are induced by L-PA and which may underlie the effect of L-PA in normal subjects, were highlighted in three recent studies. A brief exposure to L-PA was shown to increase the representation of the right visual field within the right inferior parietal lobule (IPL), enhancing thus right hemispheric dominance within the ventral attentional system (Crottaz-Herbette, Fornari, Tissieres, & Clarke, 2017). The authors proposed that the increase of right visual field representation within the ventral attentional system may strengthen the impact of the left dorsal attentional system and result in attentional bias towards the right space. This effect is likely to be enhanced by imbalance in interhemispheric inhibition, as demonstrated in two studies. An elegant electrophysiological study reported that L-PA yields unidirectional increase in interhemispheric inhibition, from the left to the right primary motor cortex (Martín-Arévalo, Schintu, Farnè, Pisella, & Reilly, 2016). Evoked visual potentials recorded during the endogenous variant of the Posner task revealed that L-PA induces asymmetry in neural activity related to attentional orienting and to attentional disengagement (Martín-Arévalo, Laube et al., 2016). The former was characterized by the reduction of the N1 amplitude elicited by the cue, which was greater for leftward than rightward cues, and the latter by the reduction of the P1 amplitude, which was greater for the invalidly cued left than right targets. Interestingly, these well documented changes in neural activity are not accompanied by changes in performance during the Posner task (Bultitude et al., 2013; Morris et al., 2004).

To our knowledge modulation induced by L-PA has not been investigated in brain damaged patients. Several neuroimaging studies have, however, examined modulation induced by rightward prismatic adaptation (R-PA) in patients with RHD. Using PET, the first study of 5 RHD patients showed a correlation between the alleviation of left neglect symptoms after R-PA and increase in activation of the right cerebellum, left thalamus, and left temporo-occipital cortex combined with a decrease in activation of the left medial temporal lobe and right posterior parietal lobule (Luauté et al., 2006). A second study of 7 patients compared R-PA-induced changes in task-related fMRI (Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013) and showed a bilateral increase in activation in parietal, frontal and occipital cortices during bisection and visual search tasks. A recent study of 15 RHD patients showed that R-PA improved the detection of target in the left and central visual field while enhancing the left hemispheric activation in the superior temporal gyrus, inferior parietal lobule and prefrontal cortex (Crottaz-Herbette, Fornari, Notter et al., 2017).

As indicated previously (Bultitude & Rafal, 2010), L-PA may offer interesting therapeutic options for right neglect. In addition, it may be also of interest for patients with LHD, who

present non-lateralized attentional deficits (Murakami et al., 2014). For these clinical indications, we need a better understanding of neural mechanisms, which underlie the effect of L-PA in patients with LHD. We have investigated here how a brief exposure to L-PA affects the representation of the visual field within the right, intact hemisphere of patients, who sustained a first left hemispheric stroke. Our study was driven by two hypotheses. First, the exposure to L-PA may lead in patients with LHD to a similar enhancement of the contralesional, right visual field within the right-dominant ventral attentional system, as it does in normal subjects (Crottaz-Herbette, Fornari, Tissieres et al., 2017). Such an enhancement of the ipsilesional visual field within the contralesional IPL has been demonstrated with rightward prismatic adaptation both in normal subjects and in patients with right hemispheric damage (Crottaz-Herbette, Fornari, Notter et al., 2017; Tissieres, Elamly, Clarke, & Crottaz-Herbette, 2017). Second, the exposure to L-PA in patients with LHD may restore visual field representations within the right hemisphere by re-sharpening them and decreasing exhuberant activations within higher-order visual areas and/or the attentional system, which appear in the wake of the contralateral lesion. Unilateral hemispheric lesions are well known to alter the processing within the contralesional, intact hemisphere. Thus, the contralesional hemisphere was shown to process auditory information pertaining to sound localization or to sound localization within a common perisylvian area and not within the dedicated specialized processing pathways, the auditory ventral and dorsal streams (Adriani et al., 2003). Following LHD the right hemisphere has been repeatedly found to increase transiently or permanently its participation in speech processing (Crinion & Leff, 2007; Saur et al., 2006).

2. Participants and methods

2.1. Participants

Twenty-three participants were included in the present study, 14 control subjects (7 men, mean age 24.1 SD = 3.0 years) and 9 patients with a left hemispheric damage (7 men, mean age = 55.7 years, SD = 8.7). Patients were recruited in the Neuropsychology and Neurorehabilitation service, Centre Hospitalier Universitaire Vaudois and in the Neurorehabilitation service, Lavigny Institution. All patients fulfilled the following inclusion criteria: i) first unilateral left hemispheric stroke; ii) absence of major comprehension deficit; iii) normal or corrected-to-normal vision; iv) absence of visual field deficit; and v) absence of prior psychiatric or neurological disease. At the time of their inclusion in this study, patients had typical residual symptoms of LHD, including language deficits, apraxia, executive dysfunction as well - in few cases - lateralized attentional deficits (Table 1). Lateralized attentional deficits were evaluated at the time of the fMRI investigation by three approaches. First, the Bell cancellation task, as formulated in the "Batterie d'évaluation de la négligence unilatétale" (BEN; Azouvi et al., 2006a), was carried out and the "Center of Cancellation" (CoC) score was calculated (Rorden & Karnath, 2010). This index varies from +1, typical for left neglect, to −1 for right neglect, a score smaller (i.e., more negative) than −.086 is indicative of right lateralized attention deficits (Suchan et al., 2012). Second, the accuracy of target detection was recorded during the fMRI sessions, an asymmetry during the pre-L-PA session reflecting lateralized attentional deficits. Third, clinical evaluation of each patient included search for lateralized attentional deficits. All patients were right handed (Oldfield, 1971) and tested in the subacute phase (delay post-stroke onset: mean = 222.8 days, SD = 163.8 days; Table 1). The study was approved by the Ethics Committee of the Canton de Vaud and all patients gave written informed consent.

2.2. Design and procedure

The procedure was similar to the one used in previous studies (Crottaz-Herbette, Fornari, & Clarke, 2014; Crottaz-Herbette, Fornari, Notter et al., 2017; Crottaz-Herbette, Fornari, Tissieres et al., 2017) and involved an MRI block of anatomical sequences and two event-related fMRI acquisitions separated by a 3 min session of adaptation using leftward deviating prisms.

2.2.1. Visual detection task

The task used during the event-related fMRI acquisitions involved visual stimuli, white stars on a black background, presented in a pseudo-randomized order on the midsagittal plane (0°), 20° to the left or 20° to the right. Visual stimuli were displayed during 500 msec and each stimulus position appeared 20 times. The jitter of inter-event intervals was up to 20 secs with steps of 1 sec. The duration of the task was 6 min 44 secs. Participants were asked to maintain their gaze on the red cross in the centre of the screen and to press on a button with their left index when a target was detected. The task was developed using the software E-Prime (Psychology Software Tools, Inc.). Statistical analyses were conducted on the behavioral performances (accuracy and reaction time) recorded during the fMRI-related task using a repeated-measures ANOVA with Stimulus position (left, centre, right) and Session (pre-PA, post-PA) as within-subjects factor.

2.2.2. Prismatic adaptation

The L-PA adaptation consisted of an adaptation phase during which the participants performed 150 pointing movements on average while wearing goggles deviating the entire visual field 10° to the left (www.optiquepeter.com). This visuomotor adaptation was performed outside the scanner. During the adaptation, participants were seating in front of a table, their head was maintained using a chinrest, the first two thirds of the pointing movements were hidden from his/her view. They were asked to use their left index to point to the two black dots presented on the table, 14° to the left and 14° to the right of the midsagittal plane. The intervals between the pointings varied between 1 and 1.5 secs to avoid automatic movements. The pointings were paced by the experimenter and kept constant across subjects. Participants showed pointing errors during the 10–15 first trials in the direction of the prisms' deviation. Then, they all adapted and pointed correctly to the black dots. The effect of the adaptation, the aftereffect, was measured as in the previous studies (Crottaz-Herbette et al., 2014; Crottaz-Herbette, Fornari, Notter et al., 2017; Crottaz-Herbette, Fornari, Tissieres et al., 2017; Tissieres I., Fornari E., Clarke S. and Crottaz-Herbette S, 2017) immediately after the L-PA

Table 1 – Patient characteristics. All patients sustained a first, left hemispheric stroke; the delay to the fMRI evaluation is indicated in days.

Patient	Sex	Age (years)	Delay (days)	Regions involved in the lesion	Lesion volume (mm3)	Language deficits	Apraxia	Executive dysfunction	Lateralized attentional deficits
LHD1	M	51.9	106	Pulvinar, BG	514	Fluent aphasia +	–	++	++ (1, 4)
LHD2	M	65.5	124	MTG, STG, AG	1073	Fluent aphasia ++	–	+	–
LHD3	M	44	214	Insula, BG, PHG	2824	Nonfluent aphasia ++	+	+	+ (2, 4)
LHD4	M	63.5	42	PreCG, PostCG, IFG, FG, insula, STG, TP	6581	Fluent aphasia +	+	+	–
LHD5	F	48.6	391	PreCG, PostCG, IFG, IPL, SMG, STG, MTG	9847	Nonfluent aphasia ++	++	+	–
LHD6	M	52.7	178	PreCG, PostCG, IFG, MFG, insula, STG, TP, SMG, IPL, BG	14097	Nonfluent aphasia +	++	+	++ (3, 4)
LHD7	F	54.9	483	PreCG, IFG, insula, IPL, ITG, MTG, TP, STG, BG	15904	Nonfluent aphasia ++	+	+++	++ (2, 3, 4)
LHD8	M	69.8	60	PreCG, IFG, MFG, Insula, MTG, STG, TP, PHG, BG	18695	Nonfluent aphasia +++	++	++	– (4)
LHD9	M	50.4	407	PreCG, PostCG, MFG, SFG, SMA, insula, IPL, SPL, SMG, STG, TP, ACC, BG	36729	Nonfluent aphasia ++	++	+	+ (3, 4)

Brain regions involved in the lesion: ACC (anterior cingulate cortex), AG (angular gyrus), BG (basal ganglia), FG (fusiform gyrus), IFG (inferior frontal gyrus), IPL (inferior parietal lobule), ITG (inferior temporal gyrus), MFG (middle frontal gyrus), MTG (middle temporal gyrus), PHG (parahippocampal gyrus), PostCG (postcentral gyrus), PreCG (precentral gyrus), SFG (superior frontal gyrus), SMA (supplementary motor area), SMG (supramarginal gyrus), SPL (superior parietal lobule), STG (superior temporal gyrus), TP (temporal pole).
At the time of the fMRI evaluation the patients presented typical residual LHD deficits, which were rated as +++ (severe); ++ (moderate); + (minor); or – (absent). Lateralized attentional deficits were found in individual patients with the Bell test (Center of Cancellation, CoC score; Rorden & Karnath, 2010; Suchan et al., 2012; indicated by (1), as asymmetry in target detection accuracy during the pre-PA fMRI session (2) or by clinical evaluation at the time of the fMRI (3). Several patients presented signs of right neglect during the acute and subacute stages (4).

exposure, once the prisms were removed. Participants were asked to look at one target, close their eyes and point without visual control towards the target. The pointing error was measured on the horizontal plane of the table and expressed in degrees, with 0° corresponding to the position of the targets, positive values representing deviations to the right of the targets and negative values deviations to the left of the target. The pointing errors for the left and the right targets (black dots on the table) were averaged.

2.2.3. *Lesion analysis*

Lesions from all nine patients were drawn using the MRI acquisitions on axial slices (Fig. 1) by using the MITK 3M3 software (http://www.mint-medical.de/) and then normalized on the Montreal Neurological Institute's (MNI) brain template by using the SPM12 software (Wellcome Department of Cognitive Neurology, London, UK). These lesions' images were included in the fMRI statistical analyses using the Clinical Toolbox for SPM (Brett, Leff, Rorden, & Ashburner, 2001; Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) that we adapted to work with SPM12. This step (see details below) prevented from adding artefacts to the results, which are often observed in patients with brain lesions (Strigel et al., 2005).

2.2.4. *fMRI acquisition and analysis*

MRI and event-related fMRI acquisitions were conducted at the Lemanic Biomedical Imaging Center (CIBM) in the CHUV, Lausanne. All the data were acquired on a 3T Siemens Magnetom Prisma scanner with a 64-channel head-coil, apart for one patient which was on a 3T Siemens Magnetom Trio scanner with a 32-channel head-coil. A single-shot echo planar imaging gradient echo sequence (repetition time = 2 sec; flip angle = 90°; echo time = 30 msec; number of slices = 32; voxel size = 2 × 2 × 3 mm for the Prisma scanner and 3 × 3 × 3 mm for the Trio scanner; 10% gap) was used for fMRI acquisitions. fMRI acquisistions were done in the AC-PC plane with 32 slices acquired in a sequential ascending order, covering the whole head volume. For each participant, a high-resolution T1-weighted 3D gradient-echo sequence was acquired (240 slices for the Prisma scanner data; 160 slices for the Trio scanner data, voxel size = 1 × 1 × 1 mm). Padding was added around the head of the participants within the coil to avoid head movements during the acquisitions.

Imaging data were processed using the Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK). First data were corrected for motion by applying a six-parameter rigid-body transformation minimizing the difference between each image and the first scan. Slice timing correction was performed on these realigned images. Then they were co-registered with the participants' anatomic images and normalized to the Montreal Neurological Institute (MNI) template using a twelve-parameters affine transformation. 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 SMP12. 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 then resliced to obtain a 2 × 2 × 2 mm voxel size and were finally spatially smoothed using an isotropic Gaussian kernel of 6 mm FWHM to increase the signal-to-noise ratio.

Subject-level statistical analyses were conducted using a general linear model, as implemented in the SPM12 software on the whole brain in a voxelwise manner. The six realignment parameters were included in the model as regressors. Linear contrasts were specified for all the participants and for both sessions in the same design matrix. Group-level statistical analyses based on the random field theory were performed using the maps generated from these linear contrasts. All group analyses were restricted to voxels with the probability of belonging to gray matter greater than 50%, as defined in the apriori template available in SPM.

General repeated-measures ANOVAs were conducted for patient and control groups separately including the within-subject factors Stimulus position (left, centre, right) and Session (pre-PA, post-PA). The interaction between these two factors (Stimulus position x Session) and the main effects of each factor were analysed. The statistical maps obtained from these interactions and main effects were set at a threshold of $p < .05$ and to a cluster extent of $k > 50$. Post hoc T-tests were performed to further investigate the effect of the adaptation on each stimulus position, using a comparison pre-PA > post-PA and a comparison post-PA > pre-PAA for left, centre and right stimuli separately. The statistical maps of these post hoc analyses were set at a threshold of $p < .05$ and to a cluster extent of $k > 50$.

3. Results

3.1. *Right neglect assessment*

Right lateralized attentional deficits were found in several patients with the Bell test (CoC < −.084; patient LHD1; Table 2); as asymmetry in target detection accuracy during the pre-L-PA fMRI session (LHD3, LHD 7; Table 2); or during clinical evaluation at the time of the fMRI investigation (LHD6, LHD7, LHD9; Table 1). In addition patients tended to be slower in detecting right than left targets during the pre-L-PA fMRI session. One patient presented signs of lateral attentional deficits during the acute stage, but not at the time of the fMRI investigation (LHD8).

3.2. *Behavioural aftereffects of L-PA*

When the prisms were removed, the first pointings deviated to the right of the target, an aftereffect which is consistent with the leftward deviation of the prisms. This deviation, called aftereffect, was present in all subjects and tended to be greater in patients (8.5°, SD = 4.8°) than in normal subjects (5.5°, SD = 2.4°).

3.3. *Detection of visual stimuli during fMRI paradigm*

The detection of visual stimuli during fMRI sessions that preceded and followed L-PA was performed readily by patients and by normal subjects. Individual performances of the

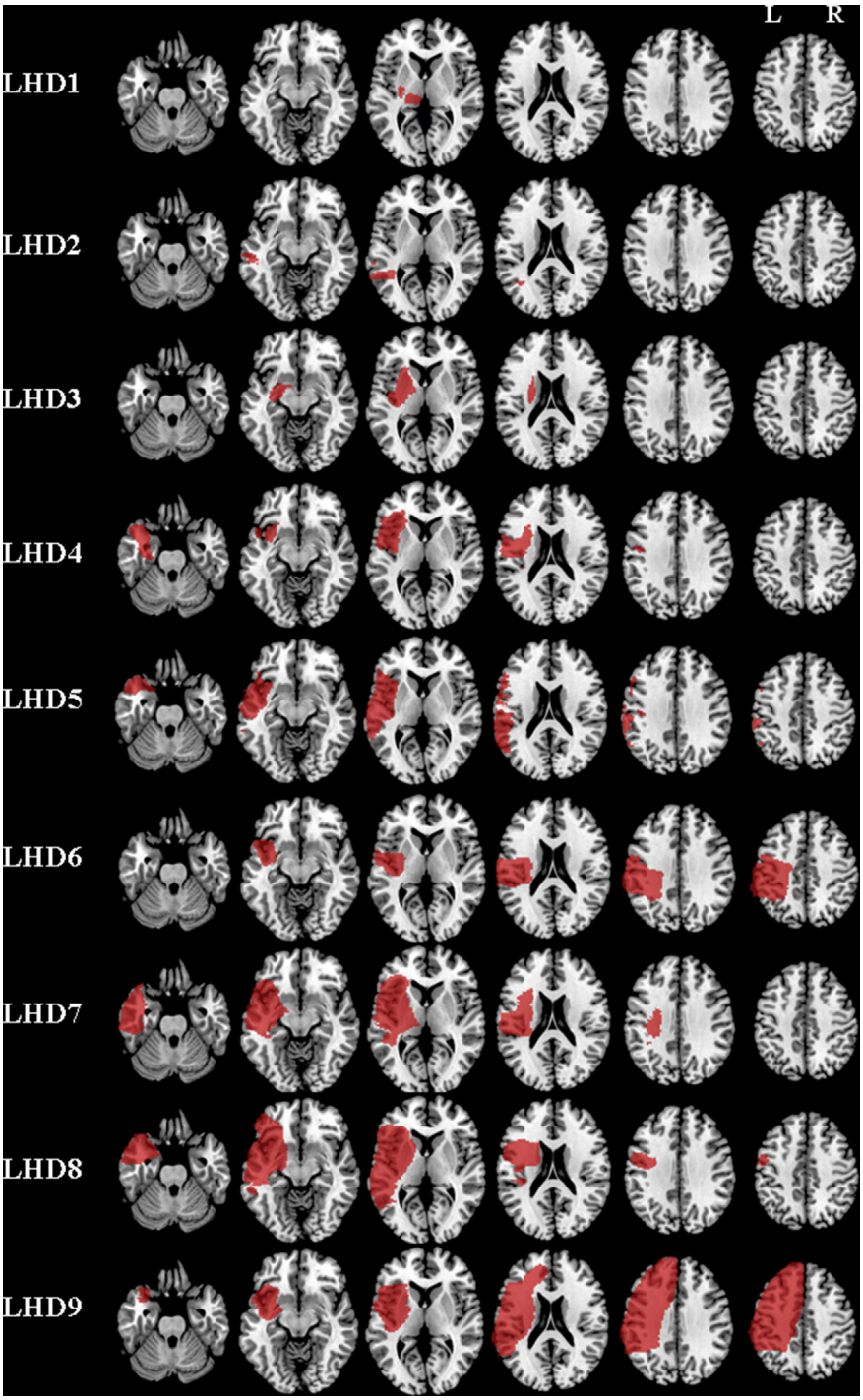

Fig. 1 – Lesions in nine patients who participated in this study on axial slices of a normalized MRI template. L: left hemisphere; R: right hemisphere.

patients are presented on Table 2. At the group level, the accuracy and reactions times were analysed in each group with a 2-way ANOVA with within-subject factors Stimulus position (left, centre, right) and Session (pre-PA, post-PA). The accuracy of patients did not show a significant interaction or main effect, although there were indications of improvement between pre-PA (left stimuli: mean = 92%, SD = .17%; centre stimuli: mean = 94%, SD = .10%; right stimuli: mean = 87%, SD = .11%) and post-PA sessions (left stimuli: mean = 99%, SD = .04%; centre stimuli: mean = 100%, SD = 0%; right stimuli: mean = 91%, SD = .23%). Reaction times of patients yielded a significant main effect Stimulus position ($F(1,7) = 15.4$, $p = .006$), driven by slower detection of stimuli on the right both before (left stimuli: mean = 460 msec, SD = 91 msec; centre stimuli: mean = 483 msec, SD = 106 msec; right stimuli: mean = 503 msec, SD = 110 msec) and after L-PA (left stimuli: mean = 440 msec, SD = 70 msec; centre stimuli: mean = 443 msec, SD = 83 msec; right stimuli:

Table 2 – A. Performance at the Bell test; Center of Cancellation (CoC) score smaller than −.086 is considered indicative of right neglect (Rorden & Karnath, 2010; Suchan et al., 2012). B & C. Accuracy and response times to targets presented during the Pre and Post fMRI session at the left, central and right positions.

Patient	A. Bell test	B. Accuracy (%)						C. Reaction time (msec)					
	CoC index	Left		Center		Right		Left		Center		Right	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
LHD1	−.1463	100	100	100	100	100	100	388	406	406	397	432	446
LHD2	0	100	100	95	100	100	100	624	590	702	638	721	667
LHD3	0	100	100	90	100	95	95	471	391	514	420	504	422
LHD4	−.0256	90	100	95	100	95	100	364	383	376	414	379	395
LHD5	.0161	100	100	100	100	100	100	484	443	480	386	542	448
LHD6	−.0141												
LHD7	.0055	50	90	70	100	10	35	547	476	527	429	569	702
LHD8	.0003	100	100	100	100	100	100	438	455	474	469	464	488
LHD9	0	95	100	100	100	95	100	367	380	383	392	410	432

mean = 500 msec, SD = 117 msec). Main effect of Session and the interaction of these factors were not significant.

The accuracy of normal subjects did not show a significant interaction or main effect, their performance being between 95% and 100%. Reaction times of normal subjects did not show a significant interaction or main effect either, pre-PA (left stimuli: mean = 388 msec, SD = 92 msec; centre stimuli: mean = 383 msec, SD = 91 msec; right stimuli: mean = 379 msec, SD = 86 msec) and post-PA reaction times (left stimuli: mean = 399 msec, SD = 61 msec; centre stimuli: mean = 385 msec, SD = 64 msec; right stimuli: mean = 403 msec, SD = 71 msec) being indeed very similar.

3.4. *Effects of L-PA on neural activity elicited by visual stimuli*

Neural activity elicited by left, centre and right stimuli was analysed by a repeated-measures 2-way ANOVA with within-subject factors Stimulus position (left, centre, right) and Session (pre-PA, post-PA). Because of the variable sizes and locations of lesions in patients, we focused our analysis on the intact, right hemisphere. The activations in patients yielded a significant interaction within the middle temporal pole (Fig. 2 top row; Table 3), driven by a significant decrease in activation by centre stimuli (Fig. 2 middle row). Main effect of Stimulus position was significant within the inferior and infero-lateral occipital cortex, driven by greater activity elicited by contralateral stimuli. Main effect of Session was significant in 4 clusters. The largest cluster was located in the posterior part of the middle and inferior temporal gyri and the adjacent inferior and middle occipital gyri; the effect was driven by a significant decrease in activation by left and centre stimuli. Another relatively large cluster was located on the temporal pole, the effect being driven by a significant decrease in activation by left and centre stimuli. A small cluster was found in the angular gyrus, the effect being driven by a significant decrease in activation by centre and right stimuli. The fourth cluster was centred on the insula.

Neural activity elicited during pre-PA and post-PA sessions was compared post-hoc with T tests. In patients few small clusters yielded significant increase in activity, none of them being located within IPL. In contrast large cluster of significant decrease were observed, mostly for centre and left stimuli, involving predominantly the lateral occipito-temporal junction (Fig. 1 middle row). In control subjects IPL presented significant increase of activity elicited by right stimuli. Additional, relatively small clusters on the temporal and prefrontal convexities yielded significant decreases, mostly to centre and right stimuli (Fig. 1 bottom row).

3.5. *Individual patterns of L-PA induced modulation of visual field representations*

Neural activity elicited during the pre-PA and post-PA sessions was compared in each individual patient with post-hoc T tests. The overall pattern, i.e., the average of the 3 positions, showed that clusters of increase and of decrease were present in all patients, but differed in size and location (Fig. 3A). Decrease in activity was analysed separately for each stimulus position, showing striking effects in almost all patients (Fig. 3B). At population level, patients but not normal subjects presented a significant decrease in activity elicited by left stimuli at the lateral occipito-temporal junction (Fig. 2 middle and bottom rows). This same decrease was present in 6 individual patients (LHD1, LHD2, LHD4, LHD7, LHD8, LHD9).

Five patients presented lateralized lateralized attention deficits (LHD1, LHD3, LHD6, LHD7, LHD9) at the time of the fMRI investigation. In four of these five patients L-PA yielded an increase in activation in response to right targets in the vicinity of the ventral attentional system. In three patients this occurred within the right inferior parietal lobule (LHD1, LHD6, LHD9; Fig. 3C) and in one within the right lateral occipital cortex (LHD 7). No such increase was observed in the fifth patient (LHD3). Patients who did not present lateralized attentional deficits tended not to increase neural activity in response to right targets within the right inferior parietal lobule and only one patient (LHD5) had an increase in the right lateral occipital cortex.

4. Discussion

4.1. *L-PA induced modulation of visual activations after LHD*

In LHD a brief exposure to L-PA modulated neural responses to visual stimuli in 4 clusters within the right hemisphere; in

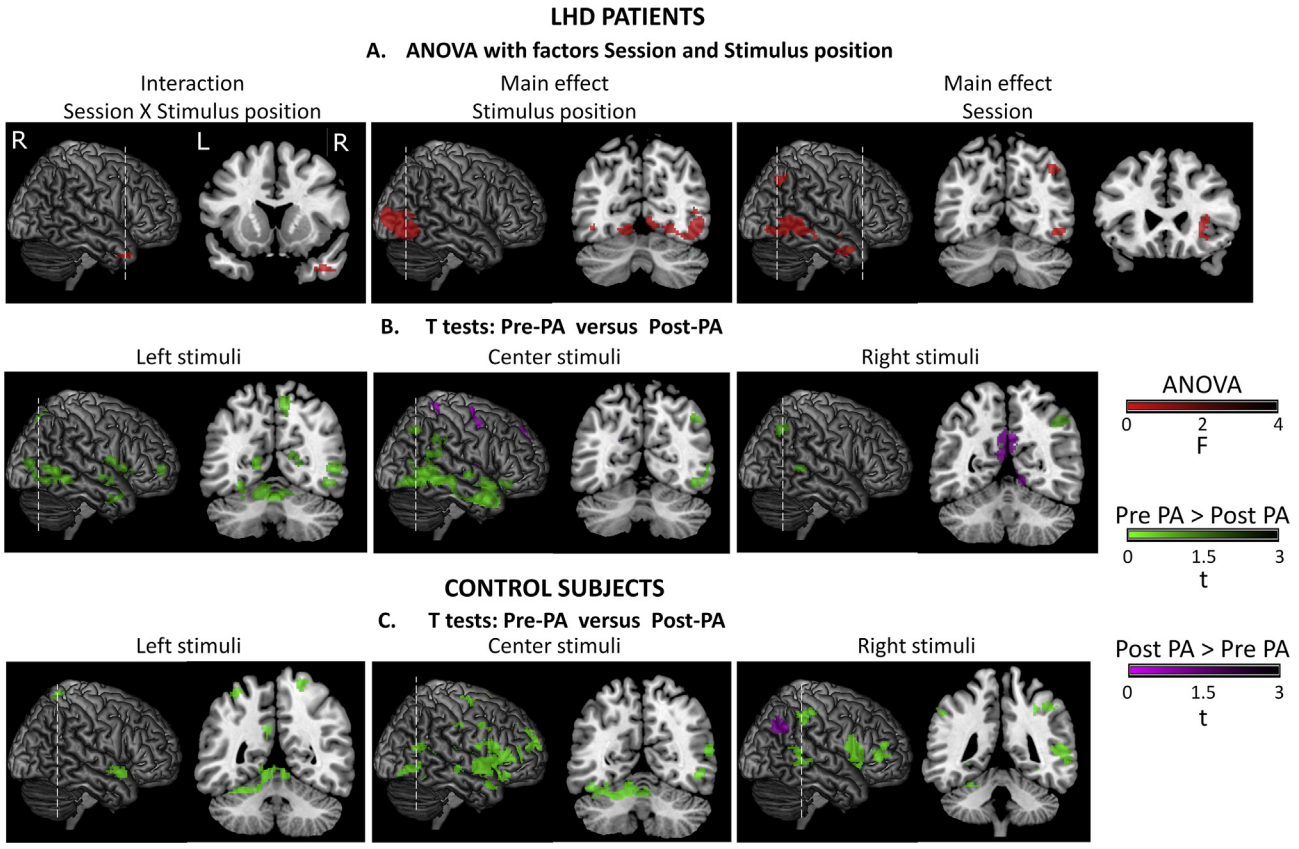

Fig. 2 – Surface renderings and coronal sections showing significant activation in the general mixed design 2 way ANOVA between the factors Session x Stimulus position in patients with LHD (top row). Surface renderings of post hoc paired T-tests (Post > Pre-intervention in purple; Pre > Post-intervention in green) are shown separately for left, centre and right stimuli in patients with LHD (middle row) and in normal subjects (bottom row). L: left hemisphere; R: right hemisphere.

these clusters the effect corresponded to decreases (Fig. 2A; Table 2). Within the IPL cluster the decrease concerned central and right stimuli; within the cluster in the posterior part of the middle and inferior temporal gyri and the inferior occipital cortex, the central and left stimuli; and within the cluster centred on the anterior part of the middle temporal gyrus, mostly the central and partially left stimuli. This same paradigm was used in normal subjects, where it yielded a different, striking effect within the right IPL by enhancing the representation of the ipsilateral, right visual field (Crottaz-Herbette, Fornari, Tissieres et al., 2017). Current evidence suggests that L-PA may affect neural processing differently in normal subject and in patients with LHD.

4.2. *Effect of L-PA adaptation in normal subjects*

In normal subjects L-PA induces a neglect-like performance in some, but not all tasks (Michel, 2016). A rightward bias was

Table 3 – Right-hemispheric clusters showing significant effects in the 2-way ANOVA (Session × Stimulus position) in LHD patients.

Comparisons	Anatomical regions	Peak MNI Coordinates	Peak Intensity	Number of voxels
Interaction Session × Stimulus position	**Middle temporal pole,** middle and superior temporal gyri	44/18/−36	7.20	100
Main effect Stimulus position	**Inferior occipital gyrus,** middle occipital gyrus lingual gyrus and fusiform gyrus	32/-88/-4	23.82	1737
	Insula, inferior frontal gyrus	30/26/6	8.88	119
Main effect of Session	**Middle temporal gyrus,** inferior temporal gyrus, inferior and middle occipital gyri	60/−46/−8	18.44	412
	Temporal pole, middle and superior temporal gyri, Parahippocampus	36/−12/−22	11.38	317
	Inferior parietal lobule, angular gyrus	42/−64/44	7.54	98
	Insula, inferior frontal gyrus	30/26/6	8.88	119

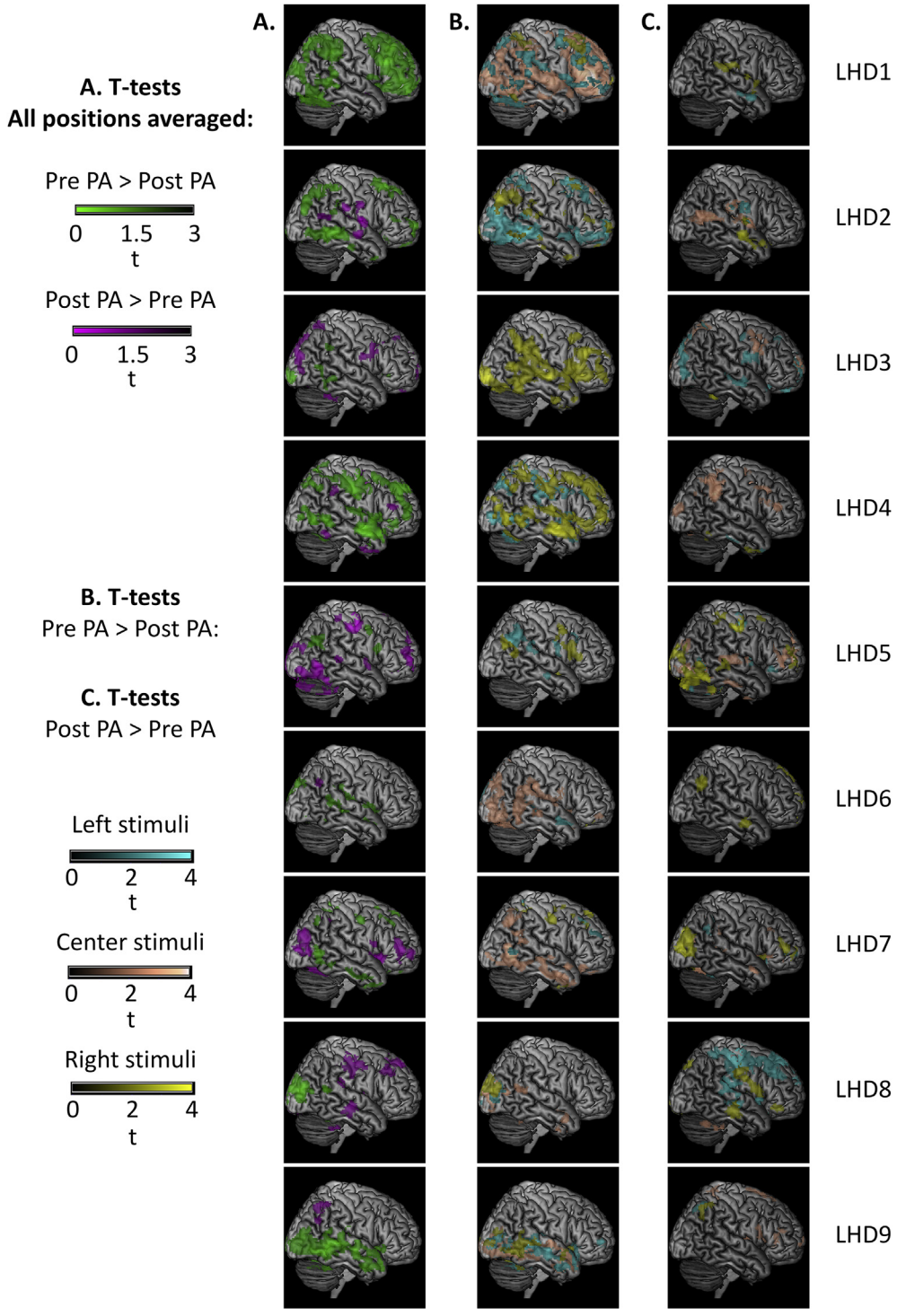

Fig. 3 – Right hemisphere surface renderings of post hoc paired T-tests in individual patients. A. Comparison for all Stimulus positions together (Post > Pre-intervention in purple; Pre > Post-intervention in green). B. Decreases (Pre > Post-intervention) for left (cyan), centre (orange) and right stimuli (yellow). C. Increases (Post > Pre-intervention) for left (cyan), centre (orange) and right stimuli (yellow).

reported in the line bisection task (Colent et al., 2000; Michel, 2003; Michel & Cruz, 2015; Schintu et al., 2014; Striemer, Russell, & Nath, 2016) and in visual midpoint judgments (Berberovic & Mattingley, 2003), but not in the Posner paradigm (Bultitude et al., 2013; Morris et al., 2004). Activation studies pinpoint possible mechanisms, which may underlie this spatial bias.

A brief exposure to L-PA was shown to increase the representation of the right visual field within the right IPL, enhancing thus right hemispheric dominance within the

ventral attentional system (Crottaz-Herbette, Fornari, Tissieres et al., 2017), which may strengthen the link between the right-dominant ventral attentional system and the left dorsal attentional system and create attentional bias towards the right space. L-PA induced processing bias was also highlighted in an electrophysiological study. The authors compared event-related potentials to different components of the endogenous variants of the Posner task before and after L-PA and observed asymmetries that were reminiscent of left neglect (Martín-Arévalo, Laube et al., 2016). The amplitude of N1 elicited by the cue was more reduced for leftward than rightward cues, suggesting asymmetry in attentional orienting. The amplitude of P1 to targets was greater for invalidly cued left than right targets, suggesting an asymmetry in attentional disengagement. Thus, L-PA affects in normal subjects different components of the ventral and dorsal attentional systems and creates a left-right attentional imbalance, possibly by over-emphasizing the representation of the right visual field within the right-dominant ventral attentional system.

4.3. *Effects of L-PA in patients with LHD*

In analogy to the use of rightward prismatic adaptation in left neglect following right hemispheric lesions, a pioneering study used L-PA in a case of a large left hemispheric lesion and lasting severe right neglect (Bultitude & Rafal, 2010). A brief exposure to L-PA yielded a rightward shift in pointing as aftereffect and normalized the performance on line bisection; the latter improvement was still partially present 18 days later. Here reaction times tended to be faster after L-PA exposure, but the effect was not significant. A previous study using a Posner paradigm and event-related potentials showed, similarly to our findings, that L-PA failed to yield significant behavioral effects but induced changes in brain activation (Martín-Arévalo, Schintu et al., 2016).

Right neglect following LHD is relatively frequent in the acute and postacute stages, but tends to recover later on more easily than does left neglect following right hemispheric lesions (Bowen et al., 1999; Kamtchum Tatuene, 2016; Kleinman et al., 2007; Ringman et al., 2005; Suchan et al., 2012). During the acute stage of LHD right neglect tends to be associated with damage to the left superior and middle temporal gyri, including their anterior parts, the inferior ventral premotor cortex, the frontal operculum, the angular gyrus, and the insula (Beume et al., 2017; Malherbe et al., 2018). The persistence of neglect symptoms into the subacute stage correlates with damage to the posterior part of the middle temporal gyrus (Beume et al., 2017).

The superior temporal region was repeatedly shown to be involved in visual attention. It is activated during attention to contralateral, visual targets (Macaluso & Frith, 2000) or the exploration of dense stimuli (Himmelbach, Erb, & Karnath, 2006). It is also part of larger attentional networks, such as those underlying the reorienting of attention (Thiel, Zilles, & Fink, 2004) or the transfer to allocentric frame of reference (Neggers, Van der Lubbe, Ramsey, & Postma, 2006). In cases of right hemispheric lesions rightward prismatic adaptation was shown to enhance visuo-spatial representation within the contralesional superior temporal regions (Clarke & Crottaz-Herbette, 2016; Crottaz-Herbette et al., 2014, Crottaz-Herbette, Fornari, Notter et al., 2017).

The effect of L-PA in LHD differs from the effect of L-PA in normal subjects and from the effect of rightward prismatic adaptation in right hemispheric lesions. Unlike in normal subjects, L-PA does not emphasize in LHD the right hemispheric dominance within the ventral attentional system by enhancing the right visual field representation within the right IPL. Unlike rightward prismatic adaptation in patients with right hemispheric lesions, L-PA does not enhance in patients with LHD the representation of the contralesional visual field in the contralesional, right superior temporal gyrus. The effect of L-PA in LHD appears to rely on a downregulation of neural activity elicited by central and left visual stimuli. This is particularly the case within the inferior occipital cortex; the lingual, fusiform and parahippocampal gyri; and the posterior parts of the middle and inferior temporal gyri. These regions contain higher order visual areas with known representations of the contralateral visual field, including the occipital place area and the face-selective occipital area within the lateral occipito-temporal cortex (Silson, Groen, Kravitz, & Baker, 2016); the parahippocampal place area within the ventral occipito-temporal cortex (Silson, Chan, Reynolds, Kravitz, & Baker, 2015); the parahippocampal visual areas (Arcaro, McMains, Singer, & Kastner, 2009); visual areas V4 and V8 (Clarke & Miklossy, 1990; Winawer & Witthoft, 2015); and the MT complex (Saygin & Sereno, 2008). These areas are known to have a monosynaptic connection with the contralateral IPL (Di Virgilio & Clarke, 1997). Thus, L-PA appears to reduce the proper, contralateral representation within right hemispheric higher-order occipito-temporal visual areas. The decrease in responsivity is very likely accompanied by a loss of salience for contralateral, left stimuli, which in turn favours the restitution of a rightward attentional bias. It is interesting to note that in normal subjects L-PA induced also a decrease within the inferior occipito-termporal cortex, which was, however, limited to the representation of the central and right, but not the left space.

Further studies will be needed to address the issue of responsiveness to L-PA. Here we had a varied population in terms of lesion site, spanning from from small pulvinar and basal ganglia lesion (LHD1) to a large fronto-parieto-temporal lesion including basal ganglia and disrupting the callosal pathway (LHD9). The importance of lesion site was recently highlighted by three studies, which compared RHD of patients who responded *vs* who did not respond to R-PA. A first study reported improvement of left extinction in a dichotic listening test in association with anterior, but not posterior lesions; the latter encroached on the callosal pathway during its paraventricular trajectory (Tissieres, Elamly et al., 2017). Similarly R-PA induced high level improvement in patients with frontal but not with posterior lesions (Gutierrez-Herrera, Eger, Keller, Hermsdörfer, & Saevarsson, 2018), including on the Bergego scale (Goedert, Chen, Foundas, & Barrett, 2018). These three studies on the effect of R-PA in RHD have clinical impact, but they are also of conceptual importance. They confirm predictions from prior fMRI studies, which have shown that R-PA adaptation switches hemispheric dominance of the ventral attentional system from the right to the left hemisphere. Hence the beneficial of R-PA effect requires intact callosal communication and left superior parietal cortex (Clarke & Crottaz-

Herbette, 2016; Crottaz-Herbette et al., 2014, Crottaz-Herbette, Fornari, Notter et al., 2017; Tissieres, Elamly et al., 2017).

5. Conclusions and clinical perspectives

Our findings that a brief exposure to L-PA reshapes visuo-spatial representation within the intact right hemisphere opens new perspectives for the rehabilitation of attentional disorders after LHD. One effect of the reshaping consists of a downregulation of the representation of the central and left space within the temporal cortex and of the central and right space in IPL. This reshaping suggests that L-PA may improve attentional abilities in LHD if applied over several days (as in a seminal study on R-PA in RHD; Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002). In a subgroup of patients, who presented lateralized attentional deficits, L-PA tended to enhance right spatial representation in IPL. This finding indicates that L-PA may also alleviate right neglect in LHD.

Conflict of interest

The authors reported no conflict of interest.

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