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

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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 supramarginal 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.

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 that 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)
Patients with neglect	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*
Patients without neglect	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 deviation. 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).