The Role of Right Temporal Lobe Structures in Off-line Action: Evidence from Lesion-Behavior Mapping in Stroke Patients

Stéphanie Rossit¹, Paresh Malhotra², Keith Muir³, Ian Reeves⁴, George Duncan⁴ and Monika Harvey⁵

¹Centre for Brain and Mind, Department of Psychology, University of Western Ontario, London W6 8RP, Canada, ²Centre for Neuroscience, Imperial College London W6 8RP, London, UK, ³Institute of Neurological Sciences and ⁴Department of Medicine for the Elderly, Southern General Hospital, Glasgow G12 8QF, UK and ⁵School of Psychology, University of Glasgow, Glasgow G12 8QB, UK

Address correspondence to Monika Harvey, School of Psychology, University of Glasgow, Glasgow G12 8QB, UK. Email: m.harvey@psy.gla.ac.uk.

Recent evidence suggests the possibility that not all action modes depend on dorsal visual stream processing but that off-line nontarget-directed actions, such as antipointing, require additional and even distinct neural networks when compared with target-directed online actions. Here, we explored this potential dissociation in a group of 11 patients with left visual neglect, a syndrome characterized by a loss of awareness of the contralesional side of space. Ten healthy participants and 10 right hemisphere–damaged patients without neglect served as controls. Participants had to point either directly toward targets presented on their left or right (i.e., propointing) or to the mirror position in the opposite hemisphere (i.e., antipointing). Compared with both control groups, neglect patients showed reduced accuracy when antipointing but not propointing. Lesion-behavior mapping revealed that the areas critically associated with these deficits were located in the middle and superior temporal and parahippocampal gyri. We argue that neglect patients present specific deficits only when the visuomotor task taps into more perceptual representations thought to rely on ventral visual stream processing and that our results indicate that right temporal brain regions are implicated in these off-line actions.

Keywords: middle temporal gyrus, parahippocampal gyrus, superior temporal gyrus, visuomotor control, voxel-based lesion-behavior mapping

Introduction

Humans can perform online target-driven actions, like grasping for an object, quickly and precisely. Nonetheless actions become qualitatively different when executed off-line, suggesting that this action mode may depend on different neural substrates than real target-directed (online) actions (e.g., Goodale et al. 1994; Westwood et al. 2000, 2001). Examples of such off-line behaviors are actions that are not directed at the target itself but instead prompted to a spatially displaced location beside it (e.g., antipointing) or actions toward a target previously seen that is no longer present (e.g., delayed pointing). During such off-line movements, visual information regarding target position cannot be used directly during action execution (in contrast to online actions).

Evidence for such differences between online and off-line action modes comes mainly from neuropsychology. D.F., a well-studied visual form agnosic patient whose ventral visual stream shape-processing system is destroyed (James et al. 2003), is unable to perform temporally and spatially displaced pantomiming movements, even though she is capable of executing real target-directed actions (Goodale et al. 1994; Rossit et al. 2010). Opposite effects have been observed in optic ataxic patients after bilateral damage to the parieto-occipital junction (Karnath and Perenin 2005). Such patients are unable to perform target-directed actions but show a paradoxical improvement in their performance when the action is delayed (Milner et al. 1999; Revol et al. 2003; Himmelbach and Karnath 2005).

Based on this double dissociation, it has been suggested that there may be separate online and off-line modes for the control of actions. The online mode is dedicated to the immediate guidance of actions directed toward targets, uses spatial information coded in egocentric coordinates and depends on visuomotor networks in the visual dorsal stream. On the other hand, the off-line mode takes over when the action is not directly target-driven and thus requires relational metrics and scene-based coordinates (e.g., antipointing). Such off-line computations are supposedly carried out by regions outside those implicated solely in real-time actions, perhaps comprising areas in the ventral visual stream (Carey et al. 2006; Milner and Goodale 2006; Schenk 2006).

Recent neuroimaging studies with healthy participants have further corroborated the proposal that online and off-line actions require different neural networks. It is well established that areas in the posterior parietal cortex (PPC) are involved in online visuomotor control (for reviews, see Culham 2004; Culham and Valyear 2006; Culham et al. 2006; Milner and Goodale 2006; Blangero et al. 2009). In particular, the parieto-occipital junction and the medial intraparietal sulcus have been shown to be preferentially activated in immediate reaching (Prado et al. 2005; Gallivan et al. 2009) and the anterior intraparietal sulcus in grasping (Binkofski et al. 1998; Culham et al. 2003). However, areas in the ventral visual stream seem to be required additionally for off-line actions. The lateral occipital complex (LOC), a large bilateral region of occipitotemporal cortex (Malach et al. 1995; Grill-Spector et al. 2001) in particular, has been shown to be activated not only during object presentation but also for delayed grasping execution, many seconds after the object was visually presented (Singhal et al. 2006). Moreover, LOC disruption with Transcranial Magnetic Stimulation impairs delayed but not immediate grasping (Rice Cohen et al. 2009). In the case of spatially displaced pantomimed pointing and grasping actions, specific activations have been found in the inferior parietal lobe, the right middle temporal gyrus, and the superior temporal sulcus (in particular when actions toward the adjacent location of the object are contrasted with real target-directed actions; Connolly et al. 2000; Krüliczak et al. 2007). Connolly et al. (2000) suggested that regions activated for antitasks (but not protasks) might be involved in the transformation of the presented target location into the antitarget location.

We have recently investigated whether the performance of online and off-line actions would also dissociate in patients with left visual neglect. These patients, who suffer typically from lesions to the right inferior parietal lobe (Mort et al. 2003)
and/or the superior temporal cortex (e.g., Karnath et al. 2004), show reduced awareness of the contralesional side of space. We found that such patients were less accurate when performing delayed leftward reaches but not when pointing directly toward targets (Rossit, Muir, et al. 2009). We further demonstrated that neglect patients were not specifically impaired in closed- or open-loop immediate reaching tasks (Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009). Our findings agree with the contentious view that visual neglect only affects actions that tap into perceptual representations and stored by the visual ventral but not the visual dorsal stream (Milner and Harvey 2006). In fact, very recently, we have reported that the neglect-specific impairment in delayed pointing seems to be associated with damage to occipitotemporal areas (in line with the neuroimaging evidence outlined earlier). On the other hand, the directional slowing for immediate target-driven actions, observed after right brain lesions “irrespective” of neglect, is related to more anterior and/or subcortical lesions (Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Muir, et al. 2009). These data allow a new interpretation of what might underpin the hotly debated issue regarding the presence or absence of neglect-specific impairments in visuomotor tasks (Coulthard et al. 2006, 2007; Himmelbach et al. 2007). In line with our very recent studies (Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009; Rossit, Muir, et al. 2009), we would argue that online target-directed actions are not impaired specifically in visual neglect yet that there is a neglect-specific deficit in more complex off-line processing, as demonstrated in patient D.F. also (e.g., Rossit et al. 2010).

Therefore, in the present study, our objective was to test if, similarly to patient D.F. (Goodale et al. 1994), neglect patients would also be specifically impaired in an action that invokes off-line perceptual processing of target locations but not when the action is directed to a target. To address this, we asked patients to either point directly to a target (i.e., propointing) or reach to the horizontal mirror location of presented targets (i.e., antipointing). It has been shown that healthy young participants present longer reaction times and decreased accuracy in antipointing when compared with propointing (Chua et al. 1992; Carey et al. 1996; Heath, Maraj, Gradkowski, and Binsted 2009; Heath, Maraj, Maddigan, and Binsted 2009; Neely and Heath 2009). Based on this evidence, and in agreement with the model of Milner and Goodale (2006), Heath, Maraj, Maddigan, and Binsted (2009) (Maraj and Heath 2010) speculated that antipointing is a perceptually based task entailing a vector inversion process, which is supported via perception-action integrative networks that work off-line. Patients with left visual neglect underperceive the visual extent of the left side of space (e.g., Milner et al. 1993; Harvey et al. 1995; Milner and Harvey 1995; Pritchard et al. 1997; Milner et al. 1998), and it could be hypothesized that they would present antipointing deficits in response to left targets only. However, as pointed out by one of the reviewers, antipointing to the left (in response to the right target) should be impaired also as the latter has to be driven by the perceived left space toward which the response is being made.

Finally, to explore the neural basis of the deficits observed, we used voxel-based lesion-behavior analysis (VBLB; Rorden and Karnath 2004; Rorden, Karnath, and Bonilla 2007). In agreement with previous findings, deficits emerged only when the action invoked off-line perceptual processing of the target locations (Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009; Rossit, Muir, et al. 2009). The impairments proved to be “bilateral” overshoots and implicated the right temporal lobe as the critical area driving these deficits.

Materials and Methods

Participants

Eleven patients with left visual neglect after right hemisphere stroke participated in the study (RH+; mean age 66.5, standard deviation [SD] 8.0). Ten patients with right hemisphere damage without neglect (RH−; mean age 66.5, SD 7.7) and 10 healthy participants (mean age 72.3, SD 4.4) served as control groups. The groups were age-matched, and all participants were right-handed (Annett 1967). All participants had normal or corrected-to-normal visual acuity. On average, patients took part in the experiment 7 months after stroke onset, and there were no differences in onset times between the 2 patient groups.

Patients were included in the RH+ group if they scored below the cut-off on the conventional subtests of the Behavioural Inattention Test (BIT; Wilson et al. 1987) or presented a significant rightward bisection error (Harvey et al. 1995) or were impaired in a lateralized manner in the subtest B of the Balloons Test (Edgeworth et al. 1998), all of which were implemented at the time of this study. Importantly, none of the RH− patients ever showed signs of neglect on these tests.

Hemianopia and extinction were formally assessed using computerized perimetry and extinction tests (adapted from Walker et al. 1991). They were presented on a laptop with a 285 × 214 mm screen with stimuli at a viewing distance of ~60 cm. On both tasks, a central fixation cross appeared for 1000 ms but was extinguished 100 ms before target onset, thus leaving a blank screen onto which targets were displayed for 100 ms. For the perimetry task, a black stimulus (circle with 2 mm of diameter) appeared on one of the 36 possible positions on a white background. The distance between the stimuli was fixed (6.5° in the x-axis and 4.8° in the y-axis). Patients were first asked to fixate on the central cross and after fixation offset were asked to press a key when they detected the target. A total of 106 trials (including 10 practice and 24 catch trials) were presented, 2 per target position. In the extinction test, squared stimuli (2 × 2 mm) were presented on a white background, unilaterally to either the left or the right of the screen or simultaneously on both sides (located at either 29° or 5.7° from the center of the screen). Patients were asked to report the number of squares they detected (i.e., left, right, both, or none). A total of 70 trials (including 7 practice and 10 catch trials) were presented, 10 for each condition and eccentricity.

Finally, spatial working memory was assessed in all patients with the perceptual version of the vertical computerized test of spatial working memory developed by Malhotra et al. (2005). Here, participants were asked to verbally indicate whether locations were either the same or different in 2 sets of vertically presented sequences of dots. Due to time constraints, we were unable to apply this measure to patients J.S.T. and F.H. Three patients (K.M., M.J., and N.F.) could not follow the instructions in the practice trials, so no score could be generated. Demographic and clinical data of all patients are presented in Table 1.

Ethical approval was granted by the South Glasgow University Hospitals Trust, and the study was carried out according to the Declaration of Helsinki. All participants gave their informed consent prior to participation in the study and were reimbursed for their travel expenses.

Clinical scans were available for all 21 patients (11 magnetic resonance imaging [MRI] scans and 10 computed tomography scans; due to clinical constraints, MRI scans could not be obtained for all patients). The extent and location of each patient’s lesion was visualized and defined using the MRIcro software package (Rorden and Brett 2000; http://www.mricro.com). For each patient, the area of damage was determined by inspection of the digital brain image, slice by slice, by a clinical neurologist (K.M.), who was blind to the design, group assignment, and purpose of the experiment. Lesions were drawn...
on 11 axial slices of a T1-weighted template, corresponding to the Talairach z coordinates of −24, −16, −8, 0, 8, 10, 24, 32, 40, 50, 60 mm using the identical or closest matching transverse slices for each patient. The extension and location of the lesions of all individuals were further evaluated by a second neurologist (P.M.) who was also unaware of the group assignment and experiment purpose.

In Figure 1A,B, we present the overlap of the reconstructed lesions for the RH+ group (damage present in 81% of neglect patients) and the RH– group (damage present in 19% of neglect patients) for the RH+ group (damage present in 81% of neglect patients) and the RH– group (damage present in 19% of neglect patients) patients respectively. The regions of maximal overlap for the RH+ group (damage present in 81% of neglect patients) were in the superior temporal gyrus gray matter (Talairach coordinates: +47, −10, 0) and nearby white matter (Talairach coordinates: −46, −11, 0), the insula gray matter (peak Talairach coordinates: 43, −9, 0) and its surrounding white matter (peak Talairach coordinates: −41, −10, 0), and the white matter around the claustrum (peak Talairach coordinates: 37, −9, 0). Regarding the patients without neglect, there appeared to be no specific regions of lesion overlap. Consistent with previous studies, the lesions of the neglect patients were significantly larger in volume than those of the nonneglect group (% of patients impaired when this index is lower than 45%); SWM represents the total score in the spatial working memory test (max = 100; according to Mulhota et al. (2005), cut-off is 78). TO, time since injury onset (months); VFD, visual field defect; EXT, extinction; BIT, Behavioural Inattention Test conventional subtests score (cut-off — available. They were presented at approximately only when illuminated, and no tactile information of their locations was visible. The target surface was 77 cm wide and 49 cm long. Targets were visible at the top of a wooden table at which the subjects were comfortably seated. The raw data from the magnetic marker were filtered with a dual-pass second-order Butterworth filter with a cut-off frequency of 10 Hz and analyzed using customized software written in the LabView programming environment (National Instruments). The start and end of each movement were defined by a velocity-based criterion of 50 mm/s. Reaction times were obtained by computing the time elapsed from target presentation to release of the start trigger.

First, a trial-by-trial analysis was performed to exclude antipointing trials in which participants failed to move in the opposite direction of the target. In the “pointing” condition, participants were required to point directly to the target. In the “antipointing” condition, subjects were asked to move in the opposite direction of the target, that is, if the target was illuminated on the right subjects had to point to its mirror position to the left and vice versa (see Fig. 2 for a drawing of the conditions). Participants pressed the start trigger to initiate target presentation. For both conditions, participants were instructed to perform their movements as quickly and as accurately as possible with their right index finger. Target positions remained visible for 1 s after start trigger release allowing vision of the target location and limb until the end of the reach. Trials were presented in a randomized order, and the 2 conditions were given in separate blocks and block order was counterbalanced across participants. Each block contained 8 practice trials (2 for each target position) and 64 experimental trials (16 for each target). Calibration coordinates were obtained at the end of each session, by continuous illumination of each target, one by one, allowing the subjects to adjust their terminal fingertip position until they felt they had perfectly occluded the target. There were 3 calibration trials per target and 3 for the start position.

Pointing responses were recorded by sampling the position of a magnetic marker, attached to the tip of the right index finger, at a rate of 108 Hz, using an electromagnetic motion analysis system (Minibird; Ascension Technology Inc.). The start trigger, the online recordings, and the stimuli presentation were simultaneously controlled and timed by a PC, by means of a Virtual Instrument generated with LabView software (National Instruments).

### Stimulation and Procedure

Targets were white circles (diameter 7 mm) projected (HITACHI CPXs45 Multimedia LCD Projector; refresh rate of 60 Hz) onto a horizontal Perspex box (77 cm width × 97 cm length × 30 cm height) via a reflection mirror (3 mm thick, 60 × 60 cm). The box was placed on top of a wooden table at which the subjects were comfortably seated. The target surface was 77 cm wide and 49 cm long. Targets were visible only when illuminated, and no tactile information of their locations was available. They were presented at approximately −6° and −12° (left hemispace) and +6° and +12° (right hemispace) with respect to the middle position located at 36 cm from the central start trigger. At the start of each trial, the participant’s right index finger rested on the start trigger, aligned with the subject’s sagittal midline. The room was slightly darkened so that the targets were clearly visible when illuminated, yet not at any other time. Given that most of our patients presented with concomitant hemianopia, eye movements were unrestricted to allow participants with visual field deficits to perceive the left targets.

In the “pointing” condition, participants were required to point directly to the target. In the “antipointing” condition, subjects were asked to move in the opposite direction of the target, that is, if the target was illuminated on the right subjects had to point to its mirror position to the left and vice versa (see Fig. 2 for a drawing of the conditions). Participants pressed the start trigger to initiate target presentation. For both conditions, participants were instructed to perform their movements as quickly and as accurately as possible with their right index finger. Target positions remained visible for 1 s after start trigger release allowing vision of the target location and limb until the end of the reach. Trials were presented in a randomized order, and the 2 conditions were given in separate blocks and block order was counterbalanced across participants. Each block contained 8 practice trials (2 for each target position) and 64 experimental trials (16 for each target). Calibration coordinates were obtained at the end of each session, by continuous illumination of each target, one by one, allowing the subjects to adjust their terminal fingertip position until they felt they had perfectly occluded the target. There were 3 calibration trials per target and 3 for the start position.

Pointing responses were recorded by sampling the position of a magnetic marker, attached to the tip of the right index finger, at a rate of 108 Hz, using an electromagnetic motion analysis system (Minibird; Ascension Technology Inc.). The start trigger, the online recordings, and the stimuli presentation were simultaneously controlled and timed by a PC, by means of a Virtual Instrument generated with LabView software (National Instruments).

### Behavioral and Statistical Analysis

The raw data from the magnetic marker were filtered with a dual-pass second-order Butterworth filter with a cut-off frequency of 10 Hz and analyzed using customized software written in the LabView programming environment (National Instruments). The start and end of each movement were defined by a velocity-based criterion of 50 mm/s. Reaction times were obtained by computing the time elapsed from target presentation to release of the start trigger.

First, a trial-by-trial analysis was performed to exclude antipointing trials in which participants failed to move in the opposite direction of
the target but instead reached incorrectly toward the side of space in which the target appeared (i.e., directional errors). For the remaining trials, we analyzed the absolute angular error, that is, the unsigned angular error relative to the ideal reach. This angular error was calculated for each trial based on the subtraction of each participant’s movement angle by the ideal reach angle either directly toward the target (propointing) or to the mirror location of the target in the opposite side of space (antipointing). The calculation of the ideal reach angles was based on the individual x and y calibration coordinates. In addition, we also analyzed the directionality of this angular error in terms of right- and leftward deviations from the ideal reach angle. Finally, we also analyzed movement time. Means for each participant were computed per condition for each variable and target position.

All variables were analyzed with a $3 \times 2 \times 4$ mixed analysis of variance (ANOVA) with group (healthy, RH-, and RH+) as a between-factor and task (pro- and antipointing) and presented target (-12°, -6°, +6°, +12°) as within-subject effects. Multiple post hoc comparisons were controlled with the Bonferroni method, $P < 0.05$. As the interest of this paper is in the potential group differences, to focus the results, significant effects are reported for such group differences only.

Moreover, we also ran correlation analyses (Pearson coefficient) to investigate if any of the deficits observed were associated with lesion volume, neglect severity (i.e., mean line bisection errors, BIT scores and the Balloons lateralized index), hemianopia (i.e., percentage of items detected in the contralesional side) or extinction (i.e., percentage of contralesional stimuli reported during bilateral stimulation), and spatial working memory performance.
Voxel-Based Lesion-Behavior Mapping

Finally, whenever a deficit was observed, we implemented the VLBM statistical approach using the nonparametric mapping software provided with MRcron software (Rorden, Bonilla, and Nichols 2007; http://www.sph.sc.edu/comd/orden/mrcron/; version 17 December 2009). This analysis was performed with voxel-based maps of the Brunner–Munzel nonparametric statistic (BM; Brunner and Munzel 2000). The BM test is a rank order test that relates lesioned voxels to behavioral performance in a continuous fashion without pre categorizing patients into RH+ or RH− groups. Thus, it takes the behavioral data from all patients and tests which voxels, when lesioned, are associated with that particular deficit. This test provides a relatively assumption-free measure of whether or not damage to each voxel is associated with a particular deficit (Rorden, Bonilla, and Nichols 2007). For each voxel, patients are divided into 2 groups according to whether they did or did not have damage affecting voxel and the behavioral scores are compared for these 2 groups (damaged/nondamaged). The BM statistic tests if the difference in behavior between the 2 groups is significant and thus provides a Z score for each voxel. Multiple comparisons were controlled with the false discovery rate (FDR; P < 0.01). Throughout this paper, we report the voxel \( x, y, \) and \( z \) Talairach space coordinates (in mm; Talairach and Tournoux 1988) for results that survived FDR correction. For each significant brain area, the voxel position that obtained the highest (peak) \( Z \) score, within the BM range, is reported.

Results

Directional Errors

We ran a 3 × 4 ANOVA on the percentage of trials excluded due to directional errors with group (healthy, RH−, and RH+) as the between-subject and target (−12°, −6°, +6°, +12°) as the within-subject factor. This revealed a significant main effect of group (\( F_{1,28} = 9.03, P = 0.001 \)) insofar that neglect patients were impaired (mean = 13.8%) when compared with the other 2 control groups (healthy controls: mean = 0.2%, \( P < 0.01 \); RH−: mean = 0.6%, \( P = 0.01 \)). Surprisingly, there were no significant effects of target nor a target by group interaction: neglect patients performed propointing (rather than antipointing) in response not only to targets presented on the left (in 14.0% of trials) but also to targets that appeared on the right side of space (in 13.6% of trials). To analyze this further, we ran a correlation analysis between the error percentage of all patients and lesion volume, severity of neglect, hemianopia, extinction, and spatial working memory measures. We found that this variable was correlated significantly with the severity of hemianopia (\( r = -0.66, N = 21, P = 0.001 \)), extinction (\( r = -0.62, N = 21, P < 0.01 \)), the performance on the Balloons (\( r = -0.61, N = 21, P < 0.01 \)), and on the spatial working memory task (\( r = -0.65, N = 16, P < 0.01 \)). However, this deficit also correlated significantly with lesion volume (\( r = 0.62, N = 21, P < 0.01 \)), indicating it to be a likely consequence of the size of the brain damage per se.

Endpoint Accuracy

The mixed ANOVA on the absolute angular error revealed a significant main effect of group (\( F_{1,28} = 13.04, P < 0.001 \)) and a significant interaction between group and task (\( F_{2,56} = 12.17, P < 0.001 \)). Post hoc comparisons showed that patients with neglect showed increased absolute angular errors solely when antipointing, when compared with both RH− patients and healthy controls (\( P < 0.001 \)). Patients without neglect were no different from healthy controls in both pro- and antipointing in response to all target positions. There was no main effect of target position and no other interactions were significant, indicating that neglect patients were inaccurate not only when the targets were on the left but also when the targets appeared on the right side (see Table 2).

In terms of directionality, the angular error shown by the RH− patients for the antipointing trials was an overshoot (with respect to the ideal horizontal mirror position of all presented targets). That is, if the target appeared on the left and patients had to reach toward its rightward equivalent position, they would reach too far rightward and vice versa (Fig. 3B,D). When propointing, however, as can be seen in the Figure 3A,C, neglect patients occluded the target perfectly, even when it appeared on the left side of space.

Also, as is apparent from the scatter plots (Fig. 3D), the overshoots in the antipointing condition seemed to occur most frequently in the horizontal \( x \)-axis and less so in the \( y \)-axis. To verify this, we ran an additional mixed analysis of ANOVA on the amplitude error (i.e., the error in respect to the targets’ \( y \) coordinates). We found that although there was a significant interaction between group and task (\( F_{2,56} = 4.60, P < 0.05 \)), neglect patients produced significant overshoots in the \( y \)-axis only when compared with healthy controls (\( P < 0.05 \)) but not when compared with patients without neglect. Moreover, the interaction between group, target, and condition did not reach significance, indicating that the amplitude error was neither target- nor neglect-specific.

To investigate endpoint accuracy further, we ran Pearson correlation analyses (for all patients) between the overall absolute angular error (collapsed across target positions) and lesion volume, severity of neglect, hemianopia, and extinction and the score obtained on the spatial working memory task. In

<table>
<thead>
<tr>
<th>Group</th>
<th>Propointing</th>
<th>Antipointing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−12 −6 +6 +12</td>
<td>−12 −6 +6 +12</td>
</tr>
<tr>
<td>Healthy controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH−</td>
<td>0.4 (0.1) 0.4 (0.0) 0.5 (0.1) 0.6 (0.1)</td>
<td>3.5 (0.3) 4.2 (1.1) 4.0 (0.9) 3.5 (0.4)</td>
</tr>
<tr>
<td>RH+</td>
<td>0.5 (0.1) 0.4 (0.0) 0.4 (0.0) 0.4 (0.0)</td>
<td>3.7 (0.5) 2.8 (0.4) 4.8 (0.8) 4.2 (0.7)</td>
</tr>
<tr>
<td>A.B.</td>
<td>0.5 0.5 0.4 0.7 5.9 10.8 25.1 20.7</td>
<td></td>
</tr>
<tr>
<td>A.M.</td>
<td>0.4 0.3 0.4 0.4 2.7 3.7 1.6 4.5</td>
<td></td>
</tr>
<tr>
<td>D.S.</td>
<td>1.1 1.0 0.7 0.6 21.2 30.5 23.3 15.2</td>
<td></td>
</tr>
<tr>
<td>F.H.</td>
<td>1.0 0.8 0.6 1.3 23.0 28.1 8.5 4.2</td>
<td></td>
</tr>
<tr>
<td>J.H.</td>
<td>0.5 0.6 0.5 0.5 29.1 29.1 15.3 9.5</td>
<td></td>
</tr>
<tr>
<td>J.K.</td>
<td>0.4 0.6 0.3 0.6 4.0 4.0 25.6 29.4</td>
<td></td>
</tr>
<tr>
<td>J.M.</td>
<td>0.7 0.7 0.5 0.9 9.4 18.0 7.2 3.1</td>
<td></td>
</tr>
<tr>
<td>J.S.</td>
<td>0.5 0.4 0.3 0.4 12.0 19.6 15.1 5.7</td>
<td></td>
</tr>
<tr>
<td>M.J.</td>
<td>0.5 0.8 0.4 0.5 6.3 2.3 2.2 8.9</td>
<td></td>
</tr>
<tr>
<td>M.M.</td>
<td>2.0 0.9 0.5 0.8 5.2 1.7 3.2 4.9</td>
<td></td>
</tr>
<tr>
<td>N.F.</td>
<td>0.5 0.4 0.4 0.4 8.4 2.4 8.4 4.7</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data are presented for each group and individually for each neglect patient.

Figure 2. Display of the pro- and antipointing conditions.
contrast to the results on directional error (see Results earlier), we found no significant correlation between the end point accuracy in antipointing and lesion volume ($r = 0.35, N = 21, P = 0.12$). Significant correlations were found between the antipointing accuracy and all neglect diagnostic measures used (BIT: $r = -0.60, N = 21, P < 0.01$; line bisection: $r = 0.75, N = 21, P < 0.001$; Balloons: $r = -0.49, N = 21, P < 0.05$), as well as hemianopia ($r = -0.55, N = 21, P = 0.01$) and extinction severity ($r = -0.61, N = 21, P < 0.01$). Furthermore, again in contrast to the results regarding the directional error, no significant correlation was found between end-point accuracy and the scores on the spatial working memory task ($r = -0.42, N = 16, P = 0.11$). These observations imply that the deficit is specific to patients with neglect and not just a mere consequence of stroke and/or task difficulty.

The VLBM analysis showed that several foci were significantly associated with impaired antipointing ($z > 2.35$; BM range = -1.65 to 3.62; see Fig. 1C). The most significantly damaged voxels were located in the white matter in the vicinity of the middle temporal gyrus (peak $z = 3.62 [29, -52, 24]$) going into the superior temporal gyrus (gray matter peak $z = 3.01 [35, 5, -16]$; white matter peak $z = 3.01 [32, 1, -16]$) and the parahippocampal gyrus (peak $z = 3.19 [38, -51, 0]$). Moreover, another cluster of significant voxels was located in and around the supramarginal gyrus (gray matter peak $z = 3.19 [57, -55, 32]$; white matter peak $z = 3.19 [51, -53, 32]$).

**Reaction Time**

In terms of reaction time (see Table 3 for descriptive statistics), the mixed ANOVA revealed a significant main effect of group ($F_{1,28} = 5.42, P = 0.01$) and post hoc comparisons showed that neglect patients took significantly longer than healthy controls to initiate a movement ($P < 0.01$) but were no different than RH- patients (see Table 3 for descriptive statistics). There were no significant interactions between group and target, but the interaction between group and task was marginally significant ($F_{2,28} = 5.42, P = 0.057$).

To investigate this increase in reaction time after right brain damage, we repeated the correlation and the VLBM analysis for each condition separately (i.e., overall reaction time in pro- and antipointing conditions).
antipointing). Although the reaction times in the propointing condition did not correlate with any of the measures, we found that the antipointing reaction times were correlated significantly with the severity of neglect (line bisection: \( r = 0.53, N = 21, P = 0.01 \); Balloons Test: \( r = -0.55, N = 21, P = 0.01 \)) and hemianopia (\( r = -0.50, N = 21, P < 0.05 \)). These observations indicate that slower RTs for antipointing (but not propointing) are specific to patients with neglect and concomitant hemianopia. In agreement with this, the VLBM analysis confirmed that the increased RTs for antipointing were associated significantly with several loci of damage, which were also the most damaged regions in our neglect group (\( z > 2.33; \mathrm{BM} \) range = \(-1.39\) to \(3.09\); see Fig. 1D); the superior temporal gyrus gray (peak \( z = 3.09 \) [48, –34, 16]) and white matter (peak \( z = 3.09 \) [48, –36, 16]), the white matter nearby the insula (peak \( z = 3.09 \) [53, –36, 16]) and the claustrum gray (peak \( z = 3.01 \) [35, –14, 8]) and white matter (peak \( z = 3.01 \) [34, –16, 8]). On the other hand, the VLBM analysis on the propointing reaction time (\( z > 2.33; \mathrm{BM} \) range = \(-1.98\) to \(3.22\); see Fig. 1E) revealed that the most significantly associated lesions were located subcortically within the basal ganglia white matter near the putamen (peak \( z = 3.22 \) [32, –3, 0]). In addition, another cluster of voxels was located in the white matter coming from the supramarginal gyrus (peak \( z = 3.09 \) [63, –32, 24]) into the postcentral gyrus gray (peak \( z = 3.09 \) [55, –23, 16]) and white matter (peak \( z = 3.09 \) [52, –28, 16]), followed by lesions in the superior temporal gyrus (peak \( z = 3.09 \) [63, –25, 16]) and to the white matter around the insula (peak \( z = 3.09 \) [42, –24, 16]).

**Movement Time**
The mixed ANOVA revealed a main effect of group (\( F_{1,29} = 3.46, P = 0.045 \)), and pairwise comparisons showed that patients with neglect took significantly longer to complete their reaches when compared with healthy controls (\( P = 0.043 \); see Table 3) but were no different than control patients without neglect. However, this time, we did not observe a significant interaction between group and target or task, and the correlation and VLBM analyses were not significant.

**Discussion**
Compared with both healthy and patient control groups, patients with left visual neglect produced greater end point errors and longer RTs when antipointing only. These impairments were observed for both sides of space and were positively correlated with neglect severity but not lesion volume. The areas critically associated with these impairments were located in the middle and superior temporal gyri. On the other hand, no neglect-specific impairments were found for propointing: both neglect and nonneglect right brain–damaged patients showed increased reaction times compared with the healthy control group, and this measure did not correlate with neglect severity. In contrast to the antipointing deficits, the brain areas most critically associated with longer propointing RTs were located within the basal ganglia white matter.

**Online versus Off-line Actions**
Culham et al. (i.e., Kroliczak et al. 2007) have strongly argued that, contrary to the general assumption that pantomimed actions are a valid proxy for real target-directed actions and can be used to investigate the neural correlates of grasping (Simon et al. 2002; Shikata et al. 2005) and tool use (Ohgami et al. 2004; Rumiati et al. 2004), off-line actions tap into a different neural system. So far, the evidence for their argument has come either from neuroimaging experiments (Connolly et al. 2000; Singhal et al. 2006; Rice Cohen et al. 2009) or single-case neuropsychological studies (Goodale et al. 1994; Milner et al. 1999; Revol et al. 2003; Himmelbach and Karnath 2005; Rossit et al. 2010). In the present study, exactly as Culham et al. (i.e., Kroliczak et al. 2007) would predict, we show that areas outside the frontoparietal visuomotor control network (e.g., Astafiev et al. 2003; Culham and Valyear 2006; Culham et al. 2006; Milner and Goodale 2006; Beurze et al. 2007; Blangero et al. 2009) are crucially involved in the successful performance of more complex motor acts (i.e., actions that require a response that goes beyond a simple target-directed movement). We show, for the first time, that patients with left visual neglect are severely impaired in an antipointing task, whereas they have no specific difficulty performing target-directed responses to the same targets in both right and left space.

One of the regions of maximal overlap (81%) in our neglect group was the superior temporal gyrus (see also Karnath et al. 2004). As superior parietal areas were largely spared in our neglect patients, it is perhaps unsurprising that their target-directed pointing performance was not specifically disrupted for leftward reaches, replicating previous studies (e.g., Karnath et al. 1997; Harvey et al. 2001; McIntosh et al. 2004; Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009; Rossit, Muir, et al. 2009). The only propointing impairment we found was an overall increase in reaction times in both patient groups compared with the healthy control group, and unlike the antipointing deficits, this increase did not correlate with neglect severity. In line with this, the VLBM analysis revealed that the area most critically associated with this increase was located in the basal ganglia white matter in the vicinity of the putamen. This observation not only agrees with a range of studies that have reported that basal ganglia lesions produce increased latencies in neglect patients (Bisiach et al. 1990; Tegner and Levander 1991; Sapir et al. 2007; Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009) but also further demonstrates that the slowing observed after right brain damage is not a consequence of damage to neglect-associated areas alone. That is, this deficit seems to result from additional lesions to crucial nodes in the visuomotor network or possibly from a disconnection between its components (see also Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009; Rossit, Muir, et al. 2009).

The novel result from the VLBM analyses was the finding that lesions in the right superior and middle temporal gyri were associated with deficits in antipointing. This result strongly corroborates the neuroimaging study of Kroliczak et al. (2007), which implicated areas in the temporal lobe in pantomimed actions. Investigating spatially displaced pantomimed pointing and grasping actions, Kroliczak et al. (2007) found activations in the middle temporal and superior gyri in the right hemisphere only. Based on these findings, they hypothesized that these areas might be necessary for the spatial transformations and/or reprogramming of the movement kinematics in actions that are not directly target-driven. The current data provide the first causal evidence toward this.
Ego- versus Allocentric Reference Frames in Action

Although we have discussed our findings in terms of separate processing mechanisms for target-directed (online) versus more indirect (off-line) actions, an alternative (or complementary) explanation is the distinction between allocentric versus egocentric visuospatial processing. Schenken (2006) reported that patient D.F. was significantly abnormal in perceptual and visuomotor tasks for which she had to use allocentric but not egocentric information (see also Dijkerman et al. 1998; Murphy et al. 1998; Carey et al. 2006). Schenken (2006) argued that the critical component that dissociates between the ventral and the dorsal visual streams is not the task (perception vs. action) but the spatial mode used to perform it (egocentric vs. allocentric). This distinction could potentially explain the observed neglect-specific deficits we found, in that allocentric (but not egocentric) coding may have been impaired in our patients. In other words, it is possible that the neglect-specific deficit in the antipointing condition was a failure to code allocentrically the spatial extent of the target location in the horizontal axis in respect to the imaginary center of the reaching platform (but see Milner and Goodale 2008 for a comprehensive critique of this view).

Functional magnetic resonance imaging (fMRI) studies with healthy individuals have also indicated that egocentric spatial representations activate distinct brain regions. During egocentric spatial computations in perceptual tasks, activations have been found in frontoparietal visuomotor regions (e.g., Committeri et al. 2004; Neggers et al. 2006; Zaehle et al. 2007). Moreover, electrophysiological recordings in primates have found neurons that code spatial position egocentrically in the PPC and premotor cortex (e.g., Colby 1998; Cohen and Andersen 2002).

On the other hand, fMRI studies have reported that allocentric coding involves activation within temporoparietal regions, mainly in the right hemisphere (i.e., the superior, middle temporal, and parahippocampal gyri; the ventrolateral occipitotemporal cortex; and the parietal lobe; Galati et al. 2000; Committeri et al. 2004; Neggers et al. 2006; Zaehle et al. 2007). Moreover, using perfusion imaging with stroke patients, Hills et al. (2005) observed that while egocentric deficits in neglect patients are associated with hypoperfusion of the right angular gyrus and inferior frontal gyrus, allocentric impairments correlate with hypoperfusion of the superior temporal gyrus. Using a visual search task, Grimsen et al. (2008) reported that while allocentric deficits were associated with lesions in ventral regions near the parahippocampal gyrus, egocentric impairments were associated with damage in the premotor cortex. Finally, very recently, Verdon et al. (2010), using VLB analysis on a large sample of right hemisphere stroke patients, demonstrated that allocentric aspects of neglect are associated with lesioned voxels located in the temporal regions, near the parahippocampal gyrus extending toward the middle temporal gyrus, while exploratory visuomotor deficits were associated with damage to the frontal lobe.

We would argue that these converging findings are in line with the view of Milner and Goodale (2006) that accurate performance of off-line actions, such as delayed or pantomimed pointing and/or grasping, involves the coding of target locations or object size in scene-based coordinates initially derived from ventral stream processing. This could explain why patient D.F. and our neglect patients are impaired when performing pantomimed (but not target-directed) and delayed actions (Goodeal et al. 1994; Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Muir, et al. 2009; Rossit et al. 2010). This view can also account for the activations observed in healthy participants in temporal regions (especially in the right hemisphere) for both pantomimed (when compared with real) actions and allocentric (when compared with egocentric) spatial judgments. Thus, we would suggest that both temporally and spatially displaced off-line actions may depend on a common perceptual neural mechanism residing in the temporal lobe.

It is important to note that we are not arguing that these off-line actions bypass dorsal visual stream processing, but instead we suggest that they depend on a tight collaboration between the 2 streams. More specifically, we would argue, in line with the proposal of Milner (1995, 1997, 1998a, 1998b), that temporoparietal areas, typically damaged in neglect patients, may form part of a high-level representational system that lies outside the 2 main visual streams and that most probably receives its visual information from the ventral stream. In line with this, our peak voxels in the middle temporal and hippocampal gyri were located in the deep white matter of the temporal lobe, which has been shown to have reciprocal connections with the parietal cortex (Catani et al. 2002).

Nonlateralized Neglect-Specific Deficits in Antipointing

The finding that the neglect group showed a bilateral impairment in antipointing might be surprising to some readers and does in fact differ from our delay data where we found an impairment for the left side of space only (Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Muir, et al. 2009). Yet, the present results mirror recent findings in which we tested neglect patients on an antisaccade task: Patients were required to saccade away from either right- or leftwardly presented targets and produced a large number of erroneous prosaccades to both stimuli (Butler et al. 2009). In the current antipointing condition, neglect patients also showed incorrect propping to both left and right targets, although the frequency of these errors was smaller than in the antisaccade task described in Butler et al. (2009).

In addition, we found that neglect patients presented bilateral overshoots when asked to antipoint. Although neglect patients overshot in our delay study also (Rossit, Malhotra, Muir, Duncan, Reeves, Birschel, and Harvey 2009; Rossit, Muir, et al. 2009), this is in contrast to Heath's observation that young participants, when antipointing, present an under- and over-shooting bias in response to left- and rightwardly presented targets, respectively (Heath, Maraj, Maddigan, and Binsted 2009; Maraj and Heath 2010; Neely and Heath 2009). One possibility is that in Heath's tasks subjects fixated centrally, whereas here this manipulation was not possible as most of our participants had concomitant visual field deficits (hence they were free to move their eyes to look at the target). It has to be granted that the neglect-specific overshooting error in antipointing was not only significantly correlated with neglect severity but also with hemianopia and extinction severities. Although future studies with "pure" neglect patients would be ideal, we do not think that hemianopia or extinction can fully account for the deficits as all patients always responded to the targets and we also failed to find reaction time differences between right and left targets.
Furthermore, in both our delay study (Rossit, Malhotra, Muir, Duncan, Reeves, Duncan, et al. 2009; Rossit, Muir, et al. 2009) and the results reported here, we found that end-point accuracy deficits did not correlate with nonlateralized spatial working memory impairments. This might not be surprising given that the memory demands in the current experiment were low as the target remained present throughout the trial. In relation to this, as pointed out by one of the reviewers, it would have been interesting to track the eye movements of all participants as it is possible that the neglect group might have made a greater number of saccades in order to "remember" where the target was. This might further explain the lack of correlation with working memory. Unfortunately our set-up did not allow us to monitor eye and hand movements simultaneously, but it is important to note that despite being free to look at the targets during both pro- and antipointing, neglect patients were still severely inaccurate in the latter condition.

It is also possible that both delay and antipointing tasks tap into different neural processes from spatial working memory. In fact, Malhotra et al. (2005) observed in their study that the nonlateralized impairment in spatial working memory correlated with cancellation but not line bisection deficits. Here, we found that the end point deficits were highly correlated with line bisection errors. This implies that the overshooting deficits are not merely caused by impairments in visual search but instead are related to a perceptual deficit. In fact, these bilateral deficits in antipointing could reflect a left-sided perceptual impairment as this would affect the response not only to left targets but also to targets presented on the right side of space since the latter also depends on the perception of the left space toward which the response is being made. This perceptual deficit could prevent accurate vector inversion.

In addition, it could be argued that the nonlateralized deficits in the antitasks resulted from competition between motor plans or simply task difficulty. However, competition does not seem a good explanation of the current data as we would have expected the stimulus on the right side to win due to reduced salience of the left stimulus. In contrast, we found a nonlateralized deficit and no differences in reaction times between left and right target positions. If task difficulty were an explanation, we would have expected longer movement times specific to neglect and antipointing, but instead we observed a general slowing irrespective of the presence of neglect or the task. Finally, our neglect patients did not seem to be guessing as the end point errors in antipointing were most marked in the horizontal (not vertical) axis. In fact, these last observations might also indicate that the neglect deficit lies in the vector inversion and/or allocentric coding but not in the reprogramming of the movement kinematics. If a reprogramming failure was the cause of the deficit, we would have expected longer movement times and possibly greater vertical errors specific to neglect and antipointing.

Therefore, we would argue that the current findings are in line with several studies that indicate that neglect can be exacerbated by deficits that may not be spatially lateralized (for reviews, see Robertson 2001; Husain and Rorden 2003; Milner and McIntosh 2005) such as sustained attention (Robertson et al. 1997), the ability to ignore central distracters (Ptak et al. 2007), spatial working memory (Malhotra et al. 2004, 2005), and vigilance (Malhotra et al. 2006, 2009). Here, we show that these deficits can also be present in the visuomotor domain but only when the task is not directly target-driven and requires off-line perceptual-based processing entailing vector inversion and/or allocentric coding.

**Conclusions**

We report bilateral neglect-specific impairments in the control of off-line reaching and argue that this mode of action is supported by an integrated network of cortical areas, including regions deep in the right temporal lobe that may be part of a high-level representational system that lies outside the 2 main visual streams but that most probably receives inputs from the ventral visual stream (Milner 1995, 1997, 1998a, 1998b; Milner and Harvey 2006). Our results indicate that off-line actions are not equivalent to target-directed reaching or grasping and that the distinction between online and off-line processes provides a better understanding of the pattern of impaired abilities in neglect patients. We believe that this dissociation will not only further our understanding of spatial awareness in humans but will also help in the development of more efficient rehabilitation methods for these patients.

**Funding**

Doctoral (SFHR/BD/23230/2005) and postdoctoral fellowships (SFHR/BPD/65951/2009) from the Portuguese Foundation for Science and Technology and Social European Fund to S.R.

**Notes**

The authors wish to thank all the patients and healthy participants for participating in the study. We would also like to thank Hans-Otto Karnath, Matthew Heath, Fraser W. Smith and Lore Thaler for useful discussions during the preparation of this manuscript. *Conflict of Interest*: None declared.

**References**


Carey DP, Hargreaves EL, Goodale MA. 1996. Reaching to ipsilateral or contralateral targets: within-hemisphere visuomotor processing