Prism adaptation enhances activity of intact fronto-parietal areas in both hemispheres in neglect patients

Arnaud Saj, Yann Cojan, Roland Vocat, Jacques Luauté and Patrik Vuilleumier

Department of Neurology, University Hospital of Geneva, Geneva, Switzerland
Department of Neurosciences, University of Geneva, Geneva, Switzerland
Health Network Valais, St-Maurice, Martigny and Sierre, Switzerland
Department of Neurological Rehabilitation, Hospital Henry Gabrielle, Saint Genis Laval, France

Abstract

Unilateral spatial neglect involves a failure to report or orient to stimuli in the contralesional (left) space due to right brain damage, with severe handicap in everyday activities and poor rehabilitation outcome. Because behavioral studies suggest that prism adaptation may reduce spatial neglect, we investigated the neural mechanisms underlying prism effects on visuo-spatial processing in neglect patients. We used functional magnetic resonance imaging (fMRI) to examine the effect of (right-deviating) prisms on seven patients with left neglect, by comparing brain activity while they performed three different spatial tasks on the same visual stimuli (bisection, search, and memory), before and after a single prism-adaptation session. Following prism adaptation, fMRI data showed increased activation in bilateral parietal, frontal, and occipital cortex during bisection and visual search, but not during the memory task. These increases were associated with significant behavioral improvement in the same two tasks. Changes in neural activity and behavior were seen only after prism adaptation, but not attributable to mere task repetition. These results show for the first time the neural substrates underlying the therapeutic benefits of prism adaptation, and demonstrate that visuo-motor adaptation induced by prism exposure can restore activation in bilateral brain networks controlling spatial attention and awareness. This bilateral recruitment of fronto-parietal networks may counteract the pathological biases produced by unilateral right hemisphere damage, consistent with recent proposals that neglect may reflect lateralized deficits induced by bilateral hemispheric dysfunction.

1. Introduction

Unilateral spatial neglect is a frequent disorder after right brain lesion, resulting in a failure to report or orient to stimuli in the contralesional (left) space (Heilman and Valenstein, 1979), with severe handicap in everyday activities and poor rehabilitation outcome. Both behavioral and anatomical studies have indicated that neglect is produced by lesions...
affecting fronto-parietal networks involved in spatial attention and spatial cognition (Corbetta et al., 2005; Thiebaut de Schotten et al., 2005; Verdon et al., 2010), which can in turn lead to secondary functional abnormalities in structurally intact brain areas including visual cortices (Corbetta et al., 2005; Rees et al., 2000; Vuilleumier et al., 2001). Many therapeutic approaches have been proposed to treat this disorder (e.g., visual scanning training, limb activation, eye-patching, etc.), but improvements are generally modest and limited to the trained situations (Luauté et al., 2006a).

A pioneer study by Rossetti et al. (1998) was the first to suggest that prism adaptation can produce long-lasting and widespread effects on spatial neglect. This approach was motivated by classic findings that, in healthy people, repetitive pointing to visual targets seen with optical prisms (shifting the perceived target locations) does not only bias pointing in the opposite direction following prism removal (so-called after-effect), but also shifts the subjective body midline in this direction. Furthermore, neglect patients typically show a rightward bias when asked to point straight-ahead (Heilman et al., 1983; Saj and Vuilleumier, 2007), although this deviation is not found in all cases (Bartolomeo and Chokron, 1999; Farne et al., 1998). The generalization and persistence of these effects are mediated by failures on three sensitive tests, namely, BellCancellation (Gauthier et al., 1989), Figure Copy (Gainotti et al., 1972), and Line Bisection (Schenkenberg et al., 1980). All patients were also examined using a routine battery of standardized clinical tests, including mini-mental state examination, to exclude dementia and any other major cognitive disorder that would impact on task performance and collaboration. Because participation in the fMRI study required normal vigilance and ability to cooperate, we excluded patients with large hemispheric stroke (affecting more than 32), when neglect symptoms were still present, as confirmed by testing on the same day, (ii) showed consistent signs of neglect on repeated testing, and (iii) had relatively small, focal damage in the right hemisphere allowing us to obtain reliable fMRI data from spared regions and perform efficient whole-brain group analysis.

2. Methods

2.1. Patients

Seven patients [mean age = 68, standard deviation (SD) = 15; min–max = 45–84 years] were recruited consecutively among stroke patients admitted to the Neurology Department, with a first right-hemisphere stroke (haemorrhagic or ischemic). All lesions were confirmed by MRI or CT scan (Fig. 1). Neglect and other neuropsychological deficits were assessed using a standard battery of clinical tests (Azouvi et al., 2002). The presence and severity of spatial neglect (Table 1) were determined by failures on three sensitive tests, namely, Bell Cancellation (Gauthier et al., 1989), Figure Copy (Gainotti et al., 1972), and Line Bisection (Schenkenberg et al., 1980). All patients were also examined using a routine battery of standardized clinical tests, including mini-mental state examination, to exclude dementia and any other major cognitive disorder that would impact on task performance and collaboration. Because participation in the fMRI study required normal vigilance and ability to cooperate, we excluded patients with large hemispheric stroke (affecting more than two lobes) and/or reduced alertness. Selecting patients with well-circumscribed lesions also ensured sufficient overlap of spared brain regions for subsequent group-based statistics of fMRI data. The scanning took place on average 19 days post-stroke onset (SD = 9; min–max: 10–32), when neglect symptoms were still present, as confirmed by testing on the same day prior to scanning.

To identify brain networks normally recruited in these tasks, a group of 26 healthy participants (29.6 ± 3.44-year-old, range 25–39; 11 women and 18 men) also underwent fMRI without prism adaptation (three sessions). These controls
were not submitted to prism adaptation since their data only served to identify patterns of brain activity associated with visuo-spatial processing in our task (for effects of prism adaptation in normals, see Danckert et al., 2008; Luauté et al., 2009). Data from controls also verified that there was no major learning-related effect on brain activation due to task

Fig. 1 – Anatomical reconstruction of brain lesions. Anatomy of brain lesions in each patient (with right hemisphere shown on the left, following radiological convention). Areas of lesion overlap across all patients are shown on axial slices of a normalized MRI brain template. Colors code for the number of patients with damage to a given area (from 1 = violet to 7 = red). The maximum overlap arose in the right subcortical temporo-parietal junction (six out of seven patients), but none of other frontal, parietal, and temporal cortical areas was damaged in more than one or two patients (see lateral brain view).
We designed a novel visual paradigm (“triplet task”) allowing us to probe distinct aspects of spatial cognition, including perceptual, attentional, and memory components, while visual inputs were kept constant (Fig. 2). There were three task conditions: (i) Bisection task: participants indicated whether the central item was located at the midpoint between the two others, or not (response: yes vs no); (ii) Visual search task: participants indicated whether the single-odd item in triplets was a square or a diamond (response: square vs diamond); (iii) Memory task: participants indicated whether the three items appeared at the same locations as in the preceding trial, or not (response: same vs different). Successful trials were constrained such that the positions of items on trial n corresponded to positions on trial n − 1 on 50% of all trials (one-back task), irrespective of the actual shape (square, diamond, triangle) of items. The same sequence was used in other task conditions.

Visual stimuli consisted of simple shapes (i.e., triangles, squares, or diamonds, each ~3° of visual angle and with same total surface area, white-colored on a black background). On each trial, these shapes were presented in a row (triplet) of three items (duration of 1 sec), preceded by a fixation point at the screen center (1 sec), and followed by a varying inter-trial interval (3–6 sec). In addition, to avoid predictability or systematic strategies, the position of shapes on the screen varied such that they could be presented in the left, right, or both (central) visual fields (with either the right-most, left-most, or central stimulus in the triplet being presented at the screen center, respectively). These factors were independently manipulated on each trial, in order to afford different tasks with the same set of stimuli (Fig. 2).

Each of these three tasks was given in one block of 30 trials for each run (10 × 3 triplet positions on the screen), separated by short rest blocks (fixation point only), and repeated in a different order in three successive scanning runs (Fig. 2). This yielded a total of 30 trials with triplet stimuli presented in left visual field (LVF), right visual field (RVF), or center visual field (CVF), for each of the three tasks (total scanning time: ~22 min in each participant). All visual

### Table 1 – Demographic and clinical data of patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Days since stroke</th>
<th>Etiology</th>
<th>VF loss</th>
<th>Left visual extinction</th>
<th>Neglect severity</th>
<th>Bells cancellation</th>
<th>Line bisection (%)</th>
<th>Scene copy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat 1</td>
<td>74</td>
<td>F</td>
<td>32</td>
<td>H</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>15</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pat 2</td>
<td>69</td>
<td>F</td>
<td>10</td>
<td>H</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>15</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Pat 3</td>
<td>51</td>
<td>M</td>
<td>12</td>
<td>I</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>15</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Pat 4</td>
<td>84</td>
<td>F</td>
<td>22</td>
<td>I</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>15</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Pat 5</td>
<td>76</td>
<td>M</td>
<td>30</td>
<td>H</td>
<td>Yes</td>
<td>No</td>
<td>+++</td>
<td>13</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pat 6</td>
<td>45</td>
<td>M</td>
<td>14</td>
<td>I</td>
<td>No</td>
<td>No</td>
<td>++</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pat 7</td>
<td>79</td>
<td>F</td>
<td>13</td>
<td>I</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

2.2. Lesion neuroanatomy

For each patient, brain lesions were demonstrated by clinical MRI scans and reconstructed on axial slices using MRicro (Rorden and Brett, 2000), according to previously described methods (Mort et al., 2003; Verdon et al., 2010; Vuilleumier et al., 2008). Lesioned areas were transformed to a three-dimensional region of interest (ROI) corresponding to the lesion volume, and normalized to a standard brain template using MRicro and statistical parametric mapping (SPM). The normalized lesion ROIs were then superimposed on a T1 MRI in order to determine the overlap of lesions across patients and define brain areas where damage was most commonly observed (Fig. 1). Because we excluded patients with large multi-lobar stroke and reduced vigilance, all patients undergoing fMRI had focal cortico-subcortical lesions that spared at least some of the cortical areas of interest, allowing us to obtain reliable functional MRI responses at the group level (see Fig. 1).
stimuli were back-projected onto a mirror mounted on the MRI head coil, and all responses were recorded by a keypad for subsequent analysis of performance.

In each patient, the fMRI experiment took place in a single session and included three successive scanning runs (each with all three tasks). The second and third scanning runs were separated by the prisms adaptation procedure, resulting in a "baseline" condition before prism adaptation that included two fMRI runs, and a "treatment" condition that corresponded to the critical fMRI run after prism adaptation. Comparing runs 1 and 2 allowed us to rule out any general learning effects due to task repetition that might have confounded the neural changes observed after prism adaptation. As described below (see Results section), no reliable differences were found between run 1 and 2. Before scanning, each participant had a brief training session for the three tasks with online feedback by the experimenter in order to ensure adequate understanding of the task.

2.4. Prism adaptation procedure

Prism adaptation took place between the fMRI sessions 2 and 3. Patients were taken out of the MRI scanner bore but remained in a supine position on the MRI bed. The MRI room was only dimly lit, to minimize visual inputs from the environment. Goggles were fitted with wide-field prismatic lenses, creating an optical shift of 20° to the right. The exposure period consisted in making 50 ballistic pointing responses to visual targets presented in front of the patient (above the MRI bed) on a cardboard, 15 to the right or to the left of the objective body midline, while wearing the prismatic goggle. Immediately after adaptation, they were tested with four to six trials to ascertain leftward deviation more than 3 cm when pointing with the eyes open to a dot previously seen, facing their body midline. The duration of prism exposure between the two fMRI sessions was approximately 5 min. Immediately, following the adaptation procedure and verification of the after-effect, patients were instructed to close their eyes and were brought back into the MRI scanner bore. They were asked to open their eyes when the fMRI scanning started again (session 3).

2.5. Acquisition of fMRI data

MRI data were acquired on a 3T whole-body TRIO system (Siemens) with a standard head-coil configuration. Functional T2*-weighted images were obtained using echoplanar imaging (EPI) with axial slices (TR/TE/Flip = 2200 msec/30 msec/85°, FOV = 235 mm, matrix = 128 × 128). Each functional image comprised 32 contiguous 3.5 mm-thick slices, parallel to the inferior surface of occipital and temporal lobes, with a final voxel-size of approximately 3 × 3 × 3 mm. For each patient, a high-resolution anatomical image was also acquired after the functional scans, at the end of the first scanning session, using a 3D-GRE T1-weighted sequence (FOV = 250 mm, TR/TE/Flip = 15 msec/5.0 msec/30°, matrix = 256 × 256, slice-thickness = 1.25 mm). This anatomical image was used for co-registration with functional images and subsequent normalization procedure.

2.6. Analysis of fMRI data

All fMRI data were processed and analyzed using the general linear model (GLM) for event-related designs in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned, corrected for slice timing, normalized to an EPI-template (with a voxel-size of 3 mm), spatially smoothed (8 mm full width at half maximum (FWHM)), and high-pass filtered (cut-off 180 sec) following standard procedures in SPM (Vuilleumier et al., 2001, 2002).

Statistical analyses were performed on a voxelwise basis across the whole-brain, using a mixed blocked and event-related design (Price et al., 2003). Individual visual events were modeled by a standard synthetic hemodynamic response function (HRF) corresponding to three stimulus types (triplets presented in LVF, RVF, or centrally) in each of the three task conditions (bisection, search, memory), resulting in nine independent event regressors. Parameter estimates for each regressor were estimated at each voxel by GLM using a least-square fit to the data, for each condition and each individual participant. Statistical parametric maps of the t-statistic (SPM[t]) generated from linear contrasts between conditions in individual subjects were then included in a second-stage random-effect analysis, using one-sample t-tests on the contrast images obtained from each condition in each subject (Friston et al., 1998). The resulting random-effect maps SPM[t] were thresholded voxelwise at conventional statistical values (p < .001 uncorrected, with a cluster threshold of p < .05), following standard procedures in SPM (Vuilleumier et al., 2001, 2002). Comparisons of main interest concerned the contrasts between each task and the rest condition (collapsed across stimulus position in visual field: right, central, left), for each group (patients and healthy volunteers), and each scanning run (before and after prism adaptation). In patients, a direct comparison was also performed for each task condition before and after prism adaptation (runs 1 and 2 vs run 3), using a whole-brain analysis of variance (ANOVA) design. The same ANOVA was used to test for repetition effects (run 1 vs run 2) and to examine any interaction with stimulus position (see Results in main text).

3. Results

3.1. Behavioral data

As expected, behavioral results during fMRI (Figs. 3 and 4) showed that neglect patients performed worse than healthy participants in all tasks and across all three runs (mean correct responses in neglect patients: session 1 = 50 ± 12%, session 2 = 48 ± 10% and session 3 = 63 ± 13%; healthy controls: session 1 = 96 ± 4%, session 2 = 97 ± 3% and session 3 = 96 ± 4%). Across tasks, errors were clearly more frequent in the left than RVF, but above chance in the RVF (Fig. 4), indicating that patients correctly understood the task instructions during scanning. Accuracy (percent correct) and response times (RTs) from the patients were analyzed first using a repeated-measure ANOVA with session (session 1, 2, or 3), visual field (right, left,
or central), and task (bisection, search, memory) as independent factors. Accuracy results showed a significant main effect of session $[F(2,18) = 7.2825, p = .0048]$. The two sessions before prism adaptation showed no significant difference between each other (session 1 vs session 2; $p = .808$), whereas the two sessions before adaptation were significantly different from the sessions after adaptation (session 1 vs session 3; $p = .005$; session 2 vs session 3; $p = .008$). There was also a significant effect of visual field $[F(2,36) = 6.971, p = .0027]$, due to worse performance for stimuli presented on the left than right-side. The effect of task was marginally significant $[F(2,38) = 5.63, p = .0061]$. The bisection ($59.2 \pm 14.1$) and search ($61.4 \pm 15.2$) tasks were different of memory task ($49.51 \pm 17.6$). No other main effect or interaction was significant.

Analysis of RTs showed no effect of session $[F(2,18) = .341, p = .715]$; session 1 vs session 2; $p = .433$; session 1 vs session 3; $p = .132$; session 2 vs session 3; $p = .459$], but a significant effect of visual field $[F(2,36) = 5.852, p = .006]$ due to longer responses to LVF stimuli ($1458.2 \pm 684.2$ msec) than CVF ($1299.3 \pm 721.1$ msec) and RVF ($1251.2 \pm 606.2$ msec). No other main effect or interaction was significant.

### 3.2. Imaging data

We first determined brain areas activated in healthy participants (without prism adaptation) by contrasting each visual task against baseline (resting screen between blocks). These maps were not directly compared to those in the neglect group.

---

**Fig. 3** – Behavioral results.

(A) Accuracy [% correct, ±SD] and (B) responses time [msec] are depicted as a function of the triplet stimulus position in visual field (left, center and right) for each task (bisection task, search task and memory task) before and after prism adaptation. The horizontal lines (dotted) indicate the performance of healthy controls group.

**Fig. 4** – Individual data for each patient.

Accuracy [% correct] is shown as a function of visual field for the three tasks, before and after prism adaptation.
patients but produced a qualitative baseline for comparison. Results demonstrated that all three tasks activated bilateral regions in parietal, frontal, and occipital cortex (Fig. 5), consistent with previous studies on visuo-spatial attention (Corbetta et al., 2005). Stronger activation was observed in right posterior parietal cortex ($xyz = 18\ -70\ 55$) and right superior frontal sulcus ($xyz = 21\ 5\ 55$) during bisection and search compared to memory, but in left parahippocampal gyrus ($xyz = -30\ -22\ -14$) and posterior cingulate ($xyz = 6\ 4\ 40$) during memory compared to bisection and search (all $p < .001$ at voxel-level and $p < .05$ at cluster level).

We then identified brain regions where activation changed after prism adaptation in neglect patients, using a random-effect voxelwise ANOVA where session (before/after) and visual field (left/center/right) were entered as separate conditions, for each task separately. When contrasting “after > before” during bisection, we found marked increases (all $p < .001$ at voxel-level and $p < .05$ at cluster level, Table 2) in both the right and left parietal cortex, as well as in bilateral occipital cortex and bilateral mid-frontal cortex. For search, significant increases were observed in the right temporo-parietal junction, in addition to bilateral superior parietal cortex, bilateral occipital cortex, and bilateral middle frontal cortex (Table 2). All these activations were independent of the visual field where stimuli were presented (no session × field interaction for any task).

By contrast, in keeping with behavioral findings, the memory task showed no significant changes in activity in any region when comparing sessions after > before prism, except for a few small clusters (size of clusters < 10) in sensorimotor cortices and occipital areas (Fig. 5).

Across all three tasks, no change was observed in the cerebellum, a region previously implicated in the online process of prism adaptation (Luauté et al., 2009; Pisella et al., 2005) and no difference was observed when comparing the two sessions before prism adaptation, suggesting no effect of repetition per se.

![Fig. 5](https://example.com/fig5.png)  
**Fig. 5** – Brain activations and prism-adaptation effects in three visuo-spatial tasks.  
(a) Neuroimaging results. Brain regions activated ($p < .001$) during each task relative to baseline, in controls and patients (before and after prisms). Activations are projected on standard anatomical template with lesioned cortical regions depicted in darker gray shades (all voxels damaged in ≥2 patients, for illustration purpose). (b) Parameter estimates of activity (beta value, in arbitrary units, averaged across voxels) are shown for the bisection and visual search tasks in SPL and MFG (for each cluster defined by the group analysis). Dark colors = before, light colors = after prism.
3.3. Brain–behavior relationships

Finally, we examined the relationships between the difference in behavioral performance and the difference in neural activity before versus after prism adaptation for cortical regions of interest. Parameter estimates of activity (betas) were extracted from activated clusters in bilateral superior parietal lobe (SPL), bilateral middle frontal gyrus (MFG) and bilateral occipital lobes (as determined by our group analysis, averaged across voxels for each individual patient). Results are presented in Fig. 6 for the bisection task and Fig. 7 for the visual search. The improvement in correct responses (%) and the increase of cortical activity (a.u.) were highly correlated (all $p < .01$). For the bisection task, a strong partial correlation was found between the percentage of correct response and cortical activity in the left superior parietal lobe (SPL), MFG and occipital ($p = .031$). However, the partial correlation between changes in performance and changes in cortical activity in the right SPL, MFG and occipital was only marginally significant ($p = .067$). For the visual search task, a strong partial correlation was again found between performance and cortical activity for both the left/right SPL, MFG and occipital ($p = .02$). These results therefore indicate that changes in cortical activity bilaterally were significantly related to changes in neglect symptoms in these two tasks.

### Table 2

<table>
<thead>
<tr>
<th>Task</th>
<th>Region</th>
<th>Hemi</th>
<th>Talairach coordinates $(x, y, z)$</th>
<th>Z</th>
<th>Brodmann area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line bisection</td>
<td>Parietal</td>
<td>Left</td>
<td>$-24, -64, 64$</td>
<td>5.75</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>$18, -64, 58$</td>
<td>6.05</td>
<td>7</td>
</tr>
<tr>
<td>Frontal</td>
<td>Left</td>
<td>$-33, 14, 43$</td>
<td>5.75</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>$21, 29, 40$</td>
<td>4.30</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>Left</td>
<td>$-33, -91, -14$</td>
<td>6.22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>$21, -88, -20$</td>
<td>5.43</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Visual Search</td>
<td>Parietal</td>
<td>Left</td>
<td>$-9, -67, 64$</td>
<td>3.85</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>$27, -64, 67$</td>
<td>3.40</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>Left</td>
<td>$-39, 5, 52$</td>
<td>4.71</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>$33, 17, 49$</td>
<td>4.16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>Left</td>
<td>$-24, -94, -14$</td>
<td>4.41</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>$30, -97, -2$</td>
<td>4.88</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>TPJ</td>
<td>Right</td>
<td>$51, -37, 22$</td>
<td>3.53</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6 – Relation between changes in cortical activity and improved behavioral performance in the bisection task (before vs after) for bilateral SPL, MFG and occipital lobe.

4. Discussion

Our results show for the first time that the beneficial effects of prism adaptation on neglect are associated with a modulation...
of several brain regions crucially involved in spatial attention, including posterior parietal and mid-frontal cortex bilaterally (Luaute et al., 2006b; Rossetti et al., 1998). These effects should be taken as preliminary given our small sample size and our within-group methodology, and will need to be confirmed with a different study design, for example by using a control group with sham prisms (as in the seminal behavioral study of Rossetti et al., 1998), or a crossed design with one group starting with a prism adaptation and a second without prism adaptation. Note however that our A-A-B design allowing us to be relatively confident that changes observed after prisms were not simply due to practice or learning effect, since all significant increases (in performance and brain activations) occurred in session 3, but not in session 2. Sessions 1 and 2 did not differ in terms of behavioral performance. Furthermore, RT data showed no significant speeding across sessions, making non-specific learning or recovery between sessions 2 and 3 highly unlikely to explain the neural changes in the post-prism session.

Our behavioral and fMRI results converged to demonstrate selective effects during bisection and visual search, but not memory, consistent with clinical observations that prism adaptation may affect some spatial tasks more than others (Rousseaux et al., 2006; Sarri et al., 2011; Serino et al., 2006; Striemer and Danckert, 2010). This dissociation suggests that adaptation could improve the perceptual encoding of visible target locations more than their storage over time; or alternatively, that our memory tasks recruited distinct (e.g., non-spatial) processes that were not influenced by prism adaptation. For example, memory for the triplet configuration might involve object-based matching abilities dependent on ventral occipito-temporal pathways, rather than purely space-based encoding abilities mediated by more dorsal parietal and frontal pathways (Humphreys, 1998; Striemer and Danckert, 2010). In accord with the latter hypothesis, some behavioral studies found no effect of prism adaptation on object-based tasks (e.g., Sarri et al., 2011). Alternatively, although visual memory in neglect patients may show spatially lateralized deficits in encoding, storage, and/or retrieval components (e.g., Kristjansson and Vuilleumier, 2010; Saj and Vuilleumier, 2007; Vuilleumier et al., 2007), performance in the current might depend also on non-lateralized processes in memory and attention, such as the capacity and rapidity of working memory resources (e.g., Husain and Rorden, 2003). In any case, the significant behavioral improvements seen during line bisection and
visual search confirm a beneficial effect of prism adaptation on the distribution of selective attention in space.

More critically, however, our findings indicate that the reduction of left neglect in bisection and search was associated with bilateral increases in the attentional brain network, rather than heightened activity in the damaged right hemisphere only. Although traditional models of neglect have often emphasized an imbalance between the two hemispheres with a relative overactivation of the left hemisphere (Kinsbourne, 1970), recent accounts have also pointed to a reduction of activity and/or blood flow in the intact hemisphere during acute neglect (Corbetta et al., 2005). Likewise, a recent fMRI study during spatial orienting task in right brain-damaged patients (Umarova et al., 2011) reported larger reduction in both hemispheres in patients with neglect compared to those without. Our new data therefore provide new support to the latter view by showing that rightward prism adaptation produced widespread changes in both hemispheres. Taken together, these data call for a refinement of the traditional interhemispheric disinhibition account of neglect (Kinsbourne, 1993), although they do not exclude asymmetrical reductions with left greater than right activations (Corbetta and Shulman, 2002; Umarova et al., 2011) which would underlie lateralized biases in attention.

We note however that patients performed the prism adaptation training with their right hand, which might potentially contribute to subsequent changes in activity in the contralateral/left hemisphere (Luaute` et al., 2009). According to this view, increases of activity in the healthy hemisphere could primarily relate to the low-level sensory-motor effects of prism adaptation, while increases in the damaged hemisphere might underlie “true” neglect recovery. Obviously, it would be difficult to experimentally disentangle these effects by testing adaptation with each hand separately since most patients suffer from left arm paresis and/or sensory loss. Moreover, behavioral studies showing beneficial effects of prism adaptation in neglect patients have also used training with the intact right limb, suggesting that any change mediated by the left hemisphere could actually contribute to the behavioral improvements. More critically, however, an effect solely due to using the right limb (and unrelated to neglect behavior) could not account for previous studies reporting changes in left hemispheric activation associated with the severity of spatial deficits (Corbetta and Shulman, 2002; Umarova et al., 2011). In keeping with this view, our data showed that changes in spatial performance correlated with increased activity in left MFG and SPL, just as well as with increases in the damaged side. Altogether, these data converge to suggest that left hemisphere dysfunction may contribute to full neglect symptoms, rather than be a simple epiphenomenon.

The exact neural effects of prism adaptation on spatial networks remain poorly known, for both healthy individuals (Clower et al., 1996; Danckert et al., 2008; Luaute` et al., 2009) and brain-damaged patients (Luaute` et al., 2006a; Rossetti et al., 1998; Striemer and Danckert, 2010). Recent fMRI work in normal volunteers during adaptation points to a modulation of activity in the cerebellum, inferior parietal cortex, and posterior parieto-occipital areas for online visuo-motor corrections in the early phase of prism exposure, but with additional increases in inferior parietal and superior temporal areas for the more sustained adaptation in later phases (realignment) when pointing errors are fully compensated (Clower et al., 1996; Chapman et al., 2010; Danckert et al., 2008; Luaute` et al., 2009). However, it has remained unclear how these visuo-motor changes may impact on spatial attention and perceptual awareness in patients even after prism removal.

Here, we found that prism exposure induced greater activation within bilateral fronto-parietal areas during subsequent visuo-spatial tasks, together with improved behavioral performance. These results suggest that the lasting effects of prisms might involve a cross-talk between the short-term plasticity mechanisms induced by visuo-motor adaptation and a more sustained reorganization of internal spatial representations mediated by fronto-parietal networks which control attention. The realignment of visuo-motor coordinates induced by prism adaptation could trigger a recalibration of internal spatial maps (Chapman et al., 2010) by allowing the recruitment of intact neuronal populations that otherwise would not respond to contralesional stimuli (Pisella et al., 2006). This could in turn improve contralesional attention and subserve neglect recovery in the longer-term (Luaute` et al., 2006b). This hypothesis accords with observations that patients may continue to improve even after prism adaptation has ended (Frassinetti et al., 2002). This recovery could be initiated by the restoration of activation in attentional networks across the two hemispheres (Thimm et al., 2008), countering the relative hyporeactivity of right-sided areas due to unilateral hemispheric damage. Similar bilateral increases have also been observed following spontaneous recovery of neglect (Corbetta et al., 2005; Thimm et al., 2008).

Taken together, these data suggest that the focal right fronto-parietal lesions of neglect patients may result in deficient neural responses to sensory stimuli in bilateral brain networks mediating spatial localization and attentional selection (Corbetta et al., 2005; Corbetta and Shulman, 2002; Thimm et al., 2008), in combination with pathological biases precluding awareness for contralesional (left-sided) inputs that are processed in the damaged right hemisphere (Corbetta and Shulman, 2002; Vuilleumier et al., 1996). By contrast, even when diminished, sensory responses to right-sided inputs in the intact left hemispheric could still overcome any attentional competition with concurrent stimuli and be sufficient to reach conscious awareness. Following prismatic exposure, however, changes in internal spatial representations that are induced by visuo-motor adaptation may now allow the contralesional inputs to gain access to intact neuronal populations in fronto-parietal networks, and thus “recapture” attentional processing resources. This may in turn promote plasticity and maintain new visuo-motor representations in these networks, perhaps due to abnormal “deadaptation” after prism removal in these patients (Farné et al., 2002; Redding and Wallace, 2006; Rossetti et al., 1998). Interestingly, in healthy participants, such deadaptation has been found to activate the inferior parietal cortex (Luaute` et al., 2009), a region that is commonly damaged in neglect patients. This damage might impair the processing of the leftward after-effect during deadaptation and prevent a return to the initial visuo-motor mappings, which would explain the
A recent neuro-anatomical hypothesis concerning the beneficial effects of prisms in neglect, proposed by Strieter and Danckert (2010). These authors postulated that rightward prism adaptation might primarily modulate cortical activity via correction signals from the right cerebellum to the left SPL/IPS, and subsequently influence spatial neglect through callosal connections from left to right SPL which would enable the leftward realignment signals processed in left parietal cortex to be transmitted to right hemispheric areas that are normally responsible for orienting leftwards. This hypothesis is consistent with imaging results in healthy subjects (Chapman et al., 2010; Danckert et al., 2008; Luauté et al., 2009) showing that both the bilateral SPL and right cerebellum are activated during the adaptation phase with left-deviating prisms. Other authors (Luauté et al., 2006b; Pisella et al., 2006) have also suggested that the effects of prism adaptation on spatial cognition could be modulated by the cerebello-parietal connections.

However, an important prediction of the model proposed by Strieter and Danckert (2010) is that prisms will primarily act on visuo-motor circuits in the dorsal occipito-parietal visual stream that control cognitive processes linked to attentional and visuo-motor behaviors (e.g., classic clinical tests of spatial exploration and orienting), but should have much less influence on tasks that rely more on the ventral occipito-temporal visual stream (e.g., object-based perceptual biases or spatial working memory). This prediction fully accords with our findings of a dissociation between positive effects of prisms on visual search and bisection, but no effect on visual memory, both at the behavioral and neural levels. A crucial role of the SPL in the lateralized (egocentric) symptoms of neglect is also suggested by several neuropsychological studies in neglect patients (Luauté et al., 2006b; Sarri et al., 2008; Verdon et al., 2010), as well as fMRI data on the spontaneous recovery of neglect after right brain damage (Corbetta et al., 2005); whereas object-based deficits seem to implicate other regions in inferior parietal, frontal, and temporal cortex (Corbetta et al., 2005; Verdon et al., 2010).

In line with this account, behavioral studies (Robertson et al., 1997; Rossit et al., 2009) have reported that spatial neglect is improved during visuo-motor tasks that require the patients to grasp and lift a rod at its midpoint, presumably due to some residual processing in dorsal occipito-parietal pathways for visually-guided actions (Milner and Goodale, 2008) and subsequent adjustment to proprioceptive error signals on incorrect trials. Remarkably, intensive practice on this task can lead to significant and prolonged improvement on a range of perceptual and representational neglect tasks, up to 1 month after training (Rossit et al., 2009). These effects suggest that visuo-motor error signals during the rod lifting task could also trigger some recalibration processes within the dorsal parietal (and presumably frontal) visuo-motor pathways, at least when these are spared by the more inferior lesions typically associated with neglect (Corbetta et al., 2005; Milner and Goodale, 2008; Mort et al., 2003), and that such changes could subsequently influence the processing of extrasensory inputs by “bootstrapping” attentional and perceptual systems (e.g., in temporal pathways) responsible for visual awareness (Rossit et al., 2009). It is thus possible that the long-term benefits of both visuo-motor feedback training and prism adaptation involve similar neural substrates via the activation of spared fronto-parietal areas of the dorsal visual stream, which could still be recruited despite left neglect and then impact on other systems to restore (at least partly) attention toward contralesional stimuli.

In summary, our results reveal that the partial recovery of neglect by prism adaptation relies on a modulation of anatomical structures intimately connected to spatial attention and visuo-motor behavior, including the posterior...
parietal cortex (Clower et al., 1996; Danckert et al., 2008; Luaute´ et al., 2009) and superior/middle frontal cortex in both hemispheres (Corbetta et al., 2005; Verdon et al., 2010), which may mediate spared visuo-motor processing and adjustment to errors. More generally, our study also highlights that functional neuroimaging in brain-damaged patients may open invaluable perspectives to uncover the pathophysiology of neuropsychological disorders, and provide useful measures to probe the neural mechanisms underlying new rehabilitation approaches and their efficacy.

Acknowledgments

This work was supported by the Swiss National Foundation (#3200BO-114014) and the Geneva Academic Society (Fund Foremane). We thank the Center for Biomedical Imaging (CIBM) at Geneva University Hospital for technical assistance. We offer our thanks to the patients and families for their time and cooperation and to anonymous reviewers for helpful suggestions.

Disclosure: The preliminary results of this study were presented in abstract form at the 2nd Meeting of the Federation of the European Societies of Neuropsychology and the 17th Meeting of the Cognitive Neuroscience Society.

References