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Mechanisms underlying neglect recovery after prism adaptation☆

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Abstract

Prism adaptation (PA) has been demonstrated to be effective in improving hemispatial neglect. However not all patients seem to benefit from this procedure. Thus, the objective of the present work is to provide behavioural and neuroanatomical predictors of recovery by exploring the reorganization of low-order visuo-motor behaviour and high-order visuo-spatial representation induced by PA. To this end, 16 neglect patients (experimental group) were submitted to a PA treatment for 10 daily sessions. Neglect and oculo-motor responses were assessed before the treatment, 1 week, 1 and 3 months after the treatment. Eight control patients, who received general cognitive stimulation, were submitted to the same tests at the same time interval. The results showed that experimental patients obtained, as a consequence of PA, a long lasting neglect recovery, a reorganization of low-order visuo-motor behaviour during and after prism exposure (error reduction and after-effect, respectively) and a leftward deviation of oculo-motor responses. Importantly, the level of error reduction obtained in the first week of treatment was predictive of neglect recovery and the amelioration of oculo-motor responses, and the degree of eye movement deviation was positively related to neglect amelioration. Finally, the study of patients' neuroanatomical data showed that severe occipital lesions were associated with a lack of error reduction, poor neglect recovery and reduced oculo-motor system amelioration. In conclusion, the present results suggest that low-order visuo-motor reorganization induced by PA promotes a resetting of the oculo-motor system leading to an improvement in high-order visuo-spatial representation able to ameliorate neglect.

Keywords: Hemispatial neglect; Prism adaptation; Eye movements; Spatial attention; Rehabilitation

1. Introduction

In the last few years it has been shown that hemispatial neglect – i.e. right brain damaged patients' failure to respond, report or orient toward stimuli presented in the left contralesional space (Heilman, Valenstein, & Watson, 2000) – could be ameliorated by a treatment based on prism adaptation (PA) (Farnè, Rossetti, Toniolo, & Ladavas, 2002; Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Rossetti et al., 1998). Prismatic lenses induce an optical deviation toward the ipsilesional side as demonstrated by *a rightward* error in limb pointing to a visual target. If the visual feedback is available, patients make a motor correction toward the controlesional side to compensate for the prism effect; thus the initial disorganization of the visuo-motor behaviour is corrected through visuo-motor adaptation, i.e. error reduction. When the prismatic goggles are removed and the limb pointing to the visual target is not visible to the subject, patients show a systematic leftward deviation of visuo-motor response with the adapted limb, the so-called after-effect. In neglect patients this after-effect is accompanied by improvements in visuo-spatial neglect tasks lasting several hours (Rossetti et al., 1998), days (Farnè et al., 2002) or weeks (Frassinetti et al., 2002). This amelioration is present both in visuo-spatial attention tasks requiring a motor response with the adapted limb, such as line cancellation, line bisection, drawing by copying or by memory (Rossetti et al., 1998) and also in visuo-spatial tasks requiring verbal responses, such as object description, object naming, word and non-word reading (Farnè et al., 2002; Frassinetti et al., 2002), or naming towns from a mental map (Rode, Rossetti, Li, & Boisson, 1998). These findings suggest that the leftward correction of the visual motor bias induced by PA could be responsible for the amelioration of

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neglect and this effect could influence not only low-order visuo-motor factors, but also higher-level spatial representations.

However, some patients described by different studies (Dijkerman et al., 2003; Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003; Frassinetti et al., 2002; Morris et al., 2004; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002) seem not to benefit from PA treatment or the improvement was limited only to some aspects of the syndrome. This finding suggests that PA is not effective in improving the deficits of all neglect patients, but some behavioural and anatomical characteristics may play an important role in determining visuo-motor responses and related neglect amelioration. This may be of crucial relevance in the clinical practice since it might allow us to distinguish patients who can or cannot benefit from the treatment. Thus, the analysis of the behavioural and neuroanatomical predictors of neglect recovery after PA is the main objective of the present study.

First of all, to individuate a possible behavioural predictor of recovery, the interaction between low-order visuo-motor and high-order visuo-spatial effects of PA was investigated, since a direct relationship between these two aspects has not been yet demonstrated. Typically, as a consequence of PA, two main modifications in visuo-motor behaviour can be observed, i.e. error reduction and after-effect.

The after-effect has been traditionally considered the core of adaptation (Harris, 1974; Welch, 1978) and in many studies the effects of PA on neglect amelioration took into account only this measure as the index of visuo-motor modification (Farnè et al., 2002; Rossetti et al., 1998). However, the relationship between after-effect and neglect amelioration is controversial. On the one hand, Farnè et al. (2002) found that the decay of after-effect has the same temporal evolution as the improvement of visuo-spatial deficits: indeed these authors found that both the after-effect and neglect improvement persisted 24 h after a single PA session and they both disappeared after 1 week. On the basis of this finding the authors speculated that this temporal relationship could have a potential causative role. On the other hand, the results from another two studies seem to contradict this conclusion. Pisella et al. (2002) described a double dissociation in two patients between the presence of after-effect in a straight-ahead pointing task and performance in a line bisection task: patient S.A. presented no deviation of pointing after prism exposure and an amelioration in line bisection after PA, whereas patient P.E. presented a significant leftward deviation of pointing, but a resistant rightward error in line bisection. Moreover, a strong dissociation between the duration of the after-effect and neglect recovery was found studying the long term effects of PA: Frassinetti et al. (2002) found that the improvement on visuo-spatial tasks, obtained after an intensive PA program, lasted at least 5 weeks from the end of treatment, whereas the after-effect decayed with time and vanished in 84 h. In addition, in this study a single patient (RD) did not show a neglect amelioration although he manifested a significant after-effect. Finally, Girardi, McIntosh, Michel, Vallar, and Rossetti (2004) recently found that straight-ahead measures of after-effect do not correlate with visuo-spatial effects of PA in normal subjects. Thus, the lack of a clear relationship between after-effect and neglect improvement represents an important question to be solved.

On the other hand, after-effect is not the only change in visuo-motor behaviour induced by prismatic visual field shift: for example, error reduction might be a good predictor of the neglect recovery. Patient RD (Frassinetti et al., 2002), who presented a substantial after-effect without an amelioration of neglect, did not show an error reduction during prismatic exposure, thus suggesting that error reduction could be an important factor to be considered in determining neglect amelioration. The relationship between the indices of visuo-motor modification and neglect amelioration can be considered at the same time both an important clinical and theoretical question to address. On the one hand, once this relation is clear, it would be possible to predict the success of the treatment for each patient starting from the first few trials of PA. On the other hand, the explanation of this relation could shed light onto the mechanism underlying neglect recovery after PA.

Thus, the first aim of the present study is to identify the relationships between visuo-motor effects of PA and neglect improvement and, in particular, to investigate whether error reduction or after-effect could predict the amelioration in visuo-spatial attention tasks. To this end, a group of 16 neglect patients were submitted to 10 daily sessions of PA treatment and visuo-spatial abilities were assessed before the treatment, 1 week, 1 and 3 months after the end of the treatment. In order to exclude the possibility that neglect amelioration was due to practice with the tests, to spontaneous recovery, or to general stimulation, eight neglect patients (control group), who received non-specific rehabilitation treatment, performed the same tests in four sessions with the same time interval as the experimental group.

A second intriguing question concerns the mechanism by which low order visuo-motor effects may produce a recovery in high-level visuo-spatial representations. It has been recently proposed that PA, by inducing a leftward eye deviation, produces a resetting of ocular scanning behaviour which facilitates the exploration of the left neglected side of the space (Angeli, Benassi, & Ladavas, 2004). Indeed it is well known that severe neglect patients present with a rightward deviation of the eyes (Hornak, 1992) and that mild neglect patients show a failure to make eye movements towards the left side of the space (Chedru, Leblanc, & Lhermitte, 1973; Girotti, Casazza, Musicco, & Avanzini, 1983; Walker & Findlay, 1996). Angeli et al. (2004) showed that a single session of PA reduced the rightward oculo-motor bias in neglect patients and induced an amelioration of reading abilities. Therefore, due to hand-eye coordination, the leftward deviation obtained in pointing during PA might also have an effect on eye movement responses. To test this hypothesis, patients' eye movements during a reading task were measured before and after the treatment and the relationship between indices of oculo-motor and visuo-motor response was studied.

The third aim of the present study was to investigate the relationship between the locations of brain lesions and the degree of neglect recovery affected by PA, in order to find out possible neuroanatomical predictors. Neglect can result from damage to different regions of the right hemisphere, mostly centred on the parietal lobe, but commonly involving also the frontal, temporal, occipital lobe, the basal ganglia and the thalamus (see Karnath, Milner, & Vallar, 2002). Therefore, it is possible that lesions involving different brain regions differently affect patients' ability to adapt to prisms and the consequent neglect recovery.

2. Methods

2.1. Subjects

Twenty-four right-brain-damaged patients with chronic (at least 3 months from the onset of illness) left hemispatial neglect participated in the study. They gave their informed consent to participate in the study according to the Declaration of Helsinki (BJM 1991; 302; 1194) and the local Ethical Committee. All patients had unilateral lesions due to a cerebro-vascular accident, confirmed by CT or MRI scan. Gender, age, education, length of illness and lesion site are provided in Table 1. All patients were right-handed and had normal or corrected-to-normal vision.

Patients were selected on the basis of their defective performance in at least one visuo-spatial neglect score of the BIT (conventional or behavioural, see Section 2.2) assessed during a screening evaluation session. Sixteen patients were included in the experimental group (EG) and eight patients in the control group (CG). Neglect severity was not significantly different between the two groups of patients [BIT conventional: EG = 99; CG = 109, $p = 0.40$; BIT behavioural: EG = 49; CG = 53, $p = 0.40$: see below for more details]. The EG and the CG were also matched for age [mean 67 and 68 years, respectively, $p = 0.71$], education [mean 8 and 7 years of schooling, respectively, $p = 0.57$] and length of illness [mean 15 and 9 months from the onset of illness, respectively, $p = 0.56$] (see Table 1).

While experimental patients were submitted to PA, control patients were submitted to general cognitive stimulation and motor treatments for a period of 2 weeks. An expert therapist conducted individual daily sessions of cognitive therapy, consisting in different exercises such as picture naming, drawing, newspaper reading, and original material was appositely designed. At the end of each task the therapist constantly gave to the patients a feedback about their performance. Moreover, motor treatments were administered twice a day. These were individually set on the basis of patients' disabilities and could involve passive and active stimulation of both the lower and the upper affected limbs.

Experimental patients' lesions were reconstructed on the basis of their recent (i.e. less than 1 month before the first assessment) CT or MRI scans with the method introduced by Damasio and Damasio (1989). On the basis of this standard template, 43 brain structures have been identified, 14 in the frontal lobe, 12 in the temporal lobe, 6 in the parietal lobe, 7 in the occipital lobe and 4 sub-cortical structures (2 in the basal ganglia, i.e. the caudate nucleus and the lenticular nucleus, the internal capsule and the thalamus). The presence of a lesion in each of these structures was evaluated for 10 experimental patients, since CT/MRI scans of 2 of them were not available for analysis (see Fig. 1 and Table 2).

2.2. Assessment of neglect

All patients underwent a standardized battery of tests for visuo-spatial deficits, the behavioural inattention test (BIT, Wilson, Cockburn, & Halligan, 1987). BIT is composed of two scales, consisting respectively of conventional and behavioural tests. The Conventional scale includes cancellation tasks, figure and shape copying, line bisection and drawing from memory. The behavioural scale includes tests which simulate different aspects of daily life activities, such as scanning a picture, dialling the telephone, reading a menu or an article, telling and setting the time, sorting coins, copying addresses and sentences, map navigation and sorting cards. The cut off scores of the conventional and behavioural scale are 129 (range 0–146) and 67 (range 0–81), respectively. Patients were classified as having neglect when their score was below the cut-off score.

The evaluation of neglect was performed on four different sessions. The first screening assessment was to verify the presence and amount of neglect before the treatment, and the remaining sessions were performed 1 week (second session), 1 month (second session) and 3 months (second session) after the end

Table 1
Summary of clinical and demographic data for experimental (E) and control (C) neglect patients

Patient	Gender	Age (years)	Education (years)	Onset of illness (months)	Lesion site	BIT-C (cut-off = 129)	BIT-B (cut-off = 67)	Visual field deficits
E1	M	65	5	3	F–T–P–O–BG–IC	68	32	+
E2	M	64	5	3	F–T–P–O	122	59	–
E3	F	64	5	5	F–T–P–O	106	40	++
E4	F	69	5	3	F–T–P–O	63	24	++
E5	M	74	8	15	F–T–P–O–BG	55	34	+
E6	F	59	5	72	BG	111	64	–
E7	M	73	5	7	F–T–P–O–BG–IC	127	53	–
E8	F	67	3	3	F–T–P–BG–IC	104	29	–
E9	F	41	8	96	F–P–O	95	65	–
E10	F	80	12	3	F–T–P–O	126	70	–
E11	M	61	23	3	F–T	93	43	+
E12	M	65	13	4	BG	94	58	–
E13	M	54	13	5	F–T–P–BG–IC	117	72	–
E14	F	73	3	8	T–P	76	61	++
E15	M	75	8	9	F–T	113	56	–
E16	F	77	5	3	F–T–P–O	106	24	–
C1	M	68	8	4	F–T–P	41	12	NA
C2	F	72	5	13	T	131	29	NA
C3	M	65	13	6	F–T–P–IC	122	69	NA
C4	M	67	5	5	BG	129	46	NA
C5	M	60	8	8	F–P	99	67	NA
C6	M	72	5	14	F–T–P	119	65	NA
C7	F	80	5	12	T–P	110	71	NA
C8	F	58	5	12	T–P	122	63	NA

Lesion site column reports the cortical and sub-cortical structures involved by the lesion—F: frontal; T: temporal; P: parietal; O: occipital; IC: internal capsule; BG: basal ganglia. The seventh and eighth columns report patients' results in visuo-spatial neglect scales during the screening evaluation—BIT-C: behavioural inattention test, conventional scale; BIT-B: behavioural inattention test, behavioural scale. The last column reports the presence of visual field deficits to a confrontation task: (++) complete left hemianopia; (+) left superior quadrantopia. NA: data not available.

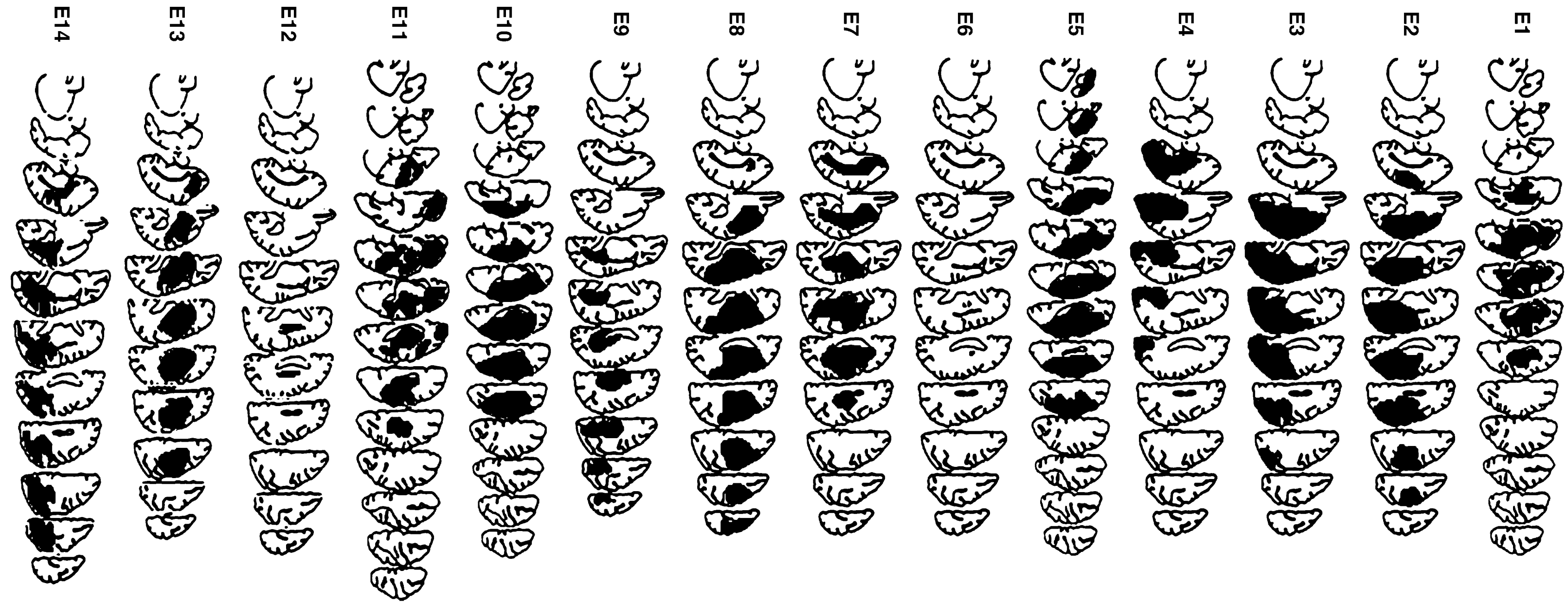

Fig. 1. Brain lesions in the experimental patients. The figure shows the location of the brain damage in each patient according to the standard template provided by Damasio and Damasio (1989).

Table 2
Summary of lesion data for experimental patients

Case	Frontal lobe														Temporal lobe											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
E1	x					x		x	x					x			x			x	x	x	x	x	x	
E2								x									x	x		x	x	x	x			
E3		x						x									x	x			x	x	x			
E4		x																x		x				x	x	
E5						x	x	x	x	x				x	x		x		x	x	x	x	x	x		x
E6																										
E7								x	x	x							x	x			x	x	x			x
E8						x		x	x	x							x	x			x	x	x			
E9		x			x					x																
E10						x		x	x	x							x			x	x	x	x			
E11						x	x		x					x	x						x	x			x	
E12																										
E13							x	x	x	x					x						x	x	x	x	x	
E14																		x					x			

Case	Parietal lobe						Occipital lobe							Sub-cortical structure			
	P1	P2	P3	P4	P5	P6	O1	O2	O3	O4	O5	O6	O7	BG 1, 2	BG 3, 4	IC	Th
E1					x				x			x	x	x	x	x	
E2	x	x			x	x					x	x					
E3	x	x		x	x		x	x		x	x	x	x				
E4		x		x			x	x	x	x	x	x	x				
E5	x	x			x	x						x		x	x		
E6															x		
E7		x			x	x						x			x	x	
E8	x					x								x	x	x	
E9		x	x	x	x	x		x				x	x				
E10	x	x			x	x					x	x					
E11	x				x	x						x					
E12															x		
E13	x				x	x						x					
E14	x	x	x	x	x	x						x	x				

Anatomical areas of interest (x) are represented using the coding system of Damasio and Damasio (1989). For case E15 and E16, CT/MRI scans were not available.

of the treatment. Control patients were tested at the same four time intervals as experimental patients.

2.3. Assessment of eye movements

Both groups of patients underwent eye movement recording during a reading task in two different sessions, performed before and after PA for the experimental group, and after about two weeks for the control group. Eye movement were recorded in 11 experimental and 6 control patients. The remaining patients (5 and 2, respectively) could not attend the eye movement recording session because they were not able to maintain a straight position for prolonged time (see below).

2.3.1. Apparatus

Subjects were seated in a dimly lit room with their head stabilized straight ahead by means of an adjustable forehead and chin rest. A strap that passed behind the head restrained head movements. The stimuli for the reading task were generated using custom software and displayed on a 15 in. colour monitor. The video screen was centred on the midsagittal plane of the subject's head and was viewed binocularly from a distance of approximately 42 cm. Horizontal eye movements were monitored using an infrared corneal reflection oculo-meter (Dr. Bouis Instruments, Germany) positioned in front of the subject's left eye. The eye movement tracker had high spatial resolution (about 5 min of arc) and its output was linearly related to eye position up to approximately 19.3° of visual angle (both horizontally and vertically). The analogue eye movements signals were sampled at 500 Hz, digitised by a lab-driver interface and stored on a hard disk for off-line analysis.

2.3.2. Stimulus material

Stimuli comprised 48 letter strings, 24 of 9 and 24 of 11 letters in length. Each string was composed of upper case letters (0.7 cm × 0.7 cm; 0.95° × 0.95°) separated by a single character space (0.7 cm × 0.7 cm; 0.95° × 0.95°). Stimuli were printed in white against a black background, and they were displayed horizontally at the centre of the video screen, one at a time. Half of the stimuli ($n = 24$) were common Italian words, and the remaining half ($n = 24$) were non-words generated by changing two letters of each word. The substituted letters were located at the beginning and at the end of the stimulus. All non-word strings were pronounceable and orthographically legal. Compound words were not used. Word and non-word stimuli were presented in four separate block of 12 trials each.

2.3.3. Calibration

Eye-position signals were calibrated before each trial. To this end, the subject viewed a central fixation cross and two outline squares, located at 9.5° to the right and to the left of central fixation cross. First, the zero point calibration was established by making the subject gaze at the central cross. Then, the subject was asked to fix his gaze on the centre of each of the two squares by tracking a pen that was moved from the central cross to each squares position.

2.3.4. Reading task

A fixation cross was presented in the centre of the video screen. When the subject appeared to be correctly fixating the stimulus, the experimenter pressed a button to initiate the display. Then the central cross was extinguished and, after 100 ms, the stimulus was displayed for a maximum of 4000 ms. Patients had to look at the string and to report verbally what they read. If the subject named the target string before the presentation time had elapsed, the experimenter pressed a button to blank the screen. Eye position recording started 100 ms before stimulus presentation and continued until the string went off. The subject was requested to refrain from blinking during the recording period.

Patients' accuracy in the reading task was calculated as a proportion of strings correctly produced in the available time. Patients' reading errors were classified as "neglect" or "visual" errors, depending on whether they involved the left or the right half of the letter string, respectively. Visual errors were few and they were excluded from the analysis.

2.3.5. Eye movement analysis

As indices of eye movement performance two main parameters were considered: the first saccade landing location which provides a measure of the first saccade amplitude, and the distribution of exploration time, which provides a measure of time spent in the left versus right hemi-space. To calculate these parameters, the recording for each trial was plotted onto the video screen as a scan path, superimposed on the original stimulus. Regions of the space occupied by each letter string were divided into a number of equally wide horizontal sectors, one for each letter composing the string. Sectors were numbered from the centre of the string outwards, with right-sided sectors coded as positive and left sectors as negative. The middle letter in the string was coded as centre and numbered 0. The first saccade landing location was calculated considering the number of the sector reached by the first eye movement performed by the subject approximately 100 ms post-stimulus onset in the 48 trials. These values were transformed into degrees of displacement from the fixation point at the centre of the letter string, each letter being separated by 2.05° of visual field. The mean displacement in the 48 trials was taken as the measure of the first saccade amplitude. To calculate the spatial distribution of exploration time the letter in the middle of the letter string was codified as centre and all letters on the left and on the right of the central one were classified as left and right, respectively. The difference between the proportion of time spent in the left and right hemi-space was taken as the measure of spatial distribution of exploration time, as recommended by Di Pellegrino, Làdavas, and Galletti (2001).

2.4. Prism adaptation procedure

Patients were seated at a table. In front of them there was a wooden box (height 20 cm, depth 34 cm at the centre and 18 cm at the periphery, width 72 cm). The box was open on the side facing the patient and on the opposite side, facing the experimenter. A visual target (a pen) was presented manually by the experimenter at the distal edge of the top face of the box. The visual target was presented randomly in one of three possible positions: a central position, straight ahead in front of the patient (0°), and in a lateral position to the left or right of the patient's body midline (−21° and +21°, respectively). The experimenter recorded patients' pointing spatial accuracy as the distance between the target position and the final position of the patient finger. A graduated transparent barrier, invisible to the patient, was used to assess pointing deviation. This measure was expressed in degrees and codified as positive or negative for a rightward or leftward displacement, respectively. Patients were asked to keep their right ipsilesional hand on their chest, at the level of the sternum (hand starting position) and to point with the index finger towards the pen, at a fast but comfortable speed. Patients pointing arm movement was executed within the wooden box whose upper side was moved forward and backward. This allowed to vary the visual feedback in the two different conditions (visible and invisible pointing, see below). Patients underwent the treatment in 10 sessions, 1 a day, which took about 20 min each, over a period of 2 weeks. The pointing task was performed in three experimental conditions: Pre-exposure (visible and invisible pointing), exposure (visible pointing) and post-exposure (invisible pointing).

2.4.1. Pre-exposure condition

Patients were required to point towards 60 targets randomly presented at the three positions (20 targets at the centre, 20 at the right and 20 at the left). Patients performed half of the pre-exposure trials with "visible" pointing, which was the baseline for exposure condition, and half with "invisible" pointing, which was the baseline for post-exposure condition (see below).

2.4.2. Exposure condition

Patients performed the same task wearing the prismatic goggles (Optique Peter, Lyon). The goggles were fitted with wide-field prismatic lenses inducing a 10° shift of the visual field to the right. Patients were asked to point rapidly to 90 targets presented in a random order (30 targets at the centre, 30 on the right and 30 on the left). During the exposure condition the pointing movement was hidden below the top face of the box, apart from the final part of the movement where the index finger emerged beyond the distal edge of the box (visible pointing).

2.4.3. Post-exposure condition

Immediately after the prism removal, patients were required to point towards 30 targets (10 at the centre, 10 on the right and 10 on the left). The pointing movement was performed entirely below the top face of the box, so that the index finger was not visible at any stage (invisible pointing).

All conditions were run in each session, with the exception of the pre-exposure condition, which was performed only in the first session of the treatment.

3. Results

3.1. Neglect recovery

In order to verify the presence and duration of neglect amelioration as a consequence of the treatment, 2 two-way ANOVAs were performed taking group (experimental and control) as a between-subjects factor, session (first, second, third and fourth session) as a within-subjects factor and the scores in BIT conventional and BIT behavioural as dependent variables, respectively. Another ANOVA was performed on reading accuracy scores. When necessary, pairwise comparisons were conducted with the Newman–Keuls test. The level of significance was always set at 0.05.

Concerning BIT conventional, the only significant main effect was session [$F(3, 66) = 5.38$; $p < 0.003$]. More importantly the interaction group × session was significant [$F(3, 66) = 5.41$; $p < 0.003$]. Post hoc comparisons showed an amelioration of BIT conventional scores in the experimental group when the scores obtained in the first session (99) were compared with those of second (121, $p < 0.01$), third (125; $p < 0.001$) and fourth (122, $p < 0.02$) session, whereas in the control group the first session (109) was not different from the second (110), third (103) and fourth (108) sessions (see Fig. 2a). Moreover, post hoc tests confirmed that the scores of the two groups were not different in the first session ($p = 0.20$), whereas the performance of the experimental patients was better than control patients in the third, and fourth sessions ($p < 0.05$ in both comparisons).

The ANOVA performed on BIT behavioural scores showed quite similar results. The main effect of session [$F(3, 63) = 8.18$; $p < 0.0002$] and the interaction group × session were significant [$F(3, 63) = 5.95$; $p < 0.002$]. Post hoc comparisons showed in the experimental group an amelioration of BIT behavioural scores when results of the first session (49) were compared with those of second (61, $p < 0.001$), third (65, $p < 0.0002$) and fourth (64, $p < 0.0002$) session, whereas in control group the first session (53) was not significantly different from second (55), third (54) and fourth (54) session (see Fig. 2b). Moreover, the scores of experimental patients were not different from those of control patient in the first session ($p = 0.19$), whereas they were higher in the second, third and forth session ($p < 0.05$ in all comparisons).

The amelioration of neglect after PA was also confirmed by accuracy scores in the reading task performed during eye movement recording. A two-way ANOVA on reading accuracy was performed with group (experimental and control) as between-subject factor and session (first and second) as within-subject factors. The interaction group × session was significant [$F(1, 14) = 7.64$; $p < 0.02$]: comparing the first (28%) and second session (51%) an improvement of reading accuracy was found in the experimental group ($p < 0.02$), whereas no difference was found in the control group (27% and 24%, respectively).

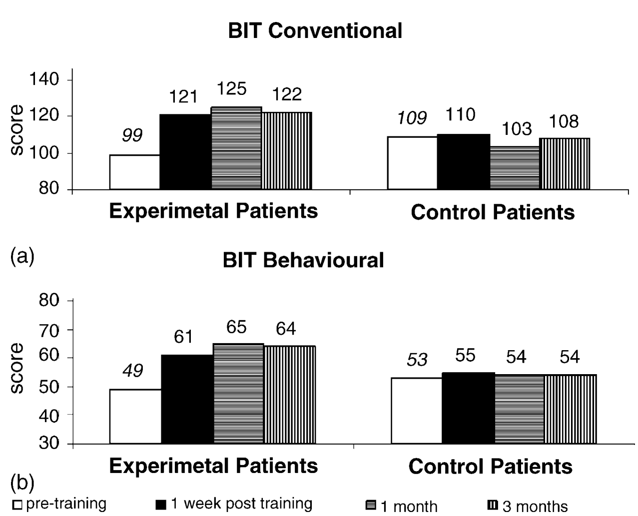

Fig. 2. Effect of prism treatment on visuo-spatial neglect tests. Patients' scores in the BIT conventional (a) and BIT behavioural scale (b) for the experimental group and control group are reported as a function of session of assessment.

3.2. PA visuo-motor effects

3.2.1. Error reduction

To demonstrate the presence of error reduction, visible pointing performance during pre-exposure and exposure condition was compared with the following prediction: if patients were actually able to adapt to the prisms, no difference should be found between exposure and pre-exposure condition, i.e. 0° or close to 0° pointing displacement should be registered in both conditions. To verify this prediction, a paired sample *t*-test was performed and no difference was found in visible pointing displacement between pre-exposure (mean deviation = 0.2°) and exposure condition (0.5°). Moreover, to study the temporal evolution of error reduction, a one-way ANOVA with condition as factor with three levels (pre-exposure, first week exposure and second week exposure) was conducted. The main effect of condition was significant [$F(2, 30) = 4.16$; $p = 0.03$]. Pointing error in the first week of PA was greater (mean = 0.8°, S.D. = 1.4) than that obtained in the pre-exposure condition (mean = 0.2°; S.D. = 0.7; $p < 0.03$) and in the second week of PA (mean = 0.2°, S.D. = 1.3, $p < 0.05$). This suggests that not all patients were able to completely adapt to prism effect in the first week of treatment (see Fig. 3).

3.2.2. After-effect

To show the presence of an after-effect, invisible pointing was compared between the post-exposure condition and the pre-exposure condition. If PA produced a leftward visuo-motor bias in response to the rightward deviation induced by prism, a leftward (i.e. negative) error during pointing should be found when prismatic goggles have been removed, whereas this effect should not be present during pre-exposure condition. To verify this prediction, a paired sample *t*-test was performed between the mean of pointing displacement during post-exposure and pre-exposure condition. A significant difference was found between post-exposure (mean displacement = −3.7°) and pre-exposure condition (−0.1°) [$t(1, 15) = 71.28$; $p < 0.0001$]. Moreover, to study the temporal evolution of the after-effect, a one-way ANOVA

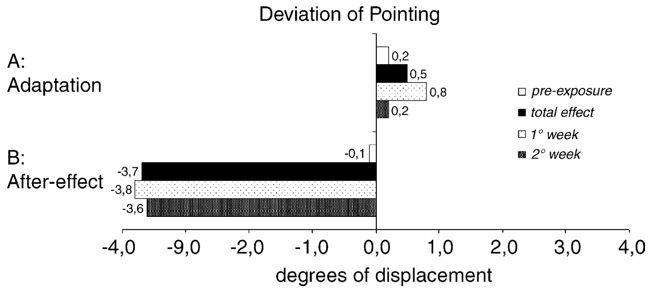

Fig. 3. Error reduction and after-effect for the whole treatment, the first and the second week of PA. Mean displacement (expressed as visual angle) of experimental patients' pointing responses in the pre-exposure with visible hand condition, exposure condition for the first 5 sessions (first week), the last 5 sessions (second week) and for all the 10 sessions of PA are reported in (A). Mean displacement in the pre-exposure with invisible pointing condition, post-exposure condition for the first 5 sessions (first week), the last 5 sessions (second week) and for all the 10 sessions of PA are reported in (B).

on pointing errors taking condition as factor with three levels (pre-exposure, first week post-exposure and second week post-exposure) was performed. The main effect of condition was significant [$F(2, 30) = 71.21$; $p < 0.0001$]. Post hoc analysis showed that pointing error after one week of PA (-3.8°) was not significantly different than that found in the second week (-3.6°) but bigger than that found in the pre-exposure condition (-0.1; $p < 0.0002$, see Fig. 3).

3.2.3. Relationship between error reduction and after-effect

In order to correlate the degree of error reduction and after-effect, we calculated an index for each measure. The mean of visible pointing displacement in exposure condition minus that in pre-exposure condition was considered as an index of error reduction. The mean of invisible pointing displacement in post-exposure condition minus that in pre-exposure condition was considered as an index of after-effect. Pearson correlation analysis showed no correlation between the two visuo-motor effects after PA. The same results were obtained when the data relating to the first week of PA were considered.

3.3. Relationship between PA visuo-motor effects and neglect recovery

As an index of neglect improvement, the difference between patients' performance obtained in the second assessment (i.e. after the treatment) and in the first assessment (i.e. at the baseline) on the BIT (conventional + behavioural scores) was calculated (BITd). To test whether error reduction or after-effect or both effects can predict neglect improvement, a multiple regression analysis was performed taking BITd as the dependent variable and error reduction and after-effect indices as independent variables. No significant correlation of error reduction or after-effect on BITd was found. This null result was probably due to the lack of variability in the mean of the overall error reduction. It is noteworthy that this index was close to 0° in all the patients. On the contrary, the index of error reduction in the first week of treatment was much more variable and thus it might a better predictor of the ability to adapt to prism and to recover from neglect. To investigate this hypothesis, a multiple regression analysis was performed taking BITd as dependent variable and the indices of error reduction and after-effect for the first week of PA as independent variables.[1] A significant negative effect of error reduction ($b = -24.52$; $p < 0.001$; $R^2 = 0.61$) but not of after-effect ($b = -0.52$; $p = 0.85$) was found on BITd. Thus patients that were more able to correct their pointing errors during the first week of PA obtained a greater improvement in BIT scores, and this independently of the amount of the after-effect obtained in the first week of PA (see Fig. 4a).

3.4. Effects of PA eye movements

To verify that PA produced leftward oculo-motor deviations, the amplitude of the first saccade in the first and second sessions was compared in the experimental patients and in the control group. Eye movement records were available for 11 experimental and 6 control patients. An ANOVA was performed on the first saccade landing location, taking group (experimental and control) as between-subjects factor and session (first and second) as within-subjects factor. Only the interaction group × session was significant [$F(1, 14) = 9.81$; $p < 0.008$]. Post hoc analysis showed that in the experimental group the first saccade landing location in the first session fell close to the middle of the string (mean deviation: -0.66°) whereas in the second session (i.e. after PA) it was displaced more towards left (-1.87°; $p < 0.006$). In contrast no difference was found in the control group between the first (0.26°) and second session (0.02°).

To study the relationship between visuo-motor and oculo-motor effects of PA, an index of oculo-motor leftward deviation was calculated as the difference between the first saccade landing location in the first and the second session. Two multiple regression analyses performed taking the index of oculo-motor deviation as the dependent variable and the indices of error reduction and after-effect for the whole treatment and for the first week of PA as independent variables showed a positive effect of error reduction for the first week of PA ($b = 0.78$; $p < 0.003$; $R^2 = 0.76$) but not for after-effect ($b = 0.30$; $p = 0.27$). Patients who were more able to correct their pointing error during the first week of PA showed a greater leftward deviation of the first saccade after treatment (see Fig. 4b).

The oculo-motor deviation index also showed a significant negative correlation with neglect improvement ($r = -0.61$; $p < 0.05$); patients who showed a greater leftward displacement of the first saccade obtained a greater improvement in visuo-spatial tasks (see Fig. 4c). A similar correlation was also obtained between the index of the oculo-motor leftward deviation and the index of the reading accuracy improvement (calculated as the

[1] Statistical tests for the normality of the data have been conducted on the indices used for multiple regression analyses by means of Kolmogorov–Smirnov test. The results confirmed that the indices of improvement obtained at the Bit tests (Bitd), the indices of error reduction and after-effect for the first week of PA, as well as the index related to the deviation of the first saccade (see below) were normally distributed [Bitd: K.S.(11) = 0.223; $p = 0.13$; 1 week of error reduction: K.S.(11) = 0.23, $p = 0.12$; 1 week of after-effect: K.S.(11) = 0.20, $p = 0.20$; deviation of the first saccade: K.S.(11) = 0.093, $p = 0.20$].

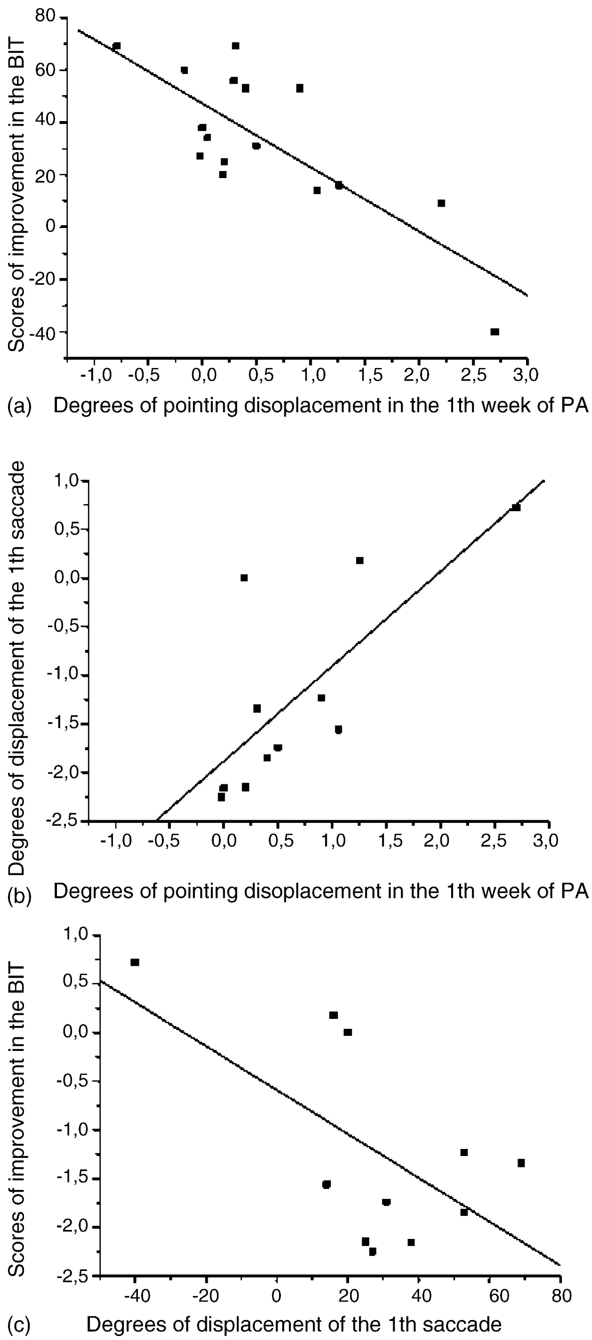

Fig. 4. Relationship between neglect amelioration, visuo-motor effects of PA and oculo-motor system plasticity. The linear regression between the index of improvement in BIT scores obtained after the treatment and the index of error reduction for the first week of PA is represented in (a). The linear regression between the index of leftward displacement of the first saccade obtained after treatment and the index of error reduction for the first week of PA is represented in (b). The linear regression between the index of improvement in BIT scores and the index of leftward displacement of the first saccade obtained after the treatment is represented in (c).

difference between reading accuracy in the first and second session) ($r = -0.69$; $p < 0.05$). Thus the more leftwardly deviated the first saccade, the greater was the improvement in reading accuracy.

Finally, in order to investigate whether PA had an effect on the spatial distribution of eye movements, space exploration

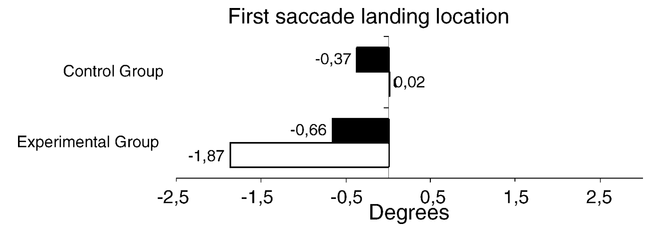

Fig. 5. Effects of PA on eye-movements. First saccade landing location during letter strings reading as function of session (first and second) and group (experimental and control). Landing location was expressed in terms of mean displacement (in degrees of visual angle) towards the left (coded as negative) and right (coded as positive). The number 0 on the *x*-axis indicates the string centre.

time was compared between the first and the second session for experimental and control patients. A two-way ANOVA on the left–right exploration time difference was performed with group (experimental and control) and session (first and second) as main factors. No main effect of group or session was found, whereas group × session was significant [$F(1, 14) = 12.19$; $p < 0.003$]: the left–right fixation time difference varied between the first and second session in the experimental group (0.15 and 0.30, respectively, $p < 0.002$), but not in the control group (0.11 and 0.07, respectively). These results confirm that PA has an effect on the distribution of exploration time: after the treatment experimental patients explored more the left hemispace with the respect to the right hemispace. However, this parameter did not correlate with the indices of adaptation, after effect and neglect recovery, as shown by Pearson correlation analysis (Fig. 5).

3.5. Relationship between brain lesions and effects of PA

To investigate whether the general extent of the brain damage could be a negative predictor of recovery, for each patient the proportion of damaged brain regions was calculated as the ratio between the number of damaged areas visible at CT/MRI scans and the total number of 43 regions individuated according to the method by Damasio and Damasio (1989). Pearson correlation analyses were conducted and the results showed that the extent of brain damage was not related to the improvement in BIT scores after the treatment, nor to the level of error reduction in the first week of PA, nor to the leftward deviation of the first saccade landing location.

To study whether the site of the brain lesion can shed light onto the effect of PA, for each patient the proportion of brain damage in each lobe was calculated as the ratio between the number of damaged regions (see Table 2) and the total number of regions in the same lobe. First of all, in order to investigate whether the lesion of a specific region can affect adaptation, the relationship between the index of error reduction for the first week of PA and the proportion of damaged structures in frontal, temporal, parietal, occipital lobe and sub-cortical regions was studied by means of Pearson's correlations. The level of significance was set at $p < 0.03$, by means of Bonferroni correction. Only a significant effect of occipital lobe lesions ($r = 0.77$; $p < 0.01$) was found, showing that the extent of brain damage in the occipital lobe affects patients' ability to quickly correct their pointing errors.

Moreover, a negative correlation was found between occipital damage and the index of improvement in BIT scores ($r = -0.61$; $p < 0.03$): patients with diffuse occipital lesions obtained less benefit from the treatment. The same analysis conducted for the remaining structures showed no correlation with BITd scores, with the exception of a negative correlation of frontal lobe lesion ($r = -0.65$; $p < 0.03$).

Finally, when the index of leftward eye movements deviation was studied, Pearson correlation analysis showed a significant positive correlation ($r = 0.86$; $p < 0.03$) only with occipital lesion, meaning that patients with more extended occipital lesions showed less leftward saccade deviation after PA.

To summarize, these findings suggest that the general extent of brain damage is not predictive of PA effectiveness, whereas wide lesions of the occipital lobe affect neglect recovery, error reduction ability and oculo-motor plasticity.

4. Discussion

The aim of the present study was to examine variables that affect the degree to which adaptation to a prismatic shift of the visual field can induce neglect recovery in right brain damaged patients, in order to search for behavioural and neuroanatomical predictors of the outcome of the treatment. To this end, 16 patients with a right hemisphere lesion and left visuo-spatial neglect were submitted to a rehabilitative program with prismatic lenses for 10 daily sessions over a period of 2 weeks and their performance was compared to that of control patients who received general cognitive stimulation and motor treatments. The results showed a long-lasting amelioration of neglect after PA (see Section 1), and significant relationships between this amelioration and both low-order visuo-motor effects and oculo-motor changes. Finally, the present study discovered a significant role of the occipital lobe in modulating the mechanism of PA and the related neglect recovery (see Section 3).

4.1. Neglect recovery after PA

First of all, after the treatment experimental neglect patients obtained a significant improvement of visuo-spatial abilities, both in traditional paper-and-pencil measures of neglect and in behavioural tests assessing everyday life abilities. Neglect amelioration was consistent and long lasting, since the improvement in visuo-spatial tasks was confirmed also in follow-up assessments performed 1 and 3 months after the end of the treatment. These effects cannot be considered the result of practice effects, general stimulation, or spontaneous recovery, since no difference was found in control patients who were submitted to non-specific rehabilitation treatment and assessed at the same time interval as the experimental group.

Second, neglect improvement was associated to a low-order reorganisation of visuo-motor response system produced by PA to compensate the rightward deviation of visual field induced by prisms. The neglect patients were able to adapt to the prismatic lens, as demonstrated by the presence of both error reduction, i.e. the ability to correct pointing displacement during prism exposure, and by the after-effect, i.e. a leftward deviation in pointing performance when prismatic goggles were removed. However, these effects were not equally present in all patients.

Finally, after PA, a leftward bias of the eye movement system was also achieved. It was found that patients submitted to PA showed an increase in the first saccade amplitude towards the left and in the exploration time of the contralesional side of the space, whereas no effect was found in control patients.

These findings confirm and extend previous results showing that PA produces a consistent reorganization in high-order visuo-spatial representation (Frassinetti et al., 2002) and in oculo-motor functions (Angeli et al., 2004). These previous studies, however, did not analyze the relationship between the recovery of neglect and the visuo-motor and oculo-motor effects of PA.

4.2. Relationships between visuo-motor, visuo-spatial and oculo-motor effects of PA

As far as the low-order visuo-motor modifications induced by PA are concerned, it was found that, in neglect patients, there is no correlation between error reduction and after-effect, thus suggesting that these measures reflect different processes (Redding & Wallace, 1993). Moreover, a great variability in the measures of error reduction assessed during the first week of PA was found, indicating that not all patients reached the same level of error reduction in the first week of treatment, whereas the after-effect was quite stable among the 2 weeks of treatment.

Second, it was found that the level of error reduction of the first week of treatment predicts neglect amelioration and the deviation of the oculo-motor system obtained after PA better than the after-effect: patients who were more able to quickly adapt to the prisms obtained greater improvement in visuo-spatial tasks and showed a greater leftward deviation of the first saccade after the treatment. In addition the effect of PA on eye movements and neglect recovery were also correlated and, in particular, patients with greater leftward deviation of the first saccade obtained also a greater improvement in visuo-spatial tasks after the treatment. Therefore, from these findings it is possible to suggest that error reduction promotes a leftward deviation of the oculo-motor system that may play a role in improving neglect.

During the adaptation process under prism exposure, patients perform pointing movements to a visual target and receive visual feedback concerning the final position of the hand with respect to the target. In the very first trials patients show a rightward error in pointing due to the visual field displacement and the error signal is codified in visual eye-centred coordinates as the distance between the finger and the target in terms of visual angle. Consequently, after a few trials, patients perform a corrective movement to the target to compensate for this error and progressively modify hand movement plans to reduce the target-finger gap. A possible strategy consists in pointing to the side of the target by an amount sufficient to reduce the visual error. Effectively, visual hand-centred coordinate systems may be reset by subtracting from the coordinates of the actual target the visual error signal (Redding & Wallace, 1993). Since there is evidence that, during pointing, eye movements are yoked to hand movements and vice versa (Buxbaum & Coslett, 1998; Carey, Coleman, & Della Sala, 1997; Neggers & Bekkering; 2000), it is possible to speculate that under prism exposure condition, due to this eye-hand coordination, the leftward deviation of hand movements could induce a leftward deviation of the oculo-motor system.

In addition, a positive correlation was found between the first saccade deviation and the improvement in visuo-spatial tasks obtained at the end of the treatment. Thus after the treatment eye movements remain leftwardly oriented, at variance with the hand movement after effects that are known to vanish after few days (Farnè et al., 2002). This dissociation might be explained by the fact that after the removal of the prisms, the leftward deviation of the oculo-motor system could enhance in neglect patients the detection of stimuli presented in the contralesional side of the space. Thus it has been shown that in normal subjects perceptual identification improves dramatically for objects presented at a future saccade target location, shortly before saccade execution, compared with objects presented in other positions of the visual field (Deubel & Schneider, 1996; Hoffman & Subramaniam, 1995; Kowler, Anderson, Dosher, & Blaser, 1995). Therefore, it is possible to speculate that the increase in the amplitude of the first leftward saccade obtained after PA produces also a shifting of visual attention towards the left side of the visual field, thus mediating the recovery of visual neglect. In this way, the initial leftward deviation of eye movements induced by PA might be continuously reinforced by stimuli from the external environment and be further implemented.

At the same time the resetting of the eye movements towards the left can also account for the improvement in neglect patients' spatial representation, i.e. in tasks such as naming towns from a mental map or drawing by memory (Farnè et al., 2002; Frassinetti et al., 2002; Rode et al., 1998). Meador, Loring, Bowers, and Heilman (1987) found that in a representational task in which patients were asked to imagine the street leading to their house and to name the buildings on the streets, recall of items improved when patients rotated their eye towards the left, thus suggesting that the direction of eye movements can influence the formation of or retrieval from spatial representations.

The measure that has been traditionally considered crucial to demonstrate PA (Harris, 1974; Redding & Wallace, 1993; Welch, 1978) is the after-effect, rather than the error reduction. But, interestingly, this effect seems to be not directly related to neglect recovery, since the after-effect indices did not correlate either with neglect amelioration or with the leftward deviation of eye movements. The explanation of this result could be found in the nature of visuo-motor correction acting during the after-effect, which mostly reflects a reorganisation of the proprioceptive hand-centred coordinate system. Indeed, during the post-exposure test, the hand is no longer visible, thus there is no longer a match between visual and proprioceptive hand information. In this case, the pointing bias after prism exposure reflects an acquired movement correction expressed mainly in terms of proprioceptive hand-centred coordinates. This may be the reason why the after-effect, as revealed with manual pointing, does not correlate with the deviation of the oculo-motor system, strictly linked with the visual system, and consequently with neglect recovery.

To summarize, the results concerning the relationships between the effects of PA on different sensory and motor representations suggest that the process of neglect improvement by PA, probably mediated by the reorganization of the oculo-motor system, needs to be guided by visual information.

4.3. Relationship between PA and brain lesions

This conclusion, i.e. the relevance of the visual component of the adaptation process, is strongly supported by the results from the analysis of the neuroanatomical characteristics of neglect patients submitted to PA. It was found that extended lesions in the occipital visual areas were associated with lack of error reduction during the first week of PA, reduced leftward deviation of the oculo-motor system and poor neglect recovery. These results cannot be a spurious effect due to the global size of brain lesions, since no relationship was found between the number of damaged regions in the whole brain and the level of error reduction in the first week of PA, the visuo-spatial neglect improvement nor the leftward deviation of oculo-motor responses. These findings may also explain the dissociation found between eye movements and neglect recovery found by Dijkerman et al. (2003): patient CS, who suffered of a lesion involving the occipital lobe, continued to demonstrate a rightward oculo-motor bias after PA and only a partial and inconstant improvement in one of the tasks used to assess neglect, showing in this way a reduced effect of PA on the amelioration of neglect.

Finally, another structure that seems to have a role in affecting the outcome of the treatment is the frontal lobe, since *in the present study* patients with more extended frontal lesions seem to show poorer neglect recovery after PA. It has been recently demonstrated that the vast majority of patients presenting chronic neglect (i.e. persisting after 3 months from the cerebral accident) are affected by extended frontal lesions (Maguire & Ogden, 2002) and that the presence of frontal lesions also characterizes neglect patients who show a poor spontaneous neglect recovery in the acute and post-acute phase, in comparison with patients showing a good recovery (Farnè et al., 2004). Moreover, it has been demonstrated that neglect patients often present a deficit in basic non-lateralized components of the attentional system, such as vigilance and sustained attention (Robertson et al., 1997; see Husain & Rorden, 2003 for a review) and it has been suggested that these deficits can be an important negative predictor of neglect recovery (Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998). It is currently accepted that the right frontal lobe is a crucial structure in mediating these attentional functions (Rueckert & Grafman, 1996; Wilkins, Shallice, & McCarthy, 1987). Therefore it is possible that frontal lesions represent a second negative predictor of neglect recovery after PA treatment because frontal neglect patients present also basic attentional deficits that interfere with neglect recovery, independently of the mechanisms of PA.

The findings of the present study concerning the anatomical structures involved in the process of neglect recovery by PA are unexpected in comparison with the current literature on the localization of PA processes, which indicates two main structures to be specifically involved in error reduction and after-effect, the posterior parietal cortex (Clower et al., 1996; Pisella et al., 2004) and the cerebellum (Martin, Keating, Goodkin, Bastia, & Thach, 1996; Weiner, Hallett, & Funksteinen, 1983), respectively. However, the results from the present study do not contradict these findings. Indeed, as far as error reduction is concerned, the absence of a negative effect of right parietal lesions is not surprising considering that all patients had intact the left parietal lobe which can mediate error reduction when pointing is performed with the right hand. It is worthwhile to note that none of the patients in the present study showing after-effects had cerebellar lesions.

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