

Cortical control of inhibition of return: Evidence from patients with inferior parietal damage and visual neglect

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ARTICLE INFO

Article history:

Received 6 October 2011

Received in revised form 6 January 2012

Accepted 11 January 2012

Available online 20 January 2012

Keywords:

Inhibition of return

Parietal lobe

Spatial attention

Visual neglect

ABSTRACT

Inhibition of return (IOR) refers to slower reaction times to targets presented at previously stimulated or inspected locations. This phenomenon biases orienting towards novel locations and is functional to an effective exploration of the environment. Patients with right brain damage and left visual neglect explore their environment asymmetrically, with strong difficulties to orient attention to left-sided objects. We show for the first time a dissociation between manual and saccadic IOR in neglect. Our patients demonstrated facilitation, instead of inhibition, for repeated right-sided targets with manual responses, but normal IOR to right-sided targets with saccadic responses. All neglect patients had damage to the supra-marginal gyrus in the right parietal lobe, or to its connections with the ipsilateral prefrontal cortex. We concluded that IOR with manual responses relies on fronto-parietal attentional networks in the right hemisphere, whose functioning is typically impaired in neglect patients. Saccadic IOR may instead depend on circuits less likely to be damaged in neglect, such as the retinotectal visual pathway.

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1. Introduction

When two consecutive visual events occur at the same spatial location, there can be an early facilitation to respond to the second event. However, when the interval between the two events is longer than 300 ms, responses to the second event are typically slower than those to the first. This phenomenon, dubbed inhibition of return (IOR, Klein, 2000; Lupiáñez, Klein, & Bartolomeo, 2006; Posner, Rafal, Choate, & Vaughan, 1985), is important for thoroughly exploring the visual environment, by avoiding repeated processing of the same location (Klein, 1988). IOR occurs both with manual responses (such as a spacebar keypress) and with saccades to peripheral visual stimuli. Activity in the retinotectal visual pathway is traditionally considered as being important for IOR (Dorris, Klein, Everling, & Muñoz, 2002; Sapir, Soroker, Berger, & Henik, 1999); indeed, focal lesions (Sapir et al., 1999) or degeneration (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988) of the superior

colliculi (SC) can lead to impaired manual IOR. However, cortical mechanisms also appear to be implicated on IOR. In particular, fronto-parietal networks involved in spatial attention (Corbetta & Shulman, 2002) are plausible candidates for the cortical control of IOR. For example, experiments with Transcranial Magnetic Stimulation (TMS) found disturbed manual IOR upon stimulation of frontal eye fields (Ro, Farne, & Chang, 2003), intraparietal sulcus (Chica, Bartolomeo, & Valero-Cabré, 2011) and temporo-parietal junction (Chica et al., 2011).

Patients with damaged attentional networks in the right hemisphere and left visual neglect display, among other deficits, impaired orienting of spatial attention (Bartolomeo & Chokron, 2002); their attention tends to be repeatedly captured by the same right-sided items (Gainotti, D'Erme, & Bartolomeo, 1991; Mannan et al., 2005). They also present difficulties in disengaging attention from these stimuli and explore the rest of the visual scene (Posner, Walker, Friedrich, & Rafal, 1984; Rastelli, Funes, Lupiáñez, Duret, & Bartolomeo, 2008). Not surprisingly, IOR can be abnormal in visual neglect (Bartolomeo, Chokron, & Sieroff, 1999). When pressing a key in response to peripheral visual targets which were occasionally repeated on the same side of space, patients with left neglect presented abnormal facilitation, instead of IOR, for repeated

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right-sided items, i.e., for items appearing in their supposedly normal hemispace (Bartolomeo et al., 1999). Other patients with right hemisphere damage but without neglect had, instead, normal IOR for both sides of space (Bartolomeo et al., 1999). These results were later confirmed in neglect patients with cue–target paradigms (Bartolomeo, Sieroff, Decaix, & Chokron, 2001; Lupiáñez et al., 2004; Sieroff, Decaix, Chokron, & Bartolomeo, 2007). Patients with parietal damage also demonstrated decreased IOR (but not facilitation) on the ipsilesional side, even in the absence of neglect signs (Vivas, Humphreys, & Fuentes, 2003; Vivas, Humphreys, & Fuentes, 2006). These results are important in suggesting that cortical networks including the right parietal lobe, which are typically dysfunctional in neglect patients (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; He et al., 2007; Mort et al., 2003; Thiebaut de Schotten et al., 2005), are implicated in the occurrence of IOR. However, in these studies eye movements were not controlled; if patients looked at ipsilesional first targets or cues (a frequent occurrence in right brain-damaged patients, Gainotti et al., 1991), they received the second stimulus on the fovea; then fast responses to foveal stimuli could have offset IOR. Moreover, the level of detail of the anatomical analysis of lesions in these studies was insufficient to draw firm conclusions about the identity of the cortical circuits implicated in the modulation of IOR. Finally, all the available evidence in these patients concerns manual IOR; no study has so far explored saccadic IOR in right brain damaged patients with or without neglect. Based on previous research demonstrating biased eye movements in neglect (Doricchi, Guariglia, Paolucci, & Pizzamiglio, 1993), one might expect to find abnormalities of saccadic IOR in these patients.

In the present study, we explored IOR with central fixation and manual responses (covert attention, Experiment 1), as well as IOR generated by saccadic responses (overt attention, Experiment 2). We used a target–target paradigm similar to the one used in the original study on IOR in neglect (Bartolomeo et al., 1999), while eye movements were monitored at all times. Neglect patients' performance was compared to that of right brain-damaged patients without neglect. Given the known role of the parietal cortex in the formation of saliency maps necessary to explore the visual environment (Sapir, Hayes, Henik, Danziger, & Rafal, 2004; Van Koningsbruggen, Gabay, Sapir, Henik, & Rafal, 2009), we explored how parietal damage or its disconnection from frontal regions affected manual or saccadic IOR (i.e. IOR generated by saccadic eye movements). Saccadic IOR could be preserved after right parietal damage if it depended on the activity of other circuits, such as the retinotectal pathways (including the SC), typically spared by the anatomical lesions resulting in neglect.

2. Methods

2.1. Participants

A total of 25 patients with right brain damage were screened for inclusion in the present study. The inclusion criteria were: (1) impaired performance on at least two tests of a systematic neglect battery of paper and pencil tests (Azouvi et al., 2002) for patients with neglect, and no deficit on all the tests for patients without neglect; (2) unilateral vascular damage to the right hemisphere; (3) right-handedness; and (4) ability to maintain gaze fixation and follow the instructions. The presence of bilateral lesions or visual field defects constituted exclusion criteria. Eight neglect patients (mean age 58 years, range 36–78) and five patients with lesions in the right hemisphere without signs of neglect (mean age 62 years, range 43–79) fulfilled the criteria and participated in the study. The mean time of testing for the included patients was 181 days since stroke onset (SD, 213 days). Table 1 shows the demographical and clinical data for the included patients.

2.2. Apparatus, stimuli and procedure

A PC Dell Latitude D600 running Eprime software (Schneider, Eschman, & Zuccolotto, 2002) controlled presentation of stimuli, timing operations and data collection. Stimuli were presented on an eye-tracker screen (Tobii 1750, 1024 × 768, 16 bit), used to monitor and record the direction of gaze every 20 ms. Participants sat at approximately 50 cm from the monitor. Four black circles were displayed on

Table 1 Demographical and clinical characteristics of patients, with their performance on visuo-spatial tests.

Patient	Sex/age/education	Onset of illness (days)	Aetiology	Bells cancellation (left/right hits, max = 15/15)	Letter cancellation (left/right hits, max = 30/30)	Line bisection (mm of rightward deviation for 200 mm lines)	Line bisection (% of deviation) ^a	Landscape drawing score	Reading (left/right hits, max = 61/55)
MJM	F/46/12	61	H	12/15*	NA	+3.5*	NA	0	61/55
ED	F/77/9	120	I	11/13*	NA	3	NA	1*	60/55*
FP	F/55/12	63	I	11/14*	28/30	+9.5*	+10.28	0	61/55
FM	M/45/9	302	I	11/14*	12/30*	-0.25	+7.41	1*	48/55*
JPC	M/70/17	42	I	8/15*	29/30	a	+13.35*	0	61/55
DO	F/78/14	89	H	14/15	25/30*	-3.5*	+16.3*	0	61/55
CC	F/36/17	119	I	9/13*	30/29	+8*	+5.5	3*	61/55
CM	M/60/7	122	I	11/15*	29/30	-0.7	+9.04	0	58/55*
FK	F/43/11	42	H	15/15	NA	+6.5	NA	0	61/55
MFM	F/72/15	68	I+H	15/15	NA	+0.5	NA	0	61/55
BB	M/72/3	66	H	13/13	NA	NA	NA	0	NA
CB	M/45/9	547	I	15/15	30/30	+0.1	+6.49	0	61/55
DV	F/79/7	718	I	14/13	30/30	-0.55	+9.87	0	61/55

I, ischemic; H, hemorrhagic. For line bisection, positive values indicate rightward deviations, and negative values indicate leftward deviations. Scores for landscape drawing indicate the number of omitted left-sided details. Asterisks denote pathological performance. NA, not available.
^a Version of the line bisection test described by Bartolomeo and Chokron (1999).

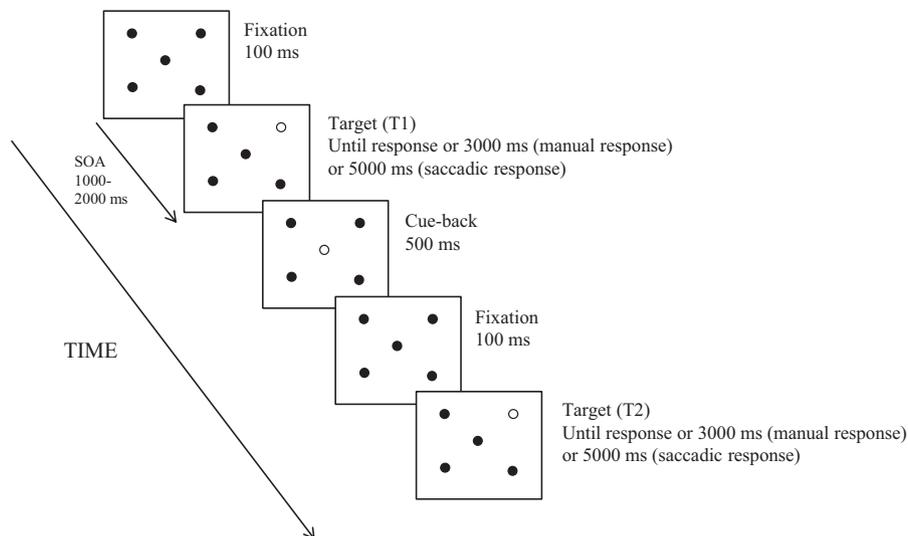


Fig. 1. Sequence of events in a given trial. In Experiment 1, participants were required to keep their eyes at fixation and manually detect the appearance of the peripheral targets. In Experiment 2, participants were required to move their eyes to the peripheral targets and back to the centre when the cue-back appeared.

a grey background around a fixation point (another circle located at the centre of the screen). Four locations (two per hemisphere) were used because IOR can affect not only targets presented at previously inspected locations but it can also spread to targets occurring in the previously explored hemisphere (Berlucchi, Tassinari, Marzi, & Di Stefano, 1989). The diameter of all circles subtended 2° of visual angle; their outline was situated at a distance of 2° of visual angle from the fixation circle (see Fig. 1).

2.2.1. Experiment 1 (manual responses and covert attention)

Participants were instructed to maintain their gaze at the central fixation circle through the trials. The fixation display (containing the fixation point and the four peripheral circles) was presented for 500 ms. After a random interval ranging from 1000 to 2000 ms, one of the peripheral circles became white. Participants were required to respond as fast and as accurately as possible by pressing the right mouse button with their right, non-paretic hand. The target disappeared when a correct response was detected or after 3000 ms if no response was made. As a cue back, the central circle turned white during 500 ms. No response was required at this time. A new fixation display was then presented and a second target appeared. The experiment consisted of a total of 200 trials. The experimental session began after 20 practice trials, during which the experimenter made sure that participants responded to all targets. Data from practice trials were not analyzed.

2.2.2. Experiment 2 (saccadic responses and overt orienting)

The procedure was identical to Experiment 1, with the following exceptions: There was no manual response, but participants were required to respond by moving their eyes to the targets as fast and as accurately as possible. The target disappeared when a correct response was made or after 5000 ms. The central circle then turned white during 500 ms and participants were required to move their eyes back to the central location. A new fixation display was presented and a second target appeared. This experiment consisted of a total of 160 trials.¹

All participants performed the two experiments in a single session. Experiment 1, which required eye fixation, was always run first because brain-damaged patients could have difficulties in shifting their set and refraining to look at targets after having performed the saccade task.

2.3. MR acquisition

Brain MRI scans including 3D T1 (IR-PSPGR; field of view = 250 mm²; acquisition matrix = 288 × 256; voxel resolution = 0.5 mm × 0.5 mm × 1.2 mm; slice thickness = 1.2 mm; space between slices = 1.2 mm), T2 propeller, fluid attenuated

inversion recovery and diffusion images were obtained with standard parameters on a 3T General Electric scanner with a standard head coil for signal reception. For Diffusion Tensor (DT) MRI, we employed single-shot spin-echo echo-planar images (EPI) with 50 directions ($b = 1000 \text{ s/mm}^2$; field of view = 240 mm²; matrix = 128 × 128; voxel size = 2 mm × 2 mm × 2 mm; slice thickness = 3 mm). For neglect patient MJM, 3DT1 MRI was not available; clinical MRI axial Flair sequences were used instead.

2.4. Lesion description

2.4.1. Study of the grey matter

Lesion analysis was performed by an expert neurologist (RM) and a clinical neuropsychologist (AB), trained to read brain scans. Both were blind to patients' clinical diagnosis and cognitive performance. In order to avoid the effect of the head size on the lesion size and to calculate automatically the lesion size, the following procedure was applied. First, lesion extent was determined for each patient by manually drawing the lesion borders directly onto the original 3D T1 MRI, by using the MRICro software (Rorden & Brett, 2000, www.mricro.com) and a graphics tablet (WACOM Intuos A6, Vancouver, Washington, USA). Then, the 3D brain scans and lesion volumes were normalized to the standard Montreal Neurological Institute (MNI) brain template in Statistical Parametric Mapping-5 (<http://www.fil.ion.ucl.ac.uk/spm>) running under Matlab 7.5 (<http://www.mathworks.com>). In detail, to reduce lesion-induced registration errors, spatial normalization was performed by using a mask that excluded the damaged areas of the brains, thereby preventing these areas from biasing the transformation (Brett, Leff, Rorden, & Ashburner, 2001). After normalization, the brain lesion was segmented and its borders were redefined in the normalized brain. Finally, MRICron software (Rorden & Brett, 2000) was used to estimate the extent of the lesion. One patient, MJM, did not undergo a 3D T1 MRI. For this patient, the lesion was delineated using a similar procedure, first drawing from the T1-weighted images and then manually transposing the drawn lesion onto the standard MNI brain template. The right frontal eye field (FEF) region, which is not detailed in MRICron, was anatomically identified in each patient as the region located 2 cm in front of the hand area knob, at the intersection of the superior frontal sulcus and the pre-central sulcus.

Reconstructions of lesions for each patient are shown in Fig. 2.

2.4.2. Study of the white matter

Diffusion Tensor Imaging (DTI) tractography was used to visualize the long-range white matter pathways whose disconnection have been implicated in the occurrence of neglect signs (Bartolomeo et al., 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Urbanski et al., 2008, 2011). DTI preprocessing was performed using ExploreDTI (<http://www.exploredti.com>; Leemans, Jeurissen, Sijbers, & Jones, 2009). Participants' motion and geometrical distortions were corrected simultaneously (Leemans & Jones, 2009). The tensor model was fitted to the data using the Levenberg-Marquardt nonlinear regression (Marquardt, 1963). The fractional anisotropy (FA) was estimated in each voxel by scaling the water diffusion orientation from zero (random diffusion) to one (one direction only; Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). Whole-brain tractography was performed using an interpolated streamline algorithm (stepsize = 0.5 mm) that propagates from voxel to voxel following a maximum angle threshold of 35° . Voxels showing a FA value inferior to 0.2 were excluded from the tractography. The whole brain tractography was imported to TrackVis (Wedeen et al., 2008; <http://www.trackvis.org>), by using a home-made software written in Matlab 2009b (<http://www.mathworks.com>). The

¹ To ensure that the present paradigm was apt to generate IOR in neurologically intact subjects, we also tested a group of 11 right-handed healthy controls without neurological or psychiatric history, matched to the patients for age and education. All participants reported having normal or corrected-to-normal vision. An ANOVA on their RTs with task, side and validity as factors revealed a main effects of task, $F(1,9) = 17.60$, $MSE = 20,684$, $p = .002$, with faster RTs for saccadic responses (301 ms) than for manual responses (387 ms), and validity $F(3,27) = 8.24$, $MSE = 857$, $p = .001$, consistent with a 21-ms IOR effect for the manual condition and a 24-ms IOR effect for the saccadic condition. No other effect or interaction reached significance.

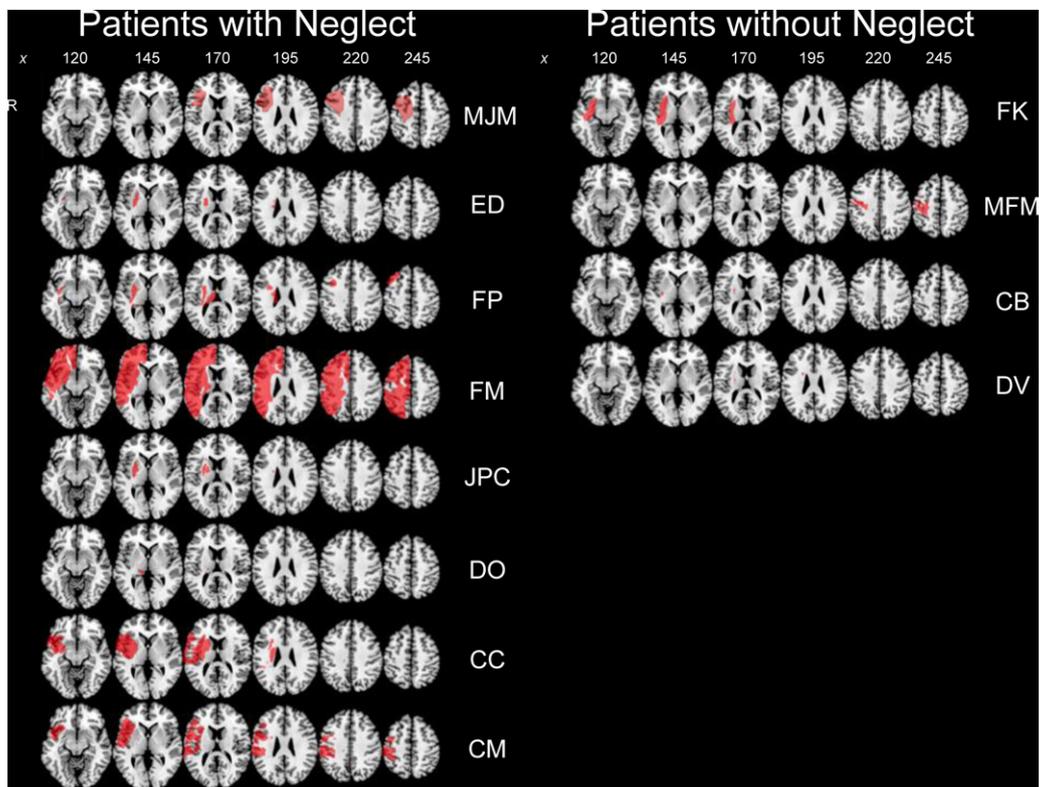


Fig. 2. Reconstruction of the brain lesions in patients with or without signs of neglect. Results are superimposed on slices of the Montreal Neurological Institute standard brain (R, right).

fiber tracking software allows the identification of the tracts, visualization in 3D, and quantitative analyses on the delineated tracts. Based on previous tractography work (Catani & Thiebaut de Schotten, 2008), regions-of-interest (ROIs) were defined manually on the axial, coronal, and sagittal FA images of each participant, and were used as seed regions for tracking. The trajectories of the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), and the inferior fronto-occipital fasciculus (IFOF) were obtained for both hemispheres, as previously described (Catani & Thiebaut de Schotten, 2008).

Mean diffusivity (MD), fractional anisotropy (FA), parallel (λ_{\parallel}), and radial (λ_{\perp}) diffusivities were obtained for each tract, as indexes of integrity of the tracts. Tractography algorithms use this information to track white matter pathways by inferring the continuity of fibers paths from a voxel to another (Basser et al., 2000).

3. Results

To assess IOR, we needed to compare RTs to targets presented at previously stimulated locations to RTs to targets occurring at “new” locations. To this end, we selected consecutively presented targets, as a function of the spatial location of the first and second target (henceforth, T1 and T2). This resulted in four different conditions:

- (1) *Same location (SL) trials* (N from 10 to 20, depending on the patient): T1 and T2 appeared consecutively at exactly the same spatial location (similar to valid trials in cue-target designs with just two spatial locations)
- (2) *Different location same side (DLS) trials* (N from 10 to 26): T2 appeared on the same side as T1, but not at the same spatial location.
- (3) *Different location opposite side near (DLON) trials* (N from 8 to 25): T2 appeared on the opposite side but at the nearest location to T1.
- (4) *Different location opposite far (DLOF) trials* (N from 8 to 27): T2 appeared on the opposite farthest side from the T1 (Table 2).

The last three conditions can be considered as invalid locations, by analogy with cue-target designs. Each target was analyzed with

respect to its predecessor. However, in the case of the *same location* trials, we excluded from the analysis trials in which a target was presented at the same location than the previous two targets. That is, if a target was presented at the same location three consecutive times, the third target was not analyzed, because it could suffer from stronger IOR after repeated cueing (Dukewich, 2009).

We calculated IOR to the inspected location as the mean RT on SL trials minus the average RT on the three other locations (DLS, DLON and DLOF conditions). This is therefore an index of IOR for the stimulated location as compared to previously non-stimulated locations. We also examined the possible spreading of IOR within the entire stimulated hemisphere, by calculating the mean RT on SL and DLS trials minus the average RT on the other two locations (DLON and DLOF conditions).

For Experiment 1 (manual response and covert attention), trials in which an eye movement was detected (i.e. trials in which participants failed to maintain fixation before the presentation of the target, or trials in which participants looked at the target before responding) were removed from analysis (15.34% for patients without neglect, 11.56% of trials for neglect patients). RTs slower than 2000 ms were considered as misses and excluded from analysis (respectively 0.78% and 0.96%).

The same participants performed Experiment 2 (saccadic response and overt attention). Trials in which participants failed to move their eyes to the target, or back to the centre, represented 1.34% of trials in the group of patients without neglect, and 1.98% in neglect patients. We also excluded RTs slower than 1500 ms (0.50% and 1.39% of trials for each patients group, respectively). We chose a different filter for the analysis of missed responses in this second experiment because saccadic RTs are much faster than manual RTs.

Data from brain-damaged patients with or without neglect were analyzed together in order to permit a direct comparison of IOR effects. Mean RTs were submitted to a repeated measures analysis of variance (ANOVA), with patient group (right-brain damaged

Table 2
Mean correct RT, in ms, and proportion of correct detections for Experiment 1 (Covert Attention and Manual Responses) and Experiment 2 (Overt Attention and Saccadic responses), for patients with or without neglect as a function of target location (DLOF, DLON, DLS, SL) and target side (left, right). Standard errors are reported in parentheses.

		Left-sided targets				Right-sided targets			
		DLOF	DLON	DLS	SL	DLOF	DLON	DLS	SL
Exp. 1: Covert attention (manual responses)	Patients with neglect	736 (58)	741 (56)	705 (58)	815 (79)	629 (60)	645 (64)	582 (61)	590 (59)
	Proportion correct	99	97	99	97	97	98	99	98
	Patients without neglect	631 (73)	605 (72)	606 (74)	705 (100)	547 (76)	574 (81)	585 (77)	603 (74)
	Proportion correct	98	99	99	97	99	97	100	96
Exp. 2: Overt attention (saccadic responses)	Patients with neglect	439 (34)	444 (36)	426 (27)	430 (44)	346 (26)	324 (19)	361 (33)	411 (37)
	Proportion correct	96	97	97	95	100	97	99	97
	Patients without neglect	325 (39)	347 (40)	353 (32)	376 (54)	327 (21)	305 (17)	338 (23)	356 (23)
	Proportion correct	100	100	99	97	100	97	99	97

patients with or without signs of neglect) as between-participant factor and task (manual, saccadic response), side of the second target (left, right), and validity (same location, SL; different location same side, DLS; different location opposite side near, DLON; different location opposite far, DLOF) as within-participant factors.

The ANOVA revealed main effects of task, $F(1,11)=37.62$, $MSE=98,733$, $p=.001$, with faster RTs for saccadic than for manual responses; side $F(1,11)=12.57$, $MSE=20,607$, $p=.005$, with faster RTs for right-sided targets as compared to left-sided targets; and validity $F(3,33)=5.38$, $MSE=19,100$, $p=.004$ (see Fig. 3). Planned comparisons indicated slower RTs for SL trials as compared to the three other invalid conditions (mean RT for SL trials minus mean RT for DLS, DLON and DLOF trials, 37 ms, $t=-2.87$, $df=13$, $p=.007$). The difference between targets appearing on the same vs. the opposite hemispace did not reach significance (mean RT on SL and DLS trials minus DLON and DLOF trials = 14 ms, $t=-1.37$, $df=13$, $p=.098$), suggesting that the overall IOR effect was restricted to the target location and did not spread to the stimulated hemispace. Finally, there was a significant interaction between task and side, $F(1,11)=9.47$, $MSE=3549$, $p=.011$, and between task, side and validity, $F(3,33)=3.41$, $MSE=4079$, $p=.029$. In order to better understand these interactions and given that at least in the group of patients with neglect, IOR was expected to be specifically impaired in the right hemispace, we conducted separate ANOVAs in the patient group for each task (manual and saccadic) and for left- and right-sided targets separately.

3.1. Experiment 1 (manual responses and covert orienting)

The analysis of left-sided targets revealed a main effect of validity, $F(3,33)=3.64$, $MSE=26,281$, $p=.023$. This effect was similar for the neglect and the non-neglect group (interaction between group and validity, $F<1$). Planned comparisons indicated slower RTs on SL trials as compared to the other three invalid conditions for both groups, revealing an IOR effect (SL minus DLS, DLON and DLOF = 89 ms, $t=-2.66$, $df=13$, $p=.01$) (see Fig. 3). IOR did not spread to the whole left hemispace (SL and DLS minus DLON and DLOF = 28 ms, $t=-1.11$, $df=13$, $p=.14$).

For right-sided targets, the interaction between validity and group was significant, $F(3,33)=3.45$, $MSE=7441$, $p=.027$. Patients without neglect displayed an IOR effect, as demonstrated by slower RTs for SL trials as compared to the other three invalid conditions (SL minus DLS, DLON and DLOF = 35 ms, $t=-1.87$, $df=13$, $p=.04$), and to a lesser extent by slower RTs for SL and DLS trials as compared to DLON and DLOF trials (SL and DLS minus DLON and DLOF = 34 ms, $t=-1.50$, $df=13$, $p=.08$). Conversely, a facilitatory effect was observed in neglect patients for right-sided targets (see Fig. 3, right panel). This effect was not restricted to the stimulated location (SL minus DLS, DLON and DLOF = -29 ms, $t=-1.17$, $df=13$, $p=.013$), but spread into the ipsilesional right hemispace (SL and DLS minus DLON and DLOF = -51 ms, $t=-2.32$, $df=13$, $p=.02$).

This “facilitation of return” for right, ipsilesional targets replicates the previous evidence obtained without monitoring patients’ eye movements (Bartolomeo et al., 1999; Bartolomeo, Sieroff, Decaix, et al., 2001).

3.2. Experiment 2 (saccadic responses and overt orienting)

As for Experiment 1, data from brain-damaged patients with or without neglect were separately analyzed for left and right-sided targets. For left-sided targets, none of the main effects or interactions were significant, $F<1$.² For right-sided targets, the main effect of validity was significant, $F(3,33)=5.35$, $MSE=1908$, $p=.004$, revealing an IOR effect (SL minus DLS, DLON and DLOF = 54 ms, $t=-3.74$, $df=13$, $p=.001$; SL and DLS minus DLON and DLOF = 43 ms, $t=-2.83$, $df=13$, $p=.007$). IOR appeared to be strong at the stimulated location but there was some diffusion, to a lesser extent, to the right hemispace. More importantly, the interaction between validity and group was far from significance, $F<1$. As can be observed in Fig. 3, comparable IOR effects were observed for both patients without neglect and for neglect patients. Thus, saccadic IOR for right-sided targets was preserved in neglect patients, in sharp contrast to the “facilitation of return” observed with manual responses.³

3.3. Anatomy of lesions

Grey matter. Table 3 and Fig. 4 show, respectively, a description of the lesions of all patients and an illustration of cortical grey matter and subcortical white matter lesions for three representative patients (CC, ED and MFM). Three patients with neglect presented a cortical damage to the right parietal lobe implicating the supra-marginal gyrus. Patients with neglect also had damage to the basal ganglia (62%), the inferior/middle frontal gyri (62%), or both. Lesions of patients without signs of neglect mainly implicated the basal ganglia. The right FEF region was damaged in three patients with

² Inspection of Fig. 3 may suggest that IOR is selectively impaired for left-sided targets in neglect. However, IOR was not significant in this condition for brain-damaged patients, presumably as a consequence of a lack of statistical power depending on increased RT variability for contralesional targets as compared to right-sided targets. Indeed, previous research with manual responses has revealed that IOR for left-sided targets in neglect patients is rarely reliable, probably due to the massive amount of RT variability for left-sided targets in these patients (Bartolomeo, Sieroff, Chokron, & Decaix, 2001).

³ The fact that IOR for repeated right-sided targets was observed in the saccadic but not in the manual task could be attributed to an effect of practice, i.e., IOR might be larger for the saccadic than the manual task because the saccadic task was always run after the manual task. We chose to always propose the manual task before the saccadic one in order not to confuse patients by asking them first to make saccades to the targets, and then to perform the more demanding covert attention experiment. However, the available evidence about the effects of practice on IOR clearly indicates that, if anything, IOR may decrease, not increase, with extended practice (Lupiáñez, Weaver, Tipper, & Madrid, 2001; Weaver, Lupiáñez, & Watson, 1998).

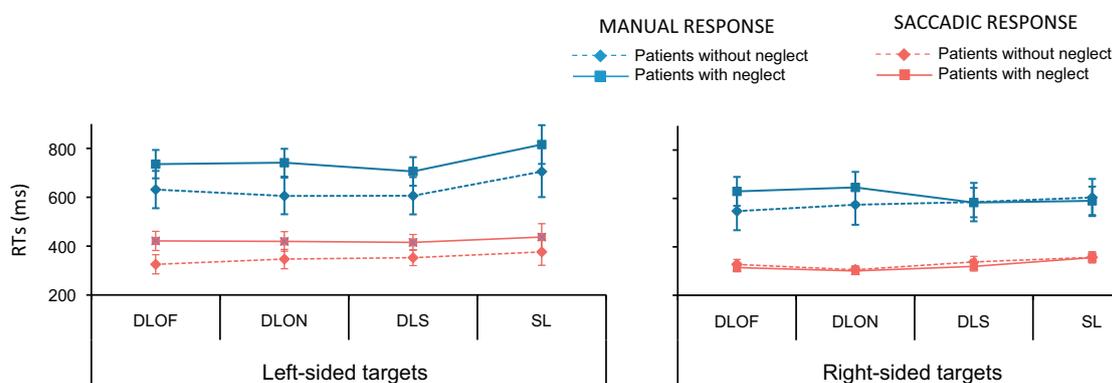


Fig. 3. Mean correct RTs (in ms) for left and right-sided second targets as a function of task (manual and saccadic responses), group (patients with or without neglect), and location of the previous target (same location as the previous target, SL; different location on the same side, DLS; different location on the opposite side near, DLON; different location on the opposite side far, DLOF).

neglect and in one patient without neglect. None of the patients of either group presented MRI evidence of collicular damage.

White matter. DT MRI was not available for three patients (MJM, JPC, BB). In a further patient with neglect (DO), the presence of leukoaraiosis rendered unreliable the tractography results. As a consequence, DT tractography study was conducted in five neglect patients and four patients without neglect. All patients with neglect presented signs of fronto-parietal disconnection; the right superior longitudinal fasciculus (SLF), a major white matter bundle connecting parietal and frontal cortical regions, was absent in four patients (FP, FM, CC and CM) (see patient CC in Fig. 4 as an example). In one case (ED), the SLF was traceable but damaged (see Fig. 4), with higher MD ($p = .007$), $\lambda_{//}$ ($p = .07$) and λ_{\perp} ($p = .008$) as compared to the group of non-neglect patients (Crawford & Garthwaite, 2002). There was no evidence of damage to the SLF for any of the non-neglect patients (see patient MFM in Fig. 4). FEF damage was associated with a concomitant white matter lesion disconnecting the right SLF in all the neglect patients, while FEF damage was not associated to any disconnection in the non-neglect patient MFM.

To summarize, the analysis of grey and white matter damage showed that all patients with neglect presented either lesions of the parietal cortex (three patients), signs of fronto-parietal disconnection in the subcortical white matter (five patients), or both (three patients). There was no significant difference in lesion size between the two groups of neglect patients and patients without neglect ($t = 1.44$, $df = 10$, $p = .36$). However, lesion size could in principle have affected IOR independently of lesion location. To investigate this issue, we performed a Pearson correlation with lesion volume and IOR (RT invalid minus RT valid) for ipsilesional right-sided targets, in the manual task and saccadic task. Results showed that, contrary to the lesion size hypothesis, neither manual nor saccadic IOR correlated with lesion volume ($r = -.11$ and $.13$, respectively; both $ps > .10$).

4. Discussion

We studied IOR after right hemisphere damage in patients with or without neglect, who were asked to produce either manual or

Table 3
Lesion data analysis.

	Patient	Grey matter lesion site	White matter lesion site (tract completely absent or disconnected*)	Lesion volume (cm ³)
Patients with neglect	MJM	PrCe gyrus, SFG, MFg	NA	NA
	ED	A, CN, Pu, Pa	Right SLF*	4.77
	FP	MFg and IFo, PrCe gyrus, STg, H, CN, Pu, Pa, Th	Right SLF, IFOF	25.81
	FM	IFg, MFg, SFG, orbitofrontal cortex, FEF, PrCe/PsCe gyri, motor and SMAs, paracentral lobule, I, A, H, STg, MTg, ITg, Pa, angular gyrus and SMg, anterior and middle cingulate, Pu, CN, Pa	Right SLF, IFOF, ILF	427.79
	JPC	CN, Pu, Pa	NA	6.38
	DO	Th	NA	1.16
	CC	IOFg, IFo and IFg pars triangularis, FEF, PrCe/PsCe gyri, Ro, I, SMg, STg, MTg, STp, A, CN, Pu, Pa	Right SLF, ILF	66.79
Patients without neglect	CM	IFg, MFg, IOFg, IFo, FEF, PrCe/PsCe gyri, Ro, I, STp and STg, SMg, IPg	Right SLF	76.57
	FK	ITg, MTg, STg, H, A, I, Pu, Pa	Right IFOF	27.39
	MFM	PrCe/PsCe gyri, SFG, FEF, paracentral lobule, SMA	No disconnection	17.41
	BB	Pu, Pa	NA	NA
	CB	CN, Pu	No disconnection	0.99
	DV	Pu	No disconnection	1.06

IFg, inferior frontal gyrus; IFo, inferior frontal operculum; IOFg, inferior orbitofrontal gyrus; MFg, middle frontal gyrus; SFG, superior frontal gyrus; PrCe, precentral gyrus; PsCe, postcentral gyrus; FEF, frontal eye field; Ro, rolandic operculum; SMA, supplementary motor area; IPg, inferior parietal gyrus; ITg, inferior temporal gyrus; MTg, middle temporal gyrus; STg, superior temporal gyrus; STp, superior temporal pole; Pa, parietal area; Th, thalamus; H, hippocampus; A, amygdala; I, insula; CN, caudate nucleus; Pu, putamen; Pa, pallidum; SMg, supramarginal gyrus; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; NA, non-available.

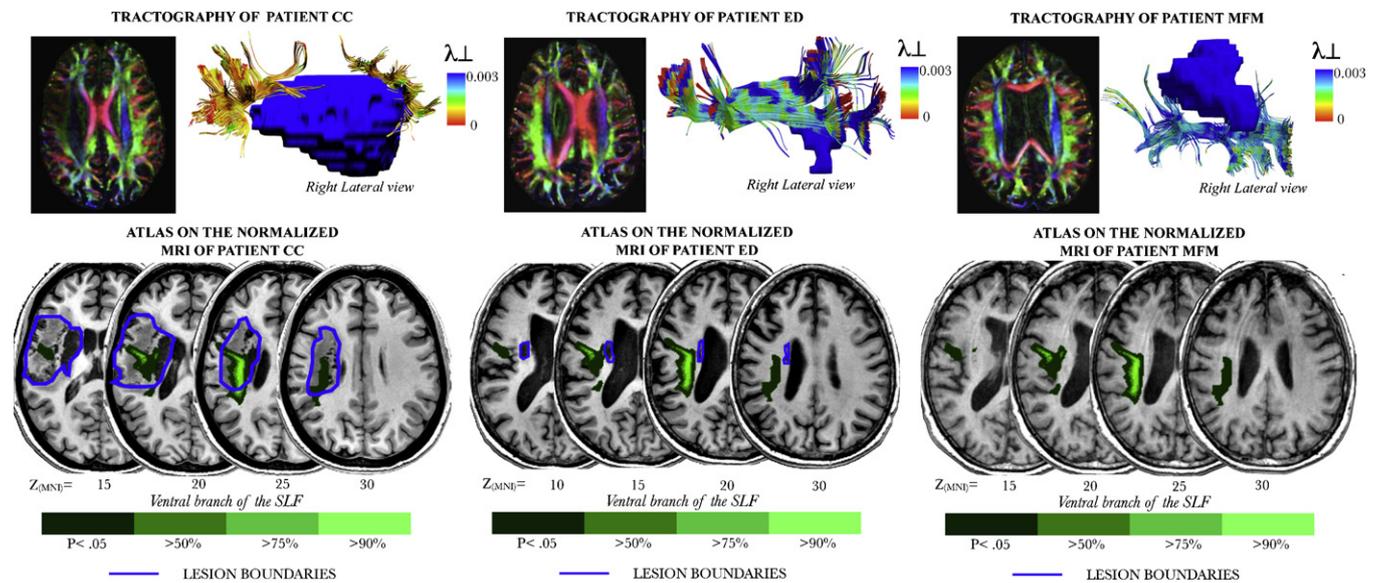


Fig. 4. Upper panel: perpendicular diffusivity (λ_{\perp}) and fractional anisotropy map of three patients: a neglect patient (CC) with cortical grey matter lesion and complete disconnection of the SLF tract; a neglect patient (ED) with cortical lesion and partially disconnected SLF tract; and a non-neglect patient (MFM) with cortical lesion and spared SLF tract. Perpendicular diffusivity scale varied from 0 (red color; relative integrity of the tract) to 0.003 (blue color; tract damaged). Lower panel: structural images of the same patients with the boundaries of their cortical grey matter lesion drawn in blue. A reconstruction of the fronto-parietal SLF (in green) from a sample of 40 healthy subjects is superimposed to the images. R, right. (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)

saccadic responses to peripherally presented targets. The manual RT results replicated previous studies (Bartolomeo et al., 1999; Bartolomeo, Sieroff, Decaix, et al., 2001) demonstrating abnormal facilitation, instead of IOR, under covert orienting for right-sided targets in neglect patients (see also Vivas et al., 2003). This abnormal facilitation was not restricted to the stimulated location, but spread to the whole right hemisphere. It was important to replicate these results, which were obtained without eye movement control. The present findings unequivocally confirm the finding of facilitation instead of IOR for repeated right-sided targets in left neglect.

Deficits in exogenous orienting of attention make an important contribution to signs of left neglect (Bartolomeo & Chokron, 2002), with impaired attentional capture by elements occurring on the left side of space. The lack of IOR observed in neglect patients for right-sided events may exacerbate their rightward bias and further impair their capacity to reorient attention to new locations. This deficit may also contribute to the pathological revisiting behavior of items presented in the right hemisphere (Mannan et al., 2005). According to a recent proposal, neglect signs such as lack of awareness of left-sided events and revisiting behavior can be accounted for by a deficit in mechanisms that prioritize spatial representations, inducing a failure to remember which locations have already been examined during visual search (Pisella & Mattingley, 2004). An alternative hypothesis is that the tendency for patients' attention to be automatically and, as it were, "magnetically" captured by right-sided events (D'Erme, Robertson, Bartolomeo, Daniele, & Gainotti, 1992; Gainotti et al., 1991) determines fast processing of events on the right side even when they were presented consecutively (Bartolomeo et al., 1999). In other words, right-sided events might present a perpetual character of "novelty" for neglect patients. According to this view, the central cue-back used in our study might not have been sufficient to bring patients' exogenous attention back to the centre in the manual task. If so, then IOR could have been cancelled by an impaired attentional disengagement from ipsilesional targets.

When attention was overtly oriented in the saccadic task, the results demonstrated a normal IOR for repeated right-sided targets in neglect. To our knowledge, this is the first time that this

dissociation (impaired manual IOR with preserved saccadic IOR in neglect) is observed. It is plausible that for saccadic IOR, the central cue-back was more effective in bringing patients' attention back to the centre, because attention typically follows eye movements (Shepherd, Findlay, & Hockey, 1986). As a consequence, patients' attention was less likely to be maintained on the right-sided placeholder when T2 occurred, with consequent slower RTs (i.e., IOR) for repeated right-sided targets. This latter assumption could be further tested with a cueing paradigm using saccadic responses. However, it is important to point out that IOR and the disengagement deficit may well be independent of one another. For example, in the Bartolomeo, Sieroff, Chokron, and Decaix's (2001) study the disengagement deficit in neglect patients decreased with increasing SOAs (see also Losier & Klein, 2001, for a review), whereas the IOR impairment was observed at longer SOAs. Furthermore, previous evidence obtained in healthy participants indicated that attentional disengagement is not a necessary condition to observe IOR, as it can be observed when attention has not been disengaged from the cued location (Berger, Henik, & Rafal, 2005; Chica & Lupiáñez, 2009; Chica, Lupiáñez, & Bartolomeo, 2006), and even at fixated locations (Rafal, Ward, & Danziger, 2006). Moreover, it has also been demonstrated that the abnormal facilitation observed in neglect for right-sided targets is independent of endogenous orienting of attention (Lupiáñez et al., 2004).

The manual-saccadic dissociation observed in neglect is also important for our understanding of the mechanisms underlying IOR. Different hypotheses have been proposed concerning the mechanisms underlying the IOR effect. While the *attentional* hypothesis proposes that the IOR effect is the result of an inhibition to orient attention to a previously attended location (Posner & Cohen, 1984), the *oculomotor* hypothesis proposes that it is caused by the inhibition of a previously prepared movement (to the cue) or the activation of an oculomotor program (Chica, Klein, Rafal, & Hopfinger, 2010; Rafal, Calabresi, Brennan, & Sciolto, 1989). However, if IOR were generated by a common mechanism (either attentional or oculomotor; Rafal et al., 1989), then neglect patients should show similar deficits in IOR when the task involves either covert or overt orienting of attention to the location of the target (Chica, Taylor, Lupiáñez, & Klein, 2010). Contrary to this

hypothesis, our results suggest the existence of different mechanisms underlying IOR, as previously suggested by several behavioral studies (Chica, Taylor, et al., 2010; Hunt & Kingstone, 2003; Sumner, Nachev, Vora, Husain, & Kennard, 2004; Taylor & Klein, 2000). Evidence suggests that IOR can produce effects either on attentional/perceptual processes or on response processes, depending on the task demands (Chica, Taylor, et al., 2010; Taylor & Klein, 2000). When the eyes are restrained throughout a trial (as it is the case for manual response and covert attention), IOR may reflect impaired perceptual processing of targets in the cued peripheral location, perhaps due to the impaired reallocation of attention to that location. In contrast, when the oculomotor system cannot be inhibited because a saccadic response is required at some point during the trial (as it is the case for saccadic responses and overt attention), IOR may reflect a motoric effect wherein responses in the direction of the cued location are slowed (Taylor & Klein, 2000). The observed dissociation between manual and saccadic IOR in left neglect may thus suggest that attentional mechanisms, but not motoric mechanisms, are impaired in neglect. Moreover, while in the manual task the same response was used for all the stimuli, the saccadic task uses different responses for each stimulus, which have a more direct stimulus–response affordance. Therefore, our manual task was more likely to produce attentional effects, while our saccadic task was more likely to produce motoric effects. Another possible basis for the observed dissociation is that the saccadic IOR paradigm involves two eye movements on each trial – a saccade to the target, and then a saccade back again to fixation. If the target then occurs in the same place, the required saccade is actually opposite to, not the same as, the last saccade made.⁴ Future research should test these issues in neglect patients by using manual localization responses (for example pointing responses) in comparison to saccadic localization responses.

Attentional and motor phenomena related to IOR might depend on the implication of different brain networks for performing manual and saccadic responses (Anderson et al., 2011). It has recently been demonstrated that BOLD signal changes of the human superior colliculi strongly correlate with measures of saccadic IOR (Anderson & Rees, 2011). Sumner et al. (2004) have also shown that S-cone stimuli, which do not activate the retino-tectal or magnocellular pathway, and do not prompt reflexive eye movements in a remote distracter paradigm, nevertheless do generate IOR when measured by manual key press responses, but not when measured with saccadic eye movements. More recent evidence, however, indicated that the SC can respond to chromatic stimuli, albeit through a slower pathway than for achromatic signals (Bompas & Sumner, 2011; White, Boehnke, Marino, Itti, & Munoz, 2009). The present findings could thus result from the fact that the saccadic system receives projections from cortical areas, belonging to visual pathways (Lock, Baizer, & Bender, 2003), which were preserved in our sample of patients. Be that as it may, the finding that S-cone stimuli fail to produce IOR when responses are saccadic while producing IOR when manual responses are made constitutes an important dissociation concerning the motoric vs. attentional nature of IOR. Abnormal IOR observed in neglect patients for right-sided events in covert orienting situations (where manual responses are required) can be explained by a disruption of fronto-parietal attentional networks with consequent spatial attention deficits (Bartolomeo et al., 2007; Thiebaut de Schotten et al., 2005). This hypothesis is consistent with the present anatomical evidence of damage to the right parietal cortex (or to its connections to ipsilateral pre-frontal cortex), associated to a deficit of manual

IOR. Conversely, relatively spared circuits implicating the SC in the present patients might account for their preserved saccadic IOR, because saccadic IOR is more related to the integrity of the retino-tectal pathway (Dorris et al., 2002; Rafal et al., 1989).

Neglect patients in the present study had damage to the right inferior parietal lobule or to its connections with the ipsilateral prefrontal cortex. The integrated functioning of this ventral fronto-parietal network is likely to be important to terminate ongoing orienting activity (Shulman et al., 2009) and to disengage attention from current targets (Friedrich et al., 1998). Correspondingly, orienting activity with predictive cues deactivates the posterior nodes of the network, perhaps to keep attention focused on the cued location by filtering out distractors (Doricchi et al., 2009; Shulman et al., 2007). Neglect patients in our study may thus have processed repeated ipsilesional targets with inappropriate priority, leading to facilitation instead of IOR. Online TMS on the right temporo-parietal junction of healthy participants during the orienting period (before targets are presented) has also shown to disrupt IOR, but on the contralateral, left side (Chica et al., 2011). This result confirms the importance of the ventral fronto-parietal network for IOR. The substantial differences between chronic vascular brain damage and the temporary virtual lesion induced by TMS may account for the laterality discrepancy. For example, vascular strokes may imbalance the activity of dorsal fronto-parietal networks, leading to a relative hyperactivity of left-hemisphere circuits and consequent rightward attentional bias (Corbetta et al., 2005). Such remote effects on large-scale brain systems may be less likely to occur during the transient disruption window used in event-related TMS (Chica et al., 2011). These results strongly support the present conclusion on the importance of fronto-parietal cortical networks in the building of manual IOR.

As it is frequently found in studies comparing neglect to non-neglect patients, patients with neglect had numerically larger lesions than patients without neglect. However, lesion volume per se (which was not significantly different between the two groups) can hardly account for the present results. Our main finding was a dissociation between manual and saccadic IOR: while saccadic IOR was preserved in patients with or without neglect, manual IOR was selectively disrupted for right-sided stimuli in neglect. Furthermore, there was no correlation between the IOR effect for right-sided targets and lesion volume for either manual or saccadic IOR.

There are some limitations concerning the identification of white matter lesions. Even if DTI has extensively been developed in recent years, and provided important insights in the white matter connections of both neurologically healthy individuals and brain damage patients (Catani & Thiebaut de Schotten, 2008; Urbanski et al., 2008, 2011), the tensor-based algorithm does not show crossing or fanning fibers (McNab et al., 2009). This could result in an underestimation of the disconnection of white matter pathways. On the other hand, decreased FA values in the perilesional area may sometimes lead to an overestimation of the disconnection (Clark, Barrick, Murphy, & Bell, 2003; Thiebaut de Schotten et al., 2011). These limitations may be overcome by new algorithms which will enable researchers to reconstruct the highly complex organization of the white matter fibers in brains with vascular damage (Dell'Acqua et al., 2010).

To conclude, the present results demonstrate for the first time a dissociation between manual and saccadic IOR in patients with left neglect resulting from right parietal damage or from fronto-parietal disconnection. While manual IOR (covert attention) was altered for repeated right-sided events, saccadic IOR (overt attention) can be normal in neglect, at least with peripherally salient stimuli like the ones used in the present design. This pattern of results may be due to direct or indirect parietal dysfunction (resulting, respectively, from parietal damage or white matter fronto-parietal

⁴ We thank Petroc Sumner for suggesting this possibility.

disconnection) with relatively spared activity in retino-tectal visual pathways.

Funding

This work was supported by a doctoral grant from the French Ministry of Research to AB, by postdoctoral grants from the *Neuropôle de Recherche Francilien* (NeRF) to ABC and RM, and by a postdoctoral grant from the *Marie Curie Intra-European Program* (FP7) to ABC.

Acknowledgements

We would like to thank Monica Toba for help with patient recruitment, Bastien Oliveiro for programming the experiment, Alexander Leemans for programming the software ExploreDTI, and Flavio Dell'Acqua for programming the software converting ExploreDTI files to Trackvis files.

References

- Anderson, E. J., Jones, D. K., O'Gorman, R. L., Leemans, A., Catani, M., & Husain, M. (2011). Cortical network for gaze control in humans revealed using multimodal MRI. *Cerebral Cortex*.
- Anderson, E. J., & Rees, G. (2011). Neural correlates of spatial orienting in the human superior colliculus. *Journal of Neurophysiology*, *106*(5), 2273–2284.
- Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J.-M., et al. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *Journal of Neurology, Neurosurgery and Psychiatry*, *73*(2), 160–166.
- Bartolomeo, P., & Chokron, S. (1999). Egocentric frame of reference: Its role in spatial bias after right hemisphere lesions. *Neuropsychologia*, *37*(8), 881–894.
- Bartolomeo, P., & Chokron, S. (2002). Orienting of attention in left unilateral neglect. *Neuroscience and Biobehavioral Reviews*, *26*(2), 217–234.
- Bartolomeo, P., Chokron, S., & Sieroff, E. (1999). Facilitation instead of inhibition for repeated right-sided events in left neglect. *NeuroReport*, *10*(16), 3353–3357.
- Bartolomeo, P., Sieroff, E., Chokron, S., & Decaix, C. (2001). Variability of response times as a marker of diverted attention. *Neuropsychologia*, *39*(4), 358–363.
- Bartolomeo, P., Sieroff, E., Decaix, C., & Chokron, S. (2001). Modulating the attentional bias in unilateral neglect: The effects of the strategic set. *Experimental Brain Research*, *137*(3–4), 432–444.
- Bartolomeo, P., Thiebaut de Schotten, M., & Doricchi, F. (2007). Left unilateral neglect as a disconnection syndrome. *Cerebral Cortex*, *17*(11), 2479–2490.
- Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using dt-MRI data. *Magnetic Resonance in Medicine*, *44*(4), 625–632.
- Berger, A., Henik, A., & Rafal, R. (2005). Competition between endogenous and exogenous orienting of visual attention. *Journal of Experimental Psychology: General*, *134*(2), 207–221.
- Berlucchi, G., Tassinari, G., Marzi, C. A., & Di Stefano, M. (1989). Spatial distribution of the inhibitory effect of peripheral non-informative cues on simple reaction time to non-fixed visual targets. *Neuropsychologia*, *27*(2), 201–221.
- Bompas, A., & Sumner, P. (2011). Saccadic inhibition reveals the timing of automatic and voluntary signals in the human brain. *Journal of Neuroscience*, *31*(35), 12501–12512.
- Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage*, *14*(2), 486–500.
- Catani, M., & Thiebaut de Schotten, M. T. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, *44*(8), 1105–1132.
- Chica, A. B., Bartolomeo, P., & Valero-Cabré, A. (2011). Dorsal and ventral parietal contributions to spatial orienting in the human brain. *Journal of Neuroscience*, *31*(22), 8143–8149.
- Chica, A. B., Klein, R. M., Rafal, R. D., & Hopfinger, J. B. (2010). Endogenous saccade preparation does not produce inhibition of return: Failure to replicate Rafal, Calabresi, Brennan, & Sciolto (1989). *Journal of Experimental Psychology: Human Perception and Performance*, *36*(5), 1193–1206.
- Chica, A. B., & Lupiáñez, J. (2009). Effects of endogenous and exogenous attention on visual processing: An inhibition of return study. *Brain Research*, *1278*, 75–85.
- Chica, A. B., Lupiáñez, J., & Bartolomeo, P. (2006). Dissociating inhibition of return from the endogenous orienting of spatial attention: Evidence from detection and discrimination tasks. *Cognitive Neuropsychology*, *23*(7), 1015–1034.
- Chica, A. B., Taylor, T. L., Lupiáñez, J., & Klein, R. M. (2010). Two mechanisms underlying inhibition of return. *Experimental Brain Research*, *201*(1), 25–35.
- Clark, C. A., Barrick, T. R., Murphy, M. M., & Bell, B. A. (2003). White matter fiber tracking in patients with space-occupying lesions of the brain: A new technique for neurosurgical planning? *Neuroimage*, *20*(3), 1601–1608.
- Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature Neuroscience*, *8*(11), 1603–1610.
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215.
- Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia*, *40*(8), 1196–1208.
- D'Erme, P., Robertson, I., Bartolomeo, P., Daniele, A., & Gainotti, G. (1992). Early rightwards orienting of attention on simple reaction time performance in patients with left-sided neglect. *Neuropsychologia*, *30*(11), 989–1000.
- Dell'Acqua, F., Scifo, P., Rizzo, G., Catani, M., Simmons, A., Scotti, G., et al. (2010). A modified damped Richardson–Lucy algorithm to reduce isotropic background effects in spherical deconvolution. *Neuroimage*, *49*(2), 1446–1458.
- Doricchi, F., Guariglia, C., Paolucci, S., & Pizzamiglio, L. (1993). Disturbances of the rapid eye movements (REMS) of REM sleep in patients with unilateral attentional neglect: Clue for the understanding of the functional meaning of REMS. *Electroencephalography and Clinical Neurophysiology*, *87*(3), 105–116.
- Doricchi, F., Macci, E., Silvetti, M., & Macaluso, E. (2009). Neural correlates of the spatial and expectancy components of endogenous and stimulus-driven orienting of attention in the posner task. *Cerebral Cortex*, *20*(7), 1574–1585.
- Doricchi, F., Thiebaut de Schotten, M., Tomaiuolo, F., & Bartolomeo, P. (2008). White matter (dis)connections and gray matter (dys)functions in visual neglect: Gaining insights into the brain networks of spatial awareness. *Cortex*, *44*(8), 983–995.
- Dorris, M. C., Klein, R. M., Everling, S., & Muñoz, D. P. (2002). Contribution of the primate superior colliculus to inhibition of return. *Journal of Cognitive Neuroscience*, *14*(8), 1256–1263.
- Dukewich, K. R. (2009). Reconceptualizing inhibition of return as habituation of the orienting response. *Psychonomic Bulletin & Review*, *16*(2), 238–251.
- Friedrich, F. J., Egly, R., Rafal, R. D., & Beck, D. (1998). Spatial attention deficits in humans: A comparison of superior parietal and temporal–parietal junction lesions. *Neuropsychology*, *12*(2), 193–207.
- Gainotti, G., D'Erme, P., & Bartolomeo, P. (1991). Early orientation of attention toward the half space ipsilateral to the lesion in patients with unilateral brain damage. *Journal of Neurology, Neurosurgery and Psychiatry*, *54*, 1082–1089.
- He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*(6), 905–918.
- Hunt, A. R., & Kingstone, A. (2003). Inhibition of return: Dissociating attentional and oculomotor components. *Journal of Experimental Psychology: Human Perception and Performance*, *29*(5), 1068–1074.
- Klein, R. M. (1988). Inhibitory tagging system facilitates visual search. *Nature*, *334*, 430–431.
- Klein, R. M. (2000). Inhibition of return. *Trends Cognitive Sciences*, *4*(4), 138–147.
- Leemans, A., Jeurissen, B., Sijbers, J., & Jones, D. K. (2009). ExploreDTI: A graphical toolbox for processing, analyzing, and visualizing diffusion MR data. Paper presented at the 17th international society for magnetic resonance in medicine Honolulu, Hawaii.
- Leemans, A., & Jones, D. K. (2009). The b-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*, *61*(6), 1336–1349.
- Lock, T. M., Baizer, J. S., & Bender, D. B. (2003). Distribution of corticotectal cells in macaque. *Experimental Brain Research*, *151*(4), 455–470.
- Losier, B. J., & Klein, R. M. (2001). A review of the evidence for a disengage deficit following parietal lobe damage. *Neuroscience and Biobehavioral Reviews*, *25*(1), 1–13.
- Lupiáñez, J., Decaix, C., Sieroff, E., Chokron, S., Milliken, B., & Bartolomeo, P. (2004). Independent effects of endogenous and exogenous spatial cueing: Inhibition of return at endogenously attended target locations. *Experimental Brain Research*, *159*(4), 447–457.
- Lupiáñez, J., Klein, R. M., & Bartolomeo, P. (2006). Inhibition of return: Twenty years after. *Cognitive Neuropsychology*, *23*(7), 1003–1014.
- Lupiáñez, J., Weaver, B., Tipper, S. P., & Madrid, E. (2001). The effects of practice on cueing in detection and discrimination tasks. *Psicológica*, *22*(1), 1–23.
- Mannan, S. K., Mort, D. J., Hodgson, T. L., Driver, J., Kennard, C., & Husain, M. (2005). Revisiting previously searched locations in visual neglect: Role of right parietal and frontal lesions in misjudging old locations as new. *Journal of Cognitive Neuroscience*, *17*(2), 340–354.
- Marquardt, D. (1963). An algorithm for least-squares estimation of nonlinear parameters. *Siam Journal on Applied Mathematics*, *11*, 431–441.
- McNab, J. A., Jbabdi, S., Deoni, S. C., Douaud, G., Behrens, T. E., & Miller, K. L. (2009). High resolution diffusion-weighted imaging in fixed human brain using diffusion-weighted steady state free precession. *Neuroimage*, *46*(3), 775–785.
- Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain*, *126*(Pt 9), 1986L 1997.
- Pisella, L., & Mattingley, J. B. (2004). The contribution of spatial remapping impairments to unilateral visual neglect. *Neuroscience and Biobehavioral Reviews*, *28*(2), 181–200.
- Posner, M. I., & Cohen, Y. (1984). Components of visual orienting. In H. Bouma, & D. Bouwhuis (Eds.), *Attention and performance x* (pp. 531–556). London: Lawrence Erlbaum.
- Posner, M. I., Rafal, R. D., Choate, L. S., & Vaughan, J. (1985). Inhibition of return: Neural basis and function. *Cognitive Neuropsychology*, *2*, 211–228.
- Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience*, *4*, 1863–1874.
- Rafal, R. D., Calabresi, P. A., Brennan, C. W., & Sciolto, T. K. (1989). Saccade preparation inhibits reorienting to recently attended locations. *Journal of Experimental Psychology: Human Perception and Performance*, *15*(4), 673–685.

- Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., & Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain*, *111*(Pt 2), 267–280.
- Rafal, R. D., Ward, R., & Danziger, S. (2006). Selection for action and selection for awareness: Evidence from hemispatial neglect. *Brain Research*, *1080*(1), 2–8.
- Rastelli, F., Funes, M. J., Lupiáñez, J., Duret, C., & Bartolomeo, P. (2008). Left visual neglect: Is the disengage deficit space- or object-based? *Experimental Brain Research*, *187*(3), 439–446.
- Ro, T., Farne, A., & Chang, E. (2003). Inhibition of return and the human frontal eye fields. *Experimental Brain Research*, *150*(3), 290–296.
- Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, *12*(4), 191–200.
- Sapir, A., Hayes, A., Henik, A., Danziger, S., & Rafal, R. (2004). Parietal lobe lesions disrupt saccadic remapping of inhibitory location tagging. *Journal of Cognitive Neuroscience*, *16*(4), 503–509.
- Sapir, A., Soroker, N., Berger, A., & Henik, A. (1999). Inhibition of return in spatial attention: Direct evidence for collicular generation. *Nature Neuroscience*, *2*(12), 1053–1054.
- Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-prime user's guide*. Pittsburgh: Psychology Software Tools Inc.
- Shepherd, M., Findlay, J. M., & Hockey, R. J. (1986). The relationship between eye movements and spatial attention. *The Quarterly Journal of Experimental Psychology*, *38A*, 475–491.
- Shulman, G. L., Astafiev, S. V., Franke, D., Pope, D. L., Snyder, A. Z., McAvoy, M. P., et al. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *Journal of Neuroscience*, *29*(14), 4392–4407.
- Shulman, G. L., Avtafiev, S. V., McAvoy, M. P., d'Avossa, G., & Corbetta, M. (2007). Right TPJ deactivation during visual search: Functional significance and support for a filter hypothesis. *Cerebral Cortex*, 1–9.
- Sieroff, E., Decaix, C., Chokron, S., & Bartolomeo, P. (2007). Impaired orienting of attention in left unilateral neglect: A componential analysis. *Neuropsychology*, *21*(1), 94–113.
- Sumner, P., Nachev, P., Vora, N., Husain, M., & Kennard, C. (2004). Distinct cortical and collicular mechanisms of inhibition of return revealed with s cone stimuli. *Current Biology*, *14*(24), 2259–2263.
- Taylor, T. L., & Klein, R. M. (2000). Visual and motor effects in inhibition of return. *Journal of Experimental Psychology. Human Perception and Performance*, *26*(5), 1639–1656.
- Thiebaut de Schotten, M., Ffytche, D. H., Bizzi, A., Dell'Acqua, F., Allin, M., Walshe, M., et al. (2011). Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage*, *54*(1), 49–59.
- Thiebaut de Schotten, M., Urbanski, M., Duffau, H., Volle, E., Lévy, R., Dubois, B., et al. (2005). Direct evidence for a parietal–frontal pathway subserving spatial awareness in humans. *Science*, *309*, 2226–2228.
- Urbanski, M., Thiebaut de Schotten, M., Rodrigo, S., Catani, M., Oppenheim, C., Touze, E., et al. (2008). Brain networks of spatial awareness: Evidence from diffusion tensor imaging tractography. *Journal of Neurology, Neurosurgery and Psychiatry*, *79*(5), 598–601.
- Urbanski, M., Thiebaut de Schotten, M., Rodrigo, S., Oppenheim, C., Touze, E., Meder, J. F., et al. (2011). DTI-MR tractography of white matter damage in stroke patients with neglect. *Experimental Brain Research*, *208*(4), 491–505.
- Van Koningsbruggen, M. G., Gabay, S., Sapir, A., Henik, A., & Rafal, R. D. (2009). Hemispheric asymmetry in the remapping and maintenance of visual saliency maps: A TMS study. *Journal of Cognitive Neuroscience*, *22*(8), 1730–1738.
- Vivas, A. B., Humphreys, G. W., & Fuentes, L. J. (2003). Inhibitory processing following damage to the parietal lobe. *Neuropsychologia*, *41*(11), 1531–1540.
- Vivas, A. B., Humphreys, G. W., & Fuentes, L. J. (2006). Abnormal inhibition of return: A review and new data on patients with parietal lobe damage. *Cognitive Neuropsychology*, *23*(7), 1049–1064.
- Weaver, B., Lupiáñez, J., & Watson, F. L. (1998). The effects of practice on object-based, location-based, and static-display inhibition of return. *Perception and Psychophysics*, *60*(6), 993–1003.
- Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y., Dai, G., et al. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage*, *41*(4), 1267–1277.
- White, B. J., Boehnke, S. E., Marino, R. A., Itti, L., & Munoz, D. P. (2009). Color-related signals in the primate superior colliculus. *Journal of Neuroscience*, *29*(39), 12159–12166.