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Neglect treatment by prism adaptation: What recovers and for how long

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Previous findings showed that a prism adaptation (PA) treatment can induce a long- lasting recovery of hemispatial neglect, at least up to five weeks after the end of the treatment programme (Frassinetti et al., 2002). The present study further evaluated the effects of PA by investigating: (1) the long-term duration of the benefits assessed one week, and one, three and six months after the treatment; (2) the generalisation of the effects to different visual and non-visual functions; and (3) the index of visuo-motor responses (adaptation effect or after-effect) that better predict neglect recovery by PA. To these aims, 21 neglect patients were submitted to PA treatment for 10 daily sessions over a period of two weeks, and their performance was assessed for visual, tactile, proprioceptive, motor and oculomotor functions. The results showed a consistent and stable amelioration of visuo-spatial abilities, both for personal and extrapersonal space. The improvement seems to be partially multimodal, since an amelioration was found for tactile modality, but not for proprioception and motor functions. Finally, neglect amelioration appeared to depend on patients' ability to adapt to prism optical displacement during the fist week of PA, since patients who were not able to correct pointing errors under prism exposure in the first week of treatment showed less neglect and oculomotor system recovery at the end of treatment.

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INTRODUCTION

Hemispatial neglect is defined as the right-brain damaged patients' failure to explore, respond or orient towards stimuli presented in the contralesional side of the space (Heilman, Valenstein, & Watson, 2000). Neglect cannot be considered a unitary deficit, but a syndrome involving different functions and different portions of the space. Indeed, even if a deficit in the visual modality is the best characterised symptom of neglect, the spatial bias has been observed also in other sensory modalities, i.e., auditory (Pavani, Làdavas, & Driver et al., 2004), touch (Faglioni, Scotti, & Spinnler, 1971), proprioception, smell (see **Q1** Vallar 1998, for a review), as well as motor (Coslett et al., 1990) and oculomotor functions (Walker & Findlay, 1996). Moreover, the deficit can concern different sectors of the space, i.e., personal space (the subject's body space; Bisiach, Perani, Vallar, & Berti, 1986; Guariglia & Antonucci, 1992), **Q2** near-peripersonal space (the space proximal to the subject's body; Làdavas, 2002; Làdavas & Farnè, 2004), extrapersonal near (the space within hand reaching; Halligan & Marshall, 1991) and far space (Vuilleumier et al., 1998). A spontaneous recovery from most obvious signs of neglect has been noted in the majority of patients in the acute (less than 6 weeks from the cerebral accident) and post-acute (less than 3 months) phase (Hier et al., 1983; Farnè et al., 2004). However, in more than 25% of cases, neglect may persist up to several years and it has been shown to be associated with poor functional and motor outcome (Farnè et. al., 2004; Pantano et al., 1996).

Therefore, in the past few years, several rehabilitation approaches have been attempted to recover neglect. Some procedures, based on bottom-up mechanisms, such as sensory stimulation (vestibular, optokinetic, transcutaneous, proprioceptive) able to enhance the representation of the contralesional space (Cappa, Sterzi, Vallar & Bisiach, 1987; Frassinetti, Rossi & Làdavas, 2001; Karnath, Christ, & Hartje, 1993; Làdavas, Berti, Ruozzi, & Barboni, 1997a; Pizzamiglio et al., 1990; Robertson & North, 1993; Rubens, 1985; Vallar et al., 1990) produced a general amelioration of both sensory and motor neglect symptoms. However, in most cases only a single application of these sensory manipulations was used and consequently their benefits lasted only a few minutes (see Kerkhoff, 2003 for a review). On the other hand, other treatments, based on top-down mechanisms, tried to train the patient to voluntarily direct attention to the neglected side of space (Antonucci et al., 1995; Diller & Weinberg, 1977; Làdavas, Carletti, & Gori, 1994; Pizzamiglio et al., 1992). These approaches produced more prolonged effects, but few studies tested the generalisation of the improvement to tasks and sensory modalities not directly trained during treatment (see Robertson & Halligan, 1999 and Kerkhoff, 2003 for comments).

Another approach that has recently been shown to be effective in improving neglect is the adaptation to a rightward deviation of the visual field induced by a prismatic lens. Neglect patients, exposed to a single session of prism adaptation (PA), which consists of a short series of pointing movements towards a visual target while wearing prismatic goggles, showed an improvement that generalised to several visual-spatial attention tasks. Indeed, after PA, an amelioration was shown in tasks performed with the hand used during PA, such as cancellation tasks, line bisection or drawing, and also in visuo-spatial tests not requiring a motor response, such as reading and mental imagery tasks (Farnè, Rossetti, Toniolo, & Làdavas, 2002; Rode, Rossetti, Li, & Boisson, 1998; Rossetti et al., 1998), and in ecological tests assessing patients' difficulties in everyday life, such as picture scanning, telephone dialling, coin and card sorting tests (Frassinetti et al., 2002). Importantly, Frassinetti et al. (2002) demonstrated that the amelioration lasted up to five weeks after the administration of an extended intensive treatment, based on twice-daily sessions of PA for a period of two weeks. Moreover, it has recently been shown that the amelioration of neglect induced by PA is not restricted to visual function, but extended to other modalities, since an amelioration of tactile inattention (Maravita et al., 2003) and of patients' postural imbalance (Tilikete et al., 2001) was demonstrated after a single PA session. These findings suggest that the visuo-motor reorganisation induced by PA can influence high-level multimodal spatial representation and therefore indicate a potential role of PA in rehabilitating multiple aspects of neglect.

Therefore, in the present study, the effectiveness of a neglect treatment based on PA was studied with three main aims. The first aim was to assess the duration of the treatment's beneficial effects and, in particular, to investigate whether the improvement persists six months after the end of the treatment. The second aim was to investigate whether the treatment effects were generalised to different visuo-spatial functions, different portions of the space and different sensory modalities. In particular, the effect of PA was tested on patients' visual exploration, internal visuo-spatial representation, neglect dyslexia and visuo-spatial competencies in everyday life situations. The effect of PA was also investigated in tasks involving the exploration of the extrapersonal and personal space. Finally, the hypothesis that PA affects multimodal spatial representation was studied by testing the amelioration in sensory domains different from vision, namely in the somatosensory modality, i.e., touch and proprioception, and in motor domain. The third aim was to study patients' responsiveness to the treatment. Indeed, previous studies showed that some neglect patients seem not to benefit completely from PA treatment (Dijkerman et al., 2003; Ferber et al., 2003; Frassinetti et al., 2002; Morris et al., 2004; Pisella et al., 2002). Recent data from our laboratory show that **Q3** patients' recovery after PA treatment correlates with patients' ability to compensate the optical displacement induced by prismatic lenses (Serino, Angeli, Frassinetti, & Làdavas, 2005). In particular, PA induces a visuo-motor deviation of manual responses during pointing movements in order to compensate the rightward optical displacement induced by the prismatic lens. Pointing deviation consists of a correction of pointing errors during prism exposure (the so-called adaptation effect) and in a subsequent leftward deviation of pointing after prism exposure (after-effect; Held & Gottlieb, 1958; Redding & Wallace, 1993). Our previous work demonstrated that the level of adaptation effect obtained in the first week of treatment was positively related to neglect improvement. In contrast, the measure that has been traditionally considered crucial to demonstrate PA, the so called after-effect, did not correlate with neglect amelioration. In the present study, we directly tested the hypothesis that the index of adaptation effect can discriminate patients who benefit from patients who do not benefit from PA treatment.

Moreover, it is possible that, due to hand–eye co-ordination, the leftward deviation of hand movements is also accompanied by a leftward deviation of eye movements, since Angeli, Benassi, and Làdavas (2004) showed that a single session of PA induced a leftward deviation of patients' oculomotor responses (see also Ferber et al., 2003). Therefore, it is possible to hypothesise that the index of adaptation to prism can also predict the effect of the treatment on the oculomotor system. Finally, long-lasting effects of PA on eye movements was also investigated at different intervals after the end of the treatment.

To study these issues, 21 neglect patients were submitted to a rehabilitative programme similar to that used by Frassinetti et al. (2002), for 10 daily sessions over a period of two weeks. First, to test the duration of PA effects, patients' visuo-spatial abilities were assessed before the treatment, one week, and one, three and six months after the end of the treatment. Only chronic patients, i.e., those recruited at least three months after the cerebral accident, were included in the study. Moreover, to study the generalisation of the treatment effects, neglect was tested in conventional paper-and-pencil visuo-spatial tests – Conventional Scale of the Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), Bell Cancellation Test (Gauthier, Dehaut, & Joanette, 1989), in ecological tasks (BIT, Behavioural Scale and Room Description Task), in a reading task (Làdavas, Shallice, & Zanella, 1997b) and in a test assessing personal neglect (Fluff Test, Cocchini, Beschin, & Jehkonen, 2001). The presence and the duration of PA effects on tactile attention, proprioception and motor function were studied by means of a tactile extinction test, a test assessing proprioceptive sensitivity and the Motricity Index (Demeurisse, Demol, & Robaye, 1980). To demonstrate the beneficial effect of PA on the oculomotor responses, patients' eye movements were recorded at different intervals before, immediately after and one month after the treatment. Finally, to study whether visuo-motor correction of pointing movement in order to compensate for prism optical displacement was predictive of neglect and oculomotor system amelioration, patients were divided into two groups according to the level of adaptation achieved in the first week of PA. If adaptation effect is a crucial factor in determining the effectiveness of the treatment, the group of patients showing poor adaptation should also demonstrate less improvement of neglect. Moreover, if adaptation effect mediates the amelioration of the oculomotor system, then the group of patients with worse adaptation effect should also show less eye movement improvement after the treatment. In contrast, previous results showed less variability on the measures of after-effect assessed during the first week of PA, indicating that all patients reached about the same level of after-effect in the first week of treatment (Serino et al., 2005). Therefore, we expect after-effect not to be predictive of patients' recovery. To directly test this prediction, subjects were divided in two groups according to the level of after-effect achieved during the first week of treatment, and then neglect and oculomotor recovery was compared between the two groups.

METHODS

Subjects

Twenty-one right-brain-damaged patients with chronic left hemispatial neglect participated in the study. They gave their informed consent to participate according to the Declaration of Helsinki and the local ethical committee.

All patients had unilateral lesions due to a cerebrovascular accident, confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan. The location and the extension of patients' brain lesions were established on the basis of their 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, six in the parietal lobe, seven in the occipital lobe and four sub-cortical structures (two 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 16 patients, since CT/MRI scans of five patients were not available for the analysis. In addition, the presence of visual field deficits was clinically evaluated by means of visual confrontation task. Gender, age, education, length of illness, lesion site, and presence of left hemianopia 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 Scale, see below).

Neuropsychological assessment

All patients underwent a standardised battery of tests for visuo-spatial deficits (BIT, Wilson et al., 1987), the Bell Cancellation Test (Gauthier et al., 1989), a

TABLE 1
Summary of patients' clinical and demographic data

Patient	*Gender*	*Age (years)*	*Education (years)*	*Onset of illness (months)*	*Lesion site*	*BIT-C (cut-off = 129)*	*BIT-B (cut-off = 67)*	*Left visual field deficits*
P1	M	54	13	5	F-T-P-O	117	72	+
P2	M	65	5	3	F-T-P-O-BG-IC	68	32	−
P3	M	64	5	3	F-T-P-O	122	59	−
P4	F	64	5	5	F-T-P-O	106	40	+
P5	M	71	5	3	F-T-P-O	109	38	+
P6	F	69	5	3	F-T-P-O	63	24	+
P7	M	50	8	30	F-T-P-O-BG-IC-Th	83	45	+
P8	M	69	13	14	F-T-P-O-BG-IC	122	68	−
P9	F	80	5	18	F-T-P-BG-IC	74	42	−
P10	M	78	13	3	NA	109	58	−
P11	M	74	8	15	F-T-P-O-BG	55	34	+
P12	F	59	5	72	NA	111	64	−
P13	F	80	12	3	IC	126	70	−
P14	M	73	5	7	F-T-P-O-BG-IC	127	53	+
P15	F	67	3	3	F-T-P-BG-IC	104	29	−
P16	F	41	8	96	F-P-O	95	65	NA
P17	F	77	5	3	F-T-P-O	106	24	NA
P18	M	75	8	10	F-T	113	56	−
P19	F	73	3	8	T-P-O	76	56	+
P20	M	65	13	3	BG	94	58	−
P21	F	58	5	3	NA	123	41	−

Lesion site column reports the cortical and sub-cortical structures involved by the lesion, as shown by reconstructions obtained following the method of Damasio and Damasio (1989): F = frontal; T = temporal; P = parietal; O = Occipital; IC = Internal capsule; BG = Basal ganglia; Th = Thalamus. Columns 7 and 8 report patients' results in visuo-spatial neglect scales: BIT-C = Behavioural Inattention Test, Conventional Scale; BIT-B = Behavioural Inattention Test, Behavioural Scale. The last column indicates the presence of left hemianopia: + and − = presence or absence of hemianopia, respectively; NA = data not available.

room description test (see Frassinetti et al., 2002), a reading test (Làdavas et al., 1997b), the Fluff Test (Cocchini et al., 2001), a clinical test for tactile extinction, a scale for proprioceptive sensibility and a standardised mobility scale (Motricity Index, Demeurisse et al., 1980). The neuropsychological evaluation was performed five times. The first screening assessment (session 1) was to verify the presence and amount of neglect-related deficits before the treatment and the remaining sessions were performed 1 week (session 2), 1 month (session 3), 3 months (session 4) and 6 months (session 5) after the end of the treatment. Data from session 5 were available only for 9 out of 17 experimental patients; the remaining patients were unavailable for the six month follow-up.

BIT

The BIT is a battery of tests for spatial deficits and is composed of two scales, the Conventional Scale and the Behavioural Scale. The Conventional Scale includes letter and star cancellation tasks, figure and shape copying, line bisection and drawing from memory. The Behavioural Scale includes tests that 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 or cards, copying addresses or sentences and map navigation. Patients were classified as having neglect when their score in one of the two scales was below the cut-off score of 129 (range 0–146) for the Conventional Scale and 67 (range 0–81) for the Behavioural Scale.

Bell cancellation test

Patients were asked to cross out bells printed, along with other objects, on a sheet of A4 paper (17 targets on the left and 17 on the right side of the paper); the proportion of correct responses was recorded.

Room description test

A room (3.6 m $\times$ 2.2 m) was equipped with various items arranged on the left (7 items) and on the right (7 items) of the room's midline. Patients were seated in the centre of the room with their back to an empty wall. On a table, placed in the centre of the room in front of the patients, there were 4 objects, 2 on the left and 2 on the right. Along the left and the right walls, 5 items were aligned (e.g., a door, a chair, a cupboard, a wastepaper basket and a fire extinguisher). Patients were asked to name the items seen in the room for a period of 2 minutes. The proportion of correct responses was recorded.

Reading test

Stimuli were 55 Italian concrete words, of at least three syllables and 55 legal non-words, obtained by substituting two letters at the beginning and at the end of the letter string. The length of the stimuli was 6 letters (10 stimuli), 7 letters (16 stimuli), 8 letters (34 stimuli), 9 letters (22 stimuli), 10 letters (18 stimuli) or 11 letters (10 stimuli). The stimuli, printed in upper-case 18-point Palatino font, were located on the centre of an A4 piece of paper and presented horizontally one at a time. The patients were instructed to read the letter string aloud. Omitting or misreading one or more letters was considered to be an error for the whole letter string. The proportion of correct responses was recorded.

Fluff test

Patients were seated and blindfolded while six pieces of adhesive paper were attached by the experimenter to their clothing on the left part of their body (chest, shoulder, elbow, wrist, knee and hip). Patients were asked to remove all the paper pieces in 2 minutes. The task was performed in two conditions: non-visual and visual, i.e., with the patient being blindfolded or not during the execution of the task, respectively. The proportion of pieces removed was recorded.

Tactile extinction test

Patients, seated and blindfolded, placed their hands on a table while an experimenter manually produced a light tactile stimulus on the dorsum of their left, right or both hands (10 trials each). Ten catch trials (no stimulation) were also intermingled. Patients were asked to verbally report their perception on each trial ("left", "right", "both", or "none"). The proportion of correct responses was recorded.

Proprioceptive scale

Patients were seated in their wheelchair and they were blindfolded. The experimenter placed and maintained the patients' left arm in a specific position: patients had to place their right arm in the same position as they perceived their left arm. The proprioceptive sensitivity was assessed for four different body parts, i.e., the shoulder (4 lateral and 4 frontal positions), the wrist (3 positions), the hand (4 positions) and the fingers (3 positions). The experimenter ranked the patients' performance according to the difference between the left and the right arm position on a 4-point scale: 1 = maximum position error (i.e., 60° or 180° of displacement depending on the motility of the body part) and 4 = correct position.

Motricity index

The Motricity Index is a measure of motor impairment of the trunk and of the right and left sides (upper and lower limb). Each component part of the Index, scored 0–100, expresses the strength of the part of the body that was evaluated.

Assessment of eye movements

Patients underwent recording of eye movements during a reading task before and after PA. For six patients, eye movements were also assessed at a third and a fourth follow-up session performed at 1 and 3 months after the end of the treatment.

Apparatus. Patients were seated in a dimly illuminated room with their head stabilised 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 by a PC using custom software and displayed on a 15 inch 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 40 cm. Horizontal eye movements were monitored using an infrared corneal reflection oculometer (Dr Bouis Instruments, Germany) positioned in front of the patient's left eye. The eye movement tracker had high resolution (about 5 min of arc) and its output was linearly related to eye position within an area of approximately 19.3° of visual angle (both horizontally and vertically). The analogue eye movement signals were sampled at 500 Hz, digitised by a lab-driver interface and stored on a hard disk for off-line analysis.

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 $\times$ 0.7 cm; $1^\circ \times 1^\circ$) separated by a single character space (0.7 cm $\times$ 0.7 cm; $1^\circ \times 1^\circ$). 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 according the criteria described for the Reading Test. Word and non-word stimuli were presented in four separate counterbalanced blocks of 12 trials each.

Calibration. Eye-position signals were calibrated before each trial. To this end, patients 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 asking the patients to fix their gaze at the central cross. Patients were then asked to fix their gaze on the centre of each of the two squares by tracking a pen that was moved from the central cross to the position of each square. Once the calibration was completed, the trial was started.

Reading Task. A fixation cross was presented in the centre of the video screen. When patients appeared to be correctly fixating the stimulus, the experimenter pressed a button to initiate the display. The central cross was then extinguished and, after 100 ms, the stimulus was displayed for a maximum of 4000 ms. Patients had to look at the string and report verbally what they read. If patients 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 patients were requested to refrain from blinking during the recording period. Trials presenting blinks were discharged from the analyses (less than 10% of trials).

Off-line analysis of eye movement recording. Two main parameters were considered as indices of eye movement responses: the 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 into the left vs. right hemispace. 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 patients approximately 100 ms post-stimulus onset in the 48 trials. These values were transformed in degrees of displacement from the fixation point fixed at the centre of the letter string, considering that at a distance of 40 cm from the subject, each letter was separated by 2° of visual angle. 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 on the middle of the letter string was coded as centre and all letters on the left and on the right of centre were classified as left and right, respectively. The proportion of the time spent on the centre, on the left and right of the letter string was calculated and the difference between the proportion of time spent on the left and right hemispace was taken as a measure of spatial distribution of exploration time. This was because Di Pellegrino, Làdavas, and Galletti (2001) showed that this parameter is the factor that better predicts the probability of reporting left-sided letters in neglect patients rather than the absolute time spent on the left or right side.

Rehabilitation procedure

Patients were seated at a table. In front of them on the table 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 the 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 $+21^\circ$, respectively).

The experimenter recorded the patient's pointing spatial accuracy as the distance between the target position and the final position of the patient's finger, expressed in degrees and coded 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. The patient's pointing arm movement was executed below the top face of the wooden box whose size varied depending on the experimental conditions (see below) in order to vary the visual feedback. Once the experimenter had recorded the patient's pointing performance, the patient retrieved the arm and prepared for the next trial. Patients underwent the treatment in 10 sessions, 1 a day, which took about 20 minutes each, over a period of 2 weeks. The pointing task was performed in three experimental conditions: Pre-exposure condition (visible and invisible pointing), exposure condition (visible pointing) and post-exposure condition (invisible pointing).

Pre-exposure condition

Patients were required to point their right index finger towards 60 targets randomly presented at one of three possible positions (20 targets in the centre, 20 on the right and 20 on the left). Patients performed half of the trials with visible pointing, i.e., pre-exposure with visible pointing condition, which was the baseline for the exposure condition, and half with invisible pointing, i.e., pre-exposure with invisible pointing condition, which was the baseline for the post-exposure condition.

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 with their right finger to 90 targets presented in a random order in each of the possible positions (30 targets in 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 top face of the box (visible pointing).

Post-exposure condition

Immediately after removal of the prism, patients were required to point towards 30 targets (10 in 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 before the treatment.

Pointing task results

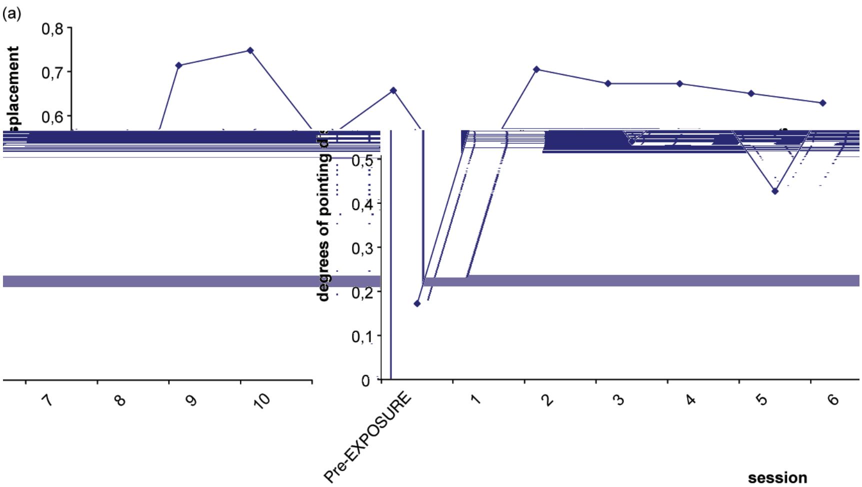
To demonstrate that neglect patients were able to adapt to the prism, the presence of adaptation and after-effect was tested. To this aim, pointing displacement in the exposure and post-exposure condition was compared with pointing displacement in the pre-exposure condition. In particular, if patients were able to compensate to the rightward optical displacement induced by the lens during prism exposure (adaptation effect), no difference should be found between pointing displacement in the pre-exposure and exposure conditions. Moreover, as a consequence of adaptation to the prism, a systematic leftward deviation of pointing should be found in the post-exposure condition compared with the pre-exposure condition (after-effect).

To test these predictions, two ANOVAs were performed on visible and invisible pointing errors, to assess adaptation and after-effect, respectively, with Session as main factor with 11 levels (pre-exposure condition and 10 PA sessions).

When visible pointing was considered, the difference of pointing displacement among different sessions was not significant. This suggests that the mean of pointing displacement in the pre-exposure condition (0.17°) did not differ from that in the 10 sessions of the exposure condition (mean of displacements = 0.64°) (see Figure 1A). This finding means that during each PA session patients were able to correct their pointing performance to compensate for the prism optical deviation, that is, adaptation effect. When invisible pointing was considered, the main effect of Session was significant, $F(10,190) = 8{,}63$; $p < .0001$, and post-hoc comparisons showed the presence of a leftward deviation of pointing in the 10 post-exposure condition sessions (mean of displacements = −3.3°) compared to the pre-exposure condition (−0.3°) (see Figure 1B). This finding means that, after prism adaptation, a systematic leftward deviation of pointing was achieved, that is, an after-effect.

RESULTS

The results showed a consistent neglect amelioration that lasted up to six months after the end of the treatment with PA. The improvement was



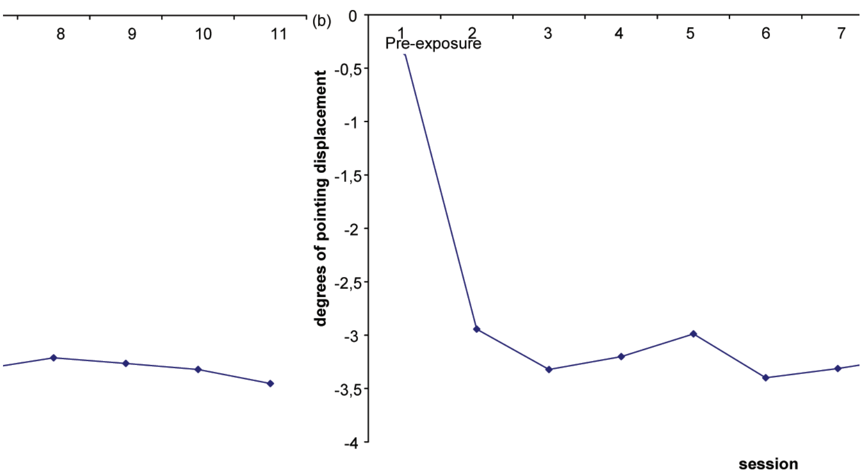


Figure 1. Adaptation (Figure 1(a)) and after-effect (Figure 1(b)) over two weeks of prism treatment. Mean displacement (expressed as visual angle) of the patients' visible (A) and invisible (B) pointing responses in the Pre-Exposure condition and in the 10 sessions of Exposure (a) and Post-exposure (b) conditions.

found for visuo-spatial abilities, as assessed both by conventional (BIT Conventional and Cancellation tasks) and behavioural tasks (BIT Behavioural and Room description), and for neglect dyslexia (Reading Test). The benefits were also generalised to the exploration of personal space (Fluff Test), to the oculomotor system's responses (first saccade amplitude and space exploration time), and to tactile attention (tactile extinction test), whereas no effect was found in proprioceptive sensitivity (Proprioceptive Scale) and motor functions (Motricity Index). Finally, patients showing poor adaptation to prismatic optical displacement during the first week of PA also showed less amelioration of neglect and eye movement recovery. This pattern of results is supported by statistical analyses: ANOVAs were performed on patients' results in the different sessions, taking Session as within-subject factor (session 1, 2, 3 and 4). Because only 9 of 21 experimental patients attended session 5, successive analogue ANOVAs were performed on these patients' scores only, taking Session as within-subjects factor (session 1, 2, 3, 4 and 5). When necessary, pairwise comparisons were conducted with the Newman-Keuls Test. The level of significance was always set at .05. The results of the ANOVAs are presented below.

Visuo-spatial tests

BIT

The ANOVA performed on BIT Conventional scores showed a significant effect of Session, $F(3,60) = 21.93$; $p < .00001$. Post-hoc comparisons showed an amelioration of BIT Conventional scores when the scores obtained in session 1 (100) were compared with those of session 2 (122, $p < .0002$), session 3 (126, $p < .0002$), and session 4 (123, $p < .0002$). The ANOVA including data from session 5 confirmed the persistence of the benefits at 6 months from the end of the treatment: Session was significant, $F(4,32 = 7$, $p < .0004$, and post-hoc comparisons showed an amelioration of patients' BIT Conventional scores when session 1 (102) was compared with session 2 (119, $p < .05$), session 3 (129, $p < .0006$), session 4 (126; $p < .003$), and session 5 (130, $p < .0004$) (see Figure 2A).

The ANOVAs performed on BIT Behavioural scores showed quite similar results. The main effect of Session, $F(3,60) = 23.56$; $p < .00001$, was significant. Post-hoc comparisons showed an amelioration of patients' BIT Behavioural scores when results of session 1 (49) were compared with those of session 2 (62, $p < .0002$), session 3 (65, $p < .0002$), and session 4 (63, $p < .0002$). The ANOVA, including data from session 5, confirmed the maintenance of treatment effects: the effect of Session, $F(4,60) = 6.86$; $p < .0002$ was significant. Post-hoc comparisons showed an improvement in patients' scores between session 1 (48), session 2 (65, $p < .0002$), session 3 (68, $\text{p} = 0.0002$), session 4 (66, $p < .0002$), and session 5 (64, $p < .0003$) (see Figure 2B).

Cancellation tasks

In order to demonstrate the effects of PA on traditional cancellation tests, an ANOVA was performed on the proportion of correctly crossed out items in

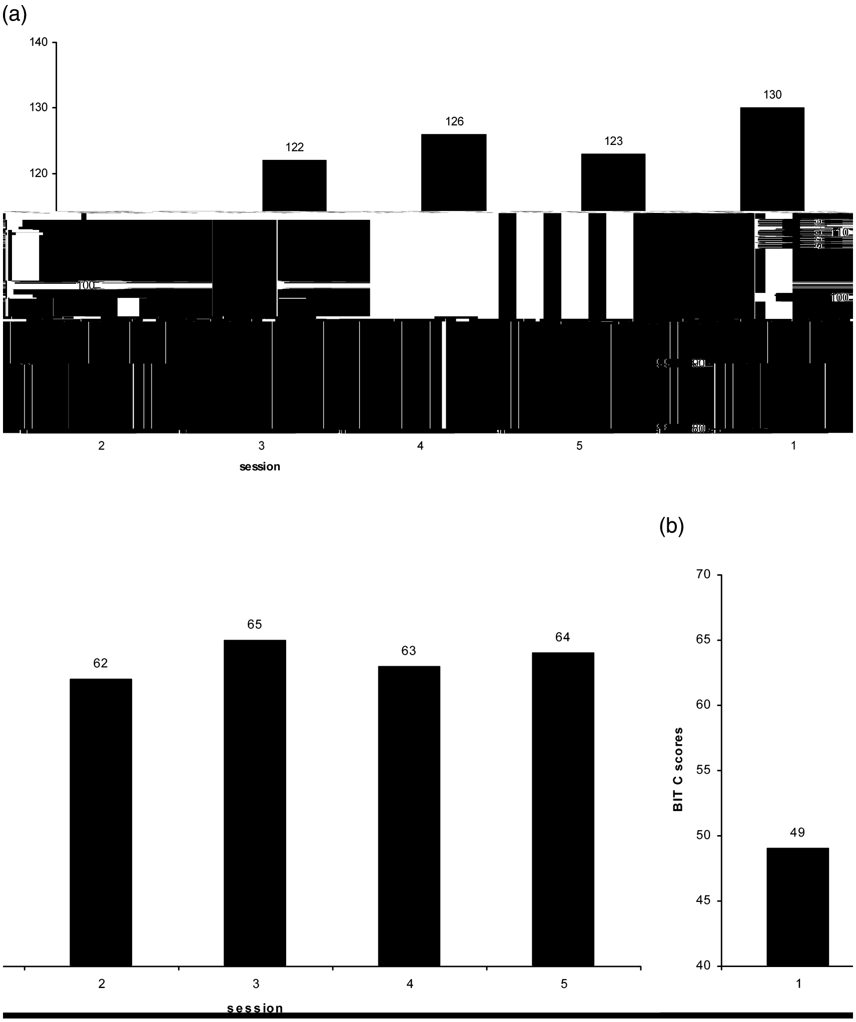


Figure 2. Long term effect of prism treatment on patients' performance in the BIT battery. Patients' scores in the BIT Conventional (Figure 2a) and BIT Behavioural (Figure 2b) scales are reported as a function of time: Before the treatment (session 1) and one week, and one, three and six months after the treatment (session 2, 3, 4 and 5, respectively). Data from session 5 were available for 9 patients.

the Bell, Letter and Star Cancellation Tests, taking Side (left and right), Test (Bell, Letter and Star Cancellation) and Session (session 1, 2, 3, 4) as within-subjects factors. The main effects of Side, $F(1,20) = 32.5$; $p < .00004$, Test, $F(2,40) = 7.55$; $p < .002$, and Session, $F(3,60) = 22.7$; $p < .000001$, were significant. More importantly, the interaction Session × Side, $F(3,60) = 9.89$; $p < .0003$, was significant. Post-hoc comparisons showed an increase of correct responses for left-sided stimuli between session 1 (46%), session 2 (69%, $p < .0002$), session 3 (77%, $p < .0002$), and session 4 (73%, $p < 0.0002$). A less important difference was also found for right-sided stimuli between session 1 (81%), session 2 (91%, $p < .003$), session 3 (93%, $p < .0009$),and session 4 (92%, $p < .002$). When the ANOVA was conducted including the scores from session 5, quite similar results were obtained. Post-hoc comparisons performed on the interaction Session × Side, $F(4,28) = 5.93$; $p < .002$, confirmed the increase of correct responses for left-sided stimuli between session 1 (47%), session 2 (64%, $p < .02$), session 3 (79%, $p < .0002$), session 4 (75%, $p < 0.0002$), and session 5 (86%; $p < .0002$) (see Figure 3A).

Room description test

Room Description Test results were available for 15 out of 21 patients. In order to demonstrate the effect of PA on the ecological task, an ANOVA was performed on the proportion of correct responses in the room description task, taking Session (sessions 1, 2, 3, and 4) and Side (left and right) as within-subjects factors. The results showed a significant effect of Side, $F(1,15) = 5.62$; $p < .04$, and Session, $F(3,45) = p < .003$. More importantly, the interaction Session × Side, $F(3,45) = 2.61$; $p < .04$, was significant. Post-hoc comparisons showed that the proportion of correct responses for left-sided items increased between session 1 (80%), session 2 (96%, $p < .03$), session 3 (96%, $p < .03$), and session 4 (99%, $p < .02$). No difference was found for right-sided correct responses (96%, 99%, 99%, 100%). (see Figure 3B).

Reading test

To verify the effect of PA on neglect dyslexia, an ANOVA was performed on the proportion of correct responses in the Reading Test, with Session (session 1, 2, 3, and 4) and Lexicality (words and non-words) as within-subjects factors. Lexicality, $F(1,20) = 51.36$; $p < .00001$, and Session, $F(3,60) = 19.95$; $p < .000001$, were significant. Patients' accuracy improved between session 1 (70%), session 2 (86%, $p < .0002$), session 3 (87%, $p < .0002$), and session 4 (87%, $p < .0002$). Quite similar results were obtained by the ANOVA performed on data collected after 6 months from the end of the treatment, and in particular post-hoc comparisons performed on Session, $F(4,32) = 5.03$; $p < .002$, showed that the amelioration of reading accuracy from session 1 (72%) to session 2 (92%, $p < .0002$), session 3 (92%, $p < .0002$), and session 4 (90%, $p < .0002$) persisted also in session 5 (92%, $p < .0002$) (see Figure 4A).

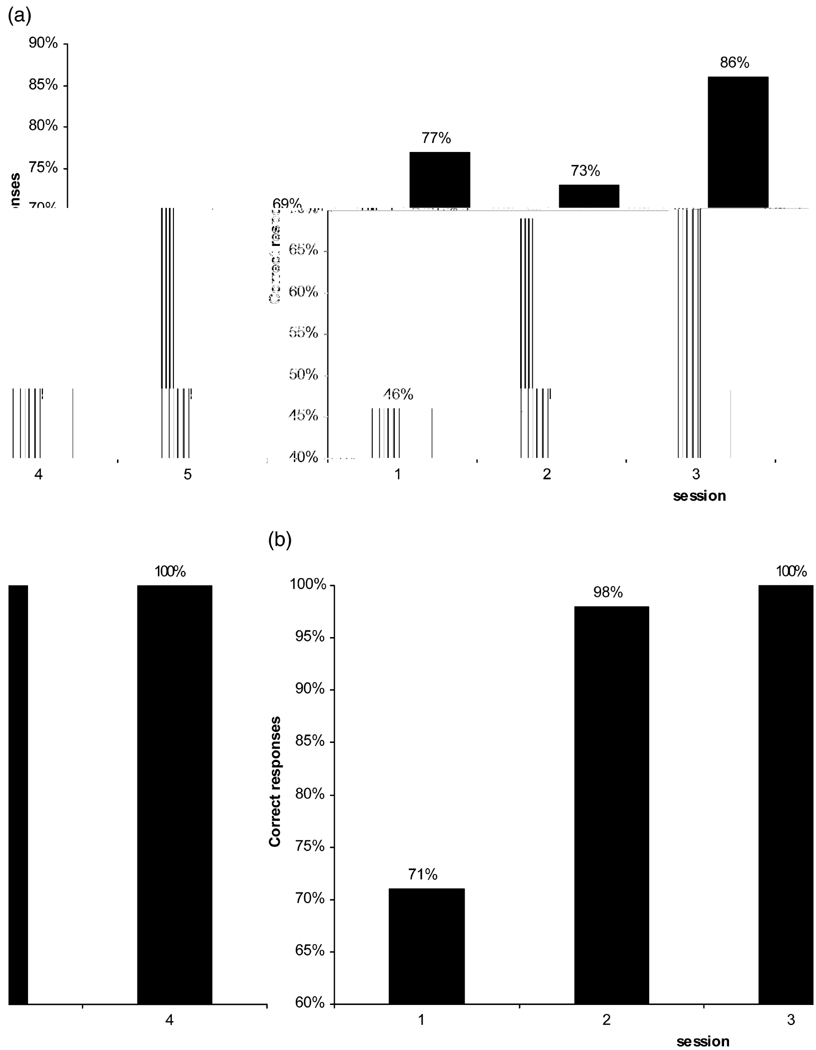


Figure 3. Long-term effect of prism treatment on patients' performance in cancellation (Figure 3a) and room description (Figure 3b) tasks. Percentages of correct responses to left-sided stimuli are reported as function of time: Before the treatment (session 1) and one week, and one, three and six months after the treatment (session 2, 3, 4 and 5, respectively). Data from session 5 were available for 9 patients.

Neglect for personal space

In order to demonstrate that PA can also improve neglect for personal space, an ANOVA was performed on the proportion of correct responses in the Fluff Test taking Session (session 1, 2 3, and 4) and Condition (visual and

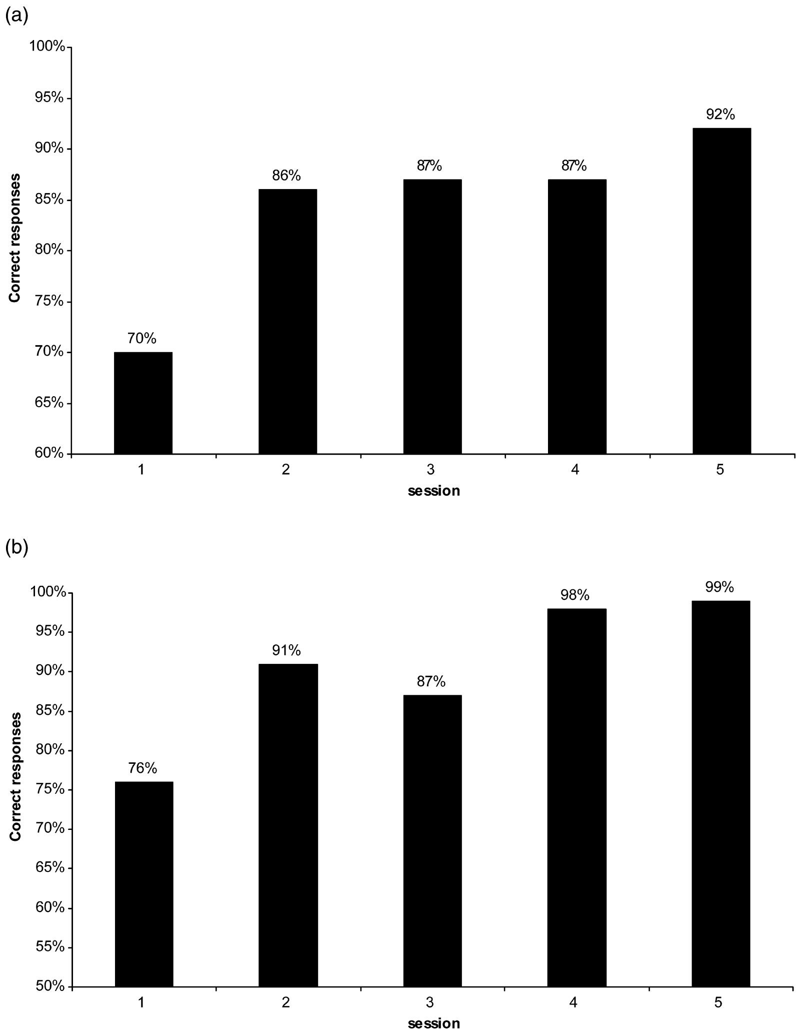


Figure 4. Long-term effect of prism treatment on neglect dyslexia (reading accuracy, Figure 4a) and personal neglect (Fluff Test, Figure 4b). Percentages of correct responses are reported as function of time: Before the treatment (session 1) and one week, and one, three and six months after the treatment (session 2, 3, 4 and 5, respectively).

non-visual) as within-subjects factors. Only patients who presented personal neglect (i.e., $< 100\%$ of correct responses in session 1) were included in the analysis (11 patients). The main effect of Session, $F(3,30) = 7.87$; $p < .0006$, and Condition, $F(1,10) = 33.27$; $p < .0002$, were significant. Patients were more accurate in visual than non-visual conditions. More importantly, an increase of correct responses between session 1 (76%), session 2 (91%, $p < .02$), session 3 (87%, $p < .04$), and session 4 (98%, $p < .0002$) was found. Analogous results were obtained when data collected 6 months after the treatment were considered (data available for 8 patients): the effect of Session was significant, $F(4,28) = 26.87$; $p < .0001$, and post hoc analyses demonstrated an improvement of patients' scores from session 1 (74%) to session 2 (93%, $p < .0002$), session 3 (97%, $p < .0002$), session 4 (99%, $p < .0002$), and session 5 (99%, $p < .0002$) (see Figure 4B).

Effect of PA in other domains

Tactile modality

To demonstrate that PA has an effect also on tactile modality, patients' performance on a tactile extinction test was analysed with the following prediction: if PA is efficacious in ameliorating tactile inattention a specific improvement in the perception of bilateral stimuli should be achieved after PA. To this aim, an ANOVA was performed on the proportion of correct responses with Session (session 1, 2, 3, and 4) and Stimulus (unilateral left and bilateral) as within-subject factors. Unilateral right-sided stimuli were not considered in the analysis because patients always responded correctly (100 % of correct responses). Patients presenting no sensation on the left hand (i.e., obtaining 0% of correct responses at unilateral left stimulation) or absence of tactile extinction (i.e., 100% of correct responses at bilateral stimulation) were excluded from the analysis: 13 patients were included. The main effects of Session, $F(3,36) = 7.30$, $p < .0007$, and Stimulus, $F(1,12) = 42.10$, $p < .00003$, were significant. More importantly, the interaction Session $\times$ Stimulus was significant, $F(3,36) = 5.31$, $p < .004$: post-hoc comparisons showed an amelioration of the performance in bilateral stimulation between session 1 (13%), session 2 (47%, $p < .0002$), session 3 (42%, $p < .0002$), and session 4 (44%, $p < .0002$).

Proprioceptive modality

An ANOVA was performed on patients' scores on the proprioceptive scale, with Session (session 1, 2, 3, and 4) and Body part (shoulder, wrist, hand, and fingers) as within-subject factors. Only patients who presented some proprioceptive deficits (i.e., score < 4) were included in the analysis (7 patients). None of the main effects was significant.

Motor functions

An ANOVA was performed on patients' scores at the Motricity Scale with Session (session 1, 2, 3, and 4) and Body part (left, right hemisoma and trunk) **Q4** as within-subjectss factors. Only patients presenting a motor deficit (i.e., score < 100) were included in the analysis (12 subjects). Body part was significant, $F(2,22) = 19.78$; $p < .00002$: not surprisingly, scores for the left hemisoma (38) were worse than those for the right hemisoma (95, $p < .0002$) and the trunk (64, $p < .01$); scores for the trunk were worse than those for the right hemisoma ($p < .003$). Session and the interaction Session $\times$ Body part were not significant, thus indicating no amelioration in motricity scores after PA.

Oculomotor system

To demonstrate an effect of PA on the oculomotor system, two analyses were conducted on the first saccade amplitude (first saccade landing location) and on the space distribution of exploration time, expressed as left–right fixation time difference. Moreover, to demonstrate that the improvement in oculomotor responses was associated with an amelioration of the behavioural performance, the same analysis was also conducted on the patients' reading accuracy during eye movement recording.

Eye movement recording before and after treatment was performed on 14 patients, whereas a follow-up assessment was performed 1 month after the treatment on 8 subjects. Thus, initially only data collected in session 1 and session 2 were compared by means of a paired t-test. As far as the amplitude of first saccade is concerned, the first saccade landing location in session 1 fell close to the middle of the letter string (mean deviation: -0.58°) whereas in session 2 (i.e., after PA) it was displaced more towards the left (-2.05°), $t(1,13) = 18.36$, $p < .0009$. When the space distribution of exploration time was considered, the left–right fixation time difference varied between session 1 (0.16) and session 2 (0.28), $t(1,13) = 18.79$; $p < .0009$. These effects were associated with an improvement in performance of the reading task during eye movement recording; reading accuracy improved between session 1 (31%) and session 2 (48%), $t(1,13) = 12.30$; $p < .004$.

To assess the duration of the beneficial effects of the treatment on eye movements, additional data collected at 1 and 3 months from the end of the treatment (data available for 6 subjects) were analysed by means of three ANOVAs with Session (with four levels, i.e. session 1, 2, 3, and 4) as main factors. When the amplitude of the first saccade was considered, only a significant effect of Session was found, $F(3,15) = 28.95$; $p < .00001$, and post-hoc analyses demonstrated that the improvement achieved by patients in session 2 (-2.35°; $p < .0003$) compared to session 1 (-0.66°) was maintained in session 3 (-2.11°, $p < .0003$) and session 4 (-2.67; $p < .0003$). An analogous result was obtained when the space exploration time was analysed: the main effect of Session was significant, $F(3,15) = 4$; $p < .04$, and post-hoc tests showed that the left–right difference increased from session 1 (0.42) to session 2 (0.53; $p < .05$), session 3 (0.60; $p < .04$), and session 4 (0.62; $p < .04$). Finally, the amelioration of reading performance was long lasting, since the ANOVA preformed on reading accuracy showed a significant effect of Session, $F(3,15) = 5.34$; $p < .02$: patients' accuracy improved from session 1 (31%) to session 2 (59%; $p < .02$), session 3 (64%; $p < .02$) and session 4 (65%; $p < .03$).

Predictors of recovery

To test whether the level of adaptation after the first week of treatment was predictive of neglect recovery, an index of adaptation during the first week of PA was calculated as the difference between pointing error in pre-exposure and exposure conditions. Data were available for 20 up to 21 subjects. **Q5** Subjects were divided in two groups according to their adaptation index: subjects showing a pointing error exceeding 1° of displacement (i.e., more than 1 standard deviation above the mean of pointing error for the whole group) were considered to show a lack of adaptation effect and they were included in the NA group (5 patients), whereas the other subjects were considered to show a good adaptation and were included in the A group (15 patients). If the level of adaptation in the first week of PA is predictive of neglect recovery, patients included in the NA group should show less amelioration after the treatment than patients in the A group. To test this prediction an index of neglect improvement was calculated as the difference in BIT scores (averaging Conventional and Behavioural scales) obtained before and after PA (d BIT). Then, d Bit scores were compared for the NA and A groups by means of a non-parametric independent sample test (Mann-Whitney). Group A showed a greater improvement at the BIT (d BIT $= 21.8$) than the NA group (d BIT $= 6$; $U = 12$; $p < .03$, Figure 5A).

To test whether the level of adaptation for the first week of PA was also predictive of oculomotor system recovery, A and NA patients were compared as far as the first saccade amplitude was concerned by means of Mann-Whitney test. Eye movement data were available for 10 patients in the A group and 3 patients from the NA group. An index of first saccade displacement was calculated as the difference between the first saccade landing location before and after the treatment (d Saccade). Group A showed a greater leftward deviation of eye movements after the treatment than the NA group (-1.69° and -0.23° of displacement respectively; $U = 3$, $p < .05$, Figure 5B).

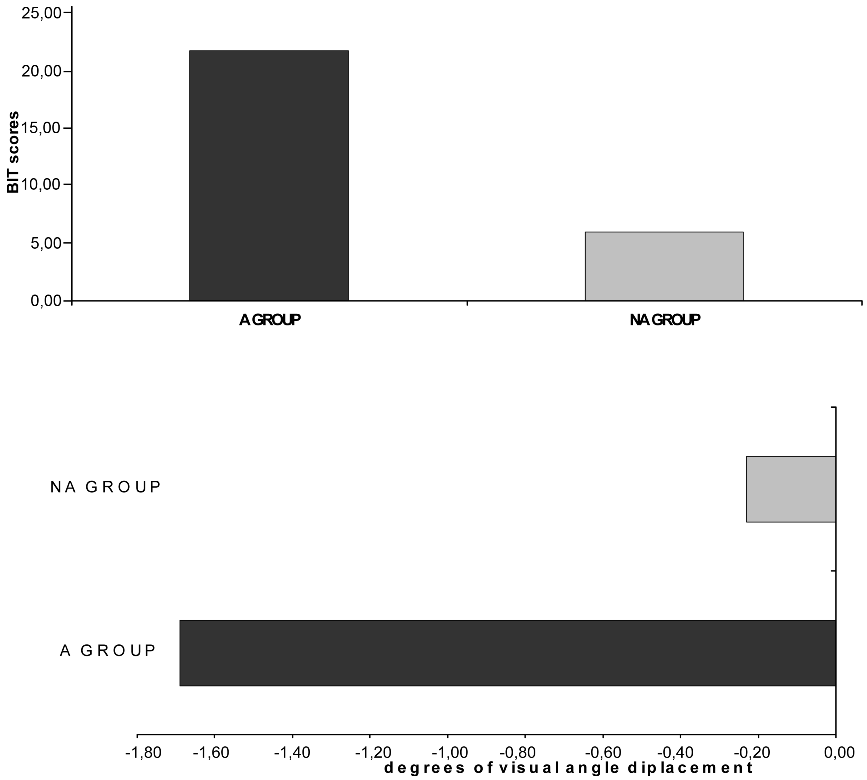


Figure 5. Adaptation effect as predictor of treatment effectiveness. Difference in BIT scores (Figure 5a) and first saccade landing location (Figure 5b) before and after the treatment are reported for Group A (good adaptation effect) and Group NA (poor adaptation effect).

To ensure that the different improvements obtained after the training in the two groups did not actually depend on any other clinical or demographic factors, the two groups were compared for age, education, time from illness, neglect severity and the presence of hemianopia. Mann-Whitney non-parametric testing did not show any difference between the groups for age (group A = 67 years, group NA = 70 years; $p = .67$), education (A = 7 years of schooling, NA = 5 years; $p = .24$), months from illness (A = 6 months, NA = 16 months; $p = .92$), BIT C score (A = 103, NA = 98; $p = .36$) BIT B score (A = 51, NA = 47; $p = .46$). However, a significant difference was found in the proportion of patients affected by visual field deficits in the two groups (Fisher's exact test: $p < .05$): in the NA group, 4 patients out of 5 presented hemianopia, whereas only 3 out of 13 patients in the A group were hemianopic (in A group, visual field assessment was not available for 2 patients). This finding suggests that the presence of a primary visual field deficit can affect patients' ability to adapt to prism optical displacement, thus interfering with neglect recovery.

To investigate whether the different ability to adapt to prisms is related to the dimension of the brain lesion, or to specific lesions in any brain area, the two groups were compared for the total extension of brain lesion and for the extension of the lesion in the frontal, temporal, parietal, or occipital lobe and subcortical regions. To this aim, 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 identified according to the method of Damasio and Damasio (1989). For each patient the proportion of brain damage in each lobe was calculated as the ratio between the number of damaged regions in that area and the total number of regions in the same lobe. Lesion analysis were available for 5 patients from group NA and 12 patients from group A. Mann-Whitney non-parametric testing showed that the total extent of the brain lesions did not differ between the two groups: 32% of brain areas were affected in the A group and 38% in the NA group ($p = -54$). Analogously, A and NA patients were not different in the proportion of damaged structures in frontal (22% and 7%, respectively, $p = .14$), temporal (30% and 41%, $p = .30$), parietal lobe (43% and 67%, $p = .30$) and subcortical regions (35% and 0, $p = .10$). However, a significant difference was found in the proportion of damaged areas in the occipital lobe: 19% of affected regions for group A patients and 60% for NA patients ($p < .04$). This finding suggests that wide lesions in the occipital lobe are associated to a less efficient prismatic adaptation, which leads to a poor neglect recovery.

Finally, to test whether the level of after-effect was also related to neglect recovery, an index of after-effect for the first week of PA was calculated as the difference of invisible pointing displacement in pre- and post-prism exposure conditions for the first week of PA. Patients were divided in two groups according to the index of after-effect: subjects showing a pointing displacement inferior to -2° of displacement (i.e., more than 1 standard deviation above the mean pointing error for the whole group) were considered to show poor after-effect and they were included in NAF group (4 patients), whereas the other subjects, showing good after-effect, were included in AF group (16 patients). AF and NAF groups differed neither in BIT recovery (d BIT = 18 for both groups, $p = .78$) nor in first saccade improvement (d Saccade = -1.16 and -0.60, for AF and NAF, respectively, $p = .17$).

DISCUSSION

The present study was conducted to study the effectiveness of a neglect treatment based on PA with three main aims, i.e., to evaluate the long-term duration of the beneficial effects induced by the treatment, to investigate the generalisation of the amelioration to different spatial, sensory and functional domains, and to find out a possible predictor of neglect recovery by PA. To this end, 21 patients with a right hemisphere lesion and left visuo-spatial neglect were submitted to a rehabilitative treatment with prismatic lenses for 10 daily sessions over a period of 2 weeks, and their performance on visuo-spatial, somatosensory, motor and oculomotor functions was assessed before the treatment and one week, and one, three and six months after the treatment.

As far as the first aim of the study is concerned, the results showed that globally patients obtained a significant amelioration of neglect and this beneficial effect was maintained up to 6 months from the end of the treatment. This finding confirms and extends previous results by Frassinetti et al. (2002), who found an improvement of neglect persisting up to 5 weeks after the PA treatment. A long-term amelioration in visual exploration tasks was also obtained in previous studies (for example, see Pizzamiglio et al., 1992; and Antonucci et al., 1995), using a visual scanning training, but this effect was achieved only after longer periods of training (5–8 weeks of 1 hour daily sessions) and required the patients to be well aware of their deficits. In contrast, the present results indicate that a stable recovery can be obtained with a short period of PA training, i.e., 2 weeks of 20 minutes daily, which, in addition, does not require the patients to voluntarily maintain attention oriented to the affected side.

The second aim of the study was to investigate the generalisation of the improvement to different visuo-spatial functions and to different domains (somatosensory and motor functions) potentially affected by neglect. First of all, the effects of PA were not restricted to tasks performed with the adapted limb, such as cancellation tasks or line bisection, but involved also tasks not requiring a motor response, such as figure scanning and room description, and complex abilities, such as reading functions. Moreover, a similar improvement was also achieved in ecological behavioural tasks, such as dialling a telephone, writing an address, sorting coins, telling and setting the time, etc., suggesting that PA might have also a positive impact on patients' everyday life activities.

Interestingly, the amelioration of neglect was not restricted to spatial functions in the visual modality, but extended to other domains. First of all, PA was effective in ameliorating neglect for personal space, since an improvement of patients' performance in the Fluff Test after the treatment was obtained and maintained in successive follow-up assessments. Importantly, the same effect was achieved both under visual and non-visual conditions, thus suggesting that the amelioration is not only due to an improvement in the patient's visual exploration, but also involves the patient's internal representation of their own body. Concerning somatosensory functions, different results were obtained when touch and proprioception were studied. Indeed an amelioration of tactile attention after PA was found, since experimental patients showed an improvement in the accuracy for bilateral stimuli in a tactile extinction test after the treatment and in the successive follow-up sessions, thus confirming and extending the results by Maravita et al. (2003).

In contrast, PA seems not to be effective in ameliorating proprioceptive sensitivity, since no difference was found on patients' performance assessed before and after the treatment. Moreover, a specific effect of PA on motor functions could not be demonstrated.

Finally, by studying the visuo-motor correction of pointing movement induced by PA it was possible to find out the best predictor of neglect recovery. Indeed, patients who were not able to compensate the optical displacement induced by prismatic lenses during the first week of treatment obtained less improvement of spatial attention after treatment. In contrast, neglect recovery was not different for patients showing good or poor after-effect, thus suggesting that after-effect cannot be considered a good predictor of treatment effectiveness.

The close link between adaptation effect and neglect recovery is important from a clinical as well as a theoretical point of view. Indeed, on the one hand, it might allow clinicians to decide early on whether a neglect patient can or cannot benefit from a treatment based on PA. It is worth noting that patients who showed poor adaptation effect were characterised by more frequent visual field deficits and wider lesions affecting the occipital lobe in comparison with patients exhibiting good adaptation and greater neglect improvement. Therefore, it seems that extensive occipital lesions and consequent hemianopia negatively affect patients' ability to adapt to prisms, and, as a consequence, neglect recovery induced by prismatic adaptation.

On the other hand, the relationship between adaptation effect and neglect amelioration found in the present study suggests a causal link between the effect of PA on visuo-motor and visuo-spatial abilities: the leftward correction of pointing movement is related to the improvement of left-sided spatial representation. We suggest that the link between these two levels of cognitive functioning is mediated by the oculomotor system. Indeed, it is well known that, during pointing response, hand and eye movements are strictly coupled (Buxbaum & Coslett, 1998; Carey, Coleman, & Della Sala, 1997; Neggers & Bekkering, 2000). In addition, single cell recording in the primate demonstrate that oculor-motor maps in different brain regions are modulated by hand movements (Mushiake, Fujii, & Tanji, 1996; Stuphorn, Bauswein, & Hoffmann, 2000; Werner, Hoffmann, & Dannenberg, 1997). Moreover, it is well known that neurons in the lateral intraparietal sulcus (LIP) are involved both in programming of saccades (Andersen, Essick, & Siegel, 1987; Colby, Duhamel, & Goldberg, 1996) and in signalling the occurrence of visual events and in attentional shifts (Colby, Duhamel, & Goldberg, 1995; Powell & Goldberg, 2000).

Therefore, it is possible to hypothesise that during PA the leftward deviation of hand movements aimed to compensate the optical displacement also drives a homologous deviation of eye movements and a related attentional shift. Two sets of results in the present work support this proposal. First, patients' eye movements were oriented more towards the left side of the space after the treatment and this oculomotor bias is accompanied by an improvement of attentional performance, as documented by a neglect recovery. Second, this effect was present only in patients who showed a good correction of hand movements during the first week of treatment.

As far as the first result is concerned, it is worth while remembering that patients with severe neglect present a rightward deviation of the eyes (Hornak, 1992) and mild neglect patients make fewer, shorter and delayed saccades towards the left hemispace and they have prolonged fixation time for right-sided stimuli (Chèdrù, Leblanc, & Lhermitte, 1973; Duhamel et al., 1992; Girotti, Casazza, Musicco, & Avanzini, 1983; Walker & Findlay, 1996). Moreover, it has been recently demonstrated that oculomotor deficits have a slower spontaneous recovery compared to other visuo-spatial abilities (Pflugshaupt et al., 2004). The present results showed that this rightward oculomotor bias can be recovered by a PA treatment, since an increase in the amplitude of the first leftward directed saccade and of the exploration time of the left visual hemifield was found. Moreover, the present results indicate that the oculomotor recovery is strongly associated with the amelioration of the behavioural performance. Indeed an improvement of patients' accuracy was found in the reading task performed during eye movement recording.

As far as the second result is concerned, it is important to point out that the effects described above are present only in patients who showed a good correction of hand movements during prism exposure in the first week of treatment. The relationship between adaptation effect and eye movement recovery on the one hand, and adaptation effect and neglect recovery on the other, strictly points to a close relationship between neglect and oculomotor amelioration.

An explanation based on eye movement deviation as a possible mechanism mediating neglect recovery can account for several aspects of the present data. PA appeared to be effective in ameliorating visuo-spatial functions, body-space representation and tactile attention, but not proprioception and motor functions. The leftward deviation of the oculomotor system can easily account for the amelioration of patients' spatial abilities in the visual modality, since it is a current opinion that eye movements towards a specific part of the visual field require a shifting of the focus of attention in the same direction (Gainotti, 1993). Therefore, a leftward deviation of the oculomotor system can increase the visual attention directed to the left hemispace and, concurrently, reduce the visual attention bias towards the right hemifield. In addition, the oculomotor system deviation can also account for the recovery of representational neglect (Bisiach & Vallar, 2000), since it has Q6 been demonstrated that in normal subjects the spatial representation of the visual field just before the execution of a saccadic eye movement is strongly reorganised as centred on the target of the saccade (Ross, Morrone, & Burr, 1997; Morrone, Ross, & Burr, 1997) and that in neglect patients the description of a mental image is improved if patients have the gaze oriented towards the left (Meador, Loring, Bowers, & Heilman, 1987).

The amelioration of visual and representational neglect mediated by the oculomotor system resetting can involve, in the same way, the extrapersonal and personal space, and this can explain why after the treatment, patients were better able to explore their body space both in visual and non-visual conditions, as shown by the results of the Fluff Test. More intriguingly, the leftward deviation of the oculomotor system might also account for the neglect amelioration in non-visual modalities, such as tactile perception. Indeed, there is much evidence indicating that eye movements may orient attention towards the appropriate part of the space not only during visual tasks, but also in the tactile or auditory modality (see Gainotti, 1993, for a review). Moreover, several results from crossmodal attention studies demonstrate a strong interaction between vision and touch in modulating spatial attention, since it has been shown that a cue in one modality can attract attention towards its location in other modalities, not solely within the cued modality (see Driver & Spence, 1998, 2004; Spence. McDonald, & Driver, 2004, for reviews). Therefore, the amelioration of the left-sided visual attention, induced by the eye movements resetting, might also promote an improvement of tactile attention for left-sided stimuli, thus reducing extinction after the treatment.

In contrast, the results obtained when proprioceptive sensitivity and motor functions were studied, do not support the hypothesis that PA can also induce an amelioration in these modalities. These negative results could be due to different reasons. First, the scales used in the present study might not be sensitive enough to account for any amelioration after PA. For instance, the Motricity Index considers overall scores for the whole left or right hemisoma and for the trunk, whereas, probably, it would be useful to assess the mobility of different body parts, and, in particular, among them, those that show a slower pattern of spontaneous recovery, such as distal movements (Farnè et al., 2004). Moreover, standardised neurological or physiatrist methods of Q7 examination, such as the measures adopted in the present study, might not be able to discriminate between neglect-related motor-sensory disorders and primary deficits (see Vallar, 1998, for a comment). In this vein, an amelioration of proprioceptive and motor functions could be expected after PA only if these deficits are strictly linked to neglect syndrome, and not mainly due to primary sensory or motor deficits. Finally, it is also possible that PA is effective in visual and tactile modalities, whereas it is not effective in ameliorating proprioception and motor function because the information regarding proprioceptive afferents and the motor system are not integrated in the complex multimodal spatial representation on which PA is effective.

To summarise, results from the present study showed that a rehabilitative intervention in neglect patients based on PA can induce beneficial effects involving different domains and lasting up to 6 months after the end of treatment. Moreover, the patient's ability to correct pointing movements during prism exposure in the first week of treatment predicts neglect recovery. Finally, this ability is negatively affected by wide occipital lesions and visual field deficits. The long duration and the generalisation of these benefits suggest that PA acts like a trigger that recovers the neglect spatial attention bias, probably by inducing a leftward resetting of the oculomotor system. These effects are maintained and continuously reinforced, in a feed-forward way, by the complex and multisensory stimulation derived from the external environment. Moreover, in clinical practice, treatment effectiveness can be evaluated early by studying patients' visuo-motor responses in the first phases of rehabilitation. For these reasons, PA seems to be a candidate for an efficacious and perhaps, at least in some patients, definitive treatment of visuo-spatial neglect.

REFERENCES

Andersen, R. A., Essick, G. K., & Siegel R. M. (1987). Neurons of area 7 activated by both visual stimuli and oculomotor behavior. *Experimental Brain Research*, *67*(2), 316–322.

Angeli, V., Benassi, M. G., & Làdavas, E. (2004). Recovery of oculomotor bias in neglect patients after prism adaptation. *Neuropsychologia*, *42*(9), 1223–1234.

Antonucci, G., Guariglia, C., Judica, A., Magnotti, L., Paolucci, S., Pizzamiglio, L., & Zoccolotti, P. (1995). Effectiveness of neglect rehabilitation in a randomized group study. *Journal of Clinical and Experimental Neuropsychology*, *17*(3), 383–389.

Bisiach, E., Perani, D., Vallar, G., & Berti, A. (1986). Unilateral neglect: Personal and extra-personal. *Neuropsychologia*, *24*(6), 759–767.

Buxbaum, L. J., & Coslett, H. B. (1998). Spatio-motor representations in reaching: Evidence for subtypes of optic ataxia. *Cognitive Neuropsychology*, *15*, 279–312.

Cappa, S., Sterzi, R., Vallar, G., & Bisiach, E. (1987). Remission of hemineglect and anosognosia during vestibular stimulation. *Neuropsychologia*, *25*(5), 775–782.

Carey, D. P., Coleman, R. J., & Della Sala, S. (1997). Magnetic misreaching. *Cortex*, *33*(4), 639–652.

Chedru, F., Leblanc, M., & Lhermitte, F. (1973). Visual searching in normal and brain-damaged subjects (contribution to the study of unilateral inattention). *Cortex*, *9*(1), 94–111.

Cocchini, G., Beschin, N., & Jehkonen, M. (2001). The Fluff Test: A simple task to assess body representation neglect. *Neuropsychological Rehabilitation*, *11*, 17–31.

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1995). Oculocentric spatial representation in parietal cortex. *Cerebral Cortex*, 5(5), 470–481.

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *Journal of Neurophysiology*, *76*(5), 2841–2852.

Coslett, H. B., Bowers, D., Fitzpatrick, E., Haws, B., Heilman, K. M. (1990). Directional hypokinesia and hemispatial inattention in neglect. *Brain*, *113*(2), 475–486.

Damasio, H., & Damasio, A. R. (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.

Demeurisse, G., Demol, O., & Robaye, E. (1980). Motor evaluation in vascular hemiplegia. *European Neurology*, *19*, 382–389.

Dijkerman, H. C., McIntosh, R. D., Milner, A. D., Rossetti, Y., Tilikete, C., & Robert,s R. C. (2003). Ocular scanning and perceptual size distortion in hemispatial neglect: Effects of prism adaptation and sequential stimulus presentation. *Experimental Brain Research*, *153*, 220–230.

Diller, L., & Weinberg, J. (1977). Hemi-inattention in rehabilitation: The evolution of a rational remediation program. *Advances in Neurology*, *18*, 63–82.

Di Pellegrino, G., Làdavas, E., & Galletti, C. (2001). Lexical processes and eye movements in neglect dyslexia. *Behavioural Neurology*, *13*(1–2), 61–74.

Driver, J., & Spence, C. (1998). Attention and the crossmodal construction of space, *Trends in Cognitive Sciences*, *2*(7), 254–262.

Driver, J., & Spence, C. (2004). Crossmodal spatial attention: Evidence from human performance. In C. Spence & J. Driver (Eds.), *Crossmodal space and crossmodal attention* (pp. 179–220). New York: Oxford University Press.

Duhamel, J. R., Goldberg, M. E., Fitzgibbon, E. J., Sirigu, A., & Grafman, J. (1992). Saccadic dysmetria in a patient with a right frontoparietal lesion. The importance of corollary discharge for accurate spatial behaviour. *Brain*, *115*(5), 1387–1402.

Faglioni, P., Scotti, G., & Spinnler, H. (1971). The performance of brain-damaged patients in spatial localization of visual and tactile stimuli. *Brain*, *94*(3), 443–454.

Farnè, A., Buxbaum, L. J., Ferraro, M., Frassinetti, F., Whyte, J., Veramonti, T., Angeli, V., Coslett, H. B., & Làdavas, E. (2004). Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *Journal of Neurology Neurosurgery and Psychiatry*, *75*(10), 1401–1410.

Farnè, A., Rossetti, Y., Toniolo, S., & Làdavas, E. (2002). Ameliorating neglect with prism adaptation: Visuo-manual and visuo-verbal measures. *Neuropsychologia*, *40*(7), 718–729.

Ferber, S., Danckert, J., Joanisse, M., Goltz, H. C., & Goodale, M. A. (2003). Eye movements tell only half of the story. *Neurology*, *60*(11), 1826–9.

Frassinetti, F., Angeli, V., Meneghello, F., Avanzi, S., & Làdavas, E. (2002). Long-lasting amelioration of visuospatial neglect by prism adaptation. *Brain*, *125*(3), 608–23.

Frassinetti, F., Rossi, M., & Làdavas, E. (2001). Passive limb movements improve visual neglect. *Neuropsychologia*, *39*(7), 725–733.

Gainotti, G. (1993). The role of spontaneous eye movements in orienting attention in unilateral neglect. In I. H. Robertson & J. C. Marshal (Eds.), *Unilateral neglect: Clinical and experimental studies* (pp. 107–122). Hove, UK: Erlbaum.

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11*, 49–54.

Girotti, Fm., Casazza, M., Musicco, M., & Avanzini, G. (1983). Oculomotor disorders in cortical lesions in man: the role of unilateral neglect. *Neuropsychologia*, *21*(5), 543–553.

Halligan, P. W., & Marshall, J. C. (1991). Left neglect for near but not far space in man. *Nature, 11*;*350*(6318), 498–500.

Held, R., & Gottlieb, N. (1958). Technique for studying adaptation to disarranged hand–eye coordination. *Perceptual and Motor Skills*, *8*, 83–86.

Heilman, K. M., Valenstein, E., & Watson, R. T. (2000). Neglect and related disorders. *Seminary in Neurology*, *20*(4), 463–470.

Hier, D. B., Mondlock, J., & Caplan, L. R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology*, *33*(3), 345–350.

Hornak, J. (1992). Ocular exploration in the dark by patients with visual neglect. *Neuropsychologia*, *30*(6), 547–52.

Karnath, H. O., Christ, K., & Hartje, W. (1993). Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline. *Brain*, *116*(2), 383–396.

Kerkhoff, G. (2003). Modulation and rehabilitation of spatial neglect by sensory stimulation. In C. Parablanc, D. Pellisson & Y. Rossetti (Eds.), *Progress in brain research* (Vol. 142, pp. 257–271). Amsterdam, NE: Elsevier Science B.V.

Làdavas, E., Berti, A., Ruozzi, E., & Barboni, F. (1997a). Neglect as a deficit determined by an imbalance between multiple spatial representations. *Experimental Brain Research*, *116*(3), 493–500.

Làdavas, E., Carletti, M., & Gori, G. (1994). Automatic and voluntary orienting of attention in patients with visual neglect: Horizontal and vertical dimensions. *Neuropsychologia*, *32*(10), 1195–1208.

Làdavas, E., Shallice, T., & Zanella, M. T. (1997b). Preserved semantic access in neglect dyslexia. *Neuropsychologia*, *35*, 257–270.

Làdavas, E. (2002). Functional and dynamic properties of visual peripersonal space. *Trends in Cognitive Sciences*, 6(1), 17–22.

Làdavas, E., & Farnè, A. (2004). Neuropsychological evidence for multimodal representations of space near specific body parts. In C. Spence & J. Driver (Eds.), *Crossmodal space and crossmodal attention* (pp. 69–98). New York: Oxford University Press.

Maravita, A., McNeil, J., Malhotra, P., Greenwood, R., Husain, M., & Driver, J. (2003). Prism adaptation can improve contralesional tactile perception in neglect. *Neurology*, *60*(11), 1829–1831.

Meador, K. J., Loring, D. W., Bowers, D., & Heilman, K. M. (1987). Remote memory and neglect syndrome. *Neurology*, *37*(3), 522–6.

Morris, A. P., Kritikos, A., Berberovic, N., Pisella, L., Chambers, C. D., & Mattingley, J. B. (2004). Prism adaptation and spatial attention: A study of visual search in normals and patients with unilateral neglect. *Cortex*, *40*, 703–721.

Morrone, M. C., Ross, J., & Burr, D. C. (1997). Apparent position of visual targets during real and simulated saccadic eye movements. *Journal of Neuroscience*, *17*(20), 7941–7953.

Mushiake, H., Fujii, N., & Tanji, J. (1996). Visually guided saccade versus eye–hand reach: Contrasting neuronal activity in the cortical supplementary and frontal eye fields. *Journal of Neurophysiology*, *75*(5), 2187–2191.

Neggers, S. F. W., & Bekkering, H. (2000). Ocular gaze is anchored to the target of an ongoing pointing movement. *Journal of Neurophysiology*, *83*(2), 639–651.

Pantano, P., Formisano, R., Ricci, M., Di Piero, V., Sabatini, U., Di Pofi, B., Rossi, R., Bozzao, L., & Lenzi, G. L. (1996). Motor recovery after stroke. Morphological and functional brain alterations. *Brain*, *119*(6),1849–1857.

Pavani, F., Làdavas, E., & Driver, J. (2003). Auditory and multisensory aspects of visuospatial neglect. *Trends in Cognitive Sciences*, *7*(9), 407–414.

Pflugshaupt, T., Almoslöchner Bopp, S., Heinemann, D., Mosimann, U. P., von Wartburg, R., Nyffeler, T., Hess, C. W., & Müri, R. M. (2004). Residual oculomotor and exploratory deficits in patients with recovered hemineglect. *Neuropsychologia*, *42*(9), 1203–1211.

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical and Experimental Neurospychology*, *14*(6), 901–923.

Pizzamiglio, L., Frasca, R., Guariglia, C., Incoccia, C., & Antonucci, G. (1990). Effect of optokinetic stimulation in patients with visual neglect. *Cortex*, *26*(4), 535–540.

Powell, K. D., & Goldberg, M. E. (2000). Response of neurons in the lateral intraparietal area to a distractor flashed during the delay period of a memory-guided saccade. *Journal of Neurophysiology*, *84*(1), 301–310.

Redding, G. M., & Wallace, B. (1993). Adaptive coordination and alignment of eye and hand. *Journal of Motor Behaviour*, *25*(2), 75–88.

Robertson, I. H., & Halligan, P. W. (1999). *Spatial neglect: A clinical handbook for diagnosis and treatment.* Hove, UK: Psychology Press.

Robertson I. H., & North, N. (1993). Active and passive activation of left limbs: Influence on visual and sensory neglect. *Neuropsychologia*, *31*(3), 293–300.

Rode, G., Rossetti, Y., Li, L., & Boisson, D. (1998). Improvement of mental imagery after prism exposure in neglect: A case study. *Behavioural Neurolology*, *11*(4), 251–258.

Ross, J., Morrone, M. C., & Burr, D. C. (1997). Compression of visual space before saccades. *Nature*, *386*(6625), 598–601.

Rossetti, Y., Rode, G., Pisella, L., Farne, A., Li, L., Boisson, D., & Perenin, M. T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, *395*(6698), 166–169.

Rubens, A. B. (1985). Caloric stimulation and unilateral visual neglect. *Neurology*, *35*(7),1019–1024.

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2005). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia*, *Dec*, 2. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd = Retrieve&db = PubMed&list_uids = 16330055&dopt = Abstract

Spence, C., McDonald, J., & Driver, J. (2004). Exogenous spatial-cuing studies of human cross-modal attention and multisensory integration. In C. Spence & J. Driver (Eds.), *Crossmodal space and crossmodal attention* (pp. 277–320). New York: Oxford University Press.

Stuphorn, V., Bauswein, E., & Hoffmann, K. P. (2000). Neurons in the primate superior colliculus coding for arm movements in gaze-related coordinates. *Journal of Neurophysiology*, *83*(3), 1283–1299.

Tilikete, C., Rode, G., Rossetti, Y., Pichon, J., Li, L., & Boisson, D. (2001). Prism adaptation to rightward optical deviation improves postural imbalance in left-hemiparetic patients. *Current Biology*, *11*(7), 524–528.

Vallar, G. (1998). Spatial hemineglect in humans. *Trends in Cognitive Sciences*, *2*(3), 87–97.

Vallar, G., Sterzi, R., Bottini, G., Cappa, S., & Rusconi, M. L. (1990). Temporary remission of left hemianesthesia after vestibular stimulation. A sensory neglect phenomenon. *Cortex*, *26*(1), 123–131.

Vuilleumier, P., Valenza, N., Mayer, E., Reverdin, A., & Landis, T. (1998). Near and far visual space in unilateral neglect. *Annuals of Neurology*, *43*(3), 406–410.

Walker, R., & Findlay, J. M. (1996). Saccadic eye movements programming in unilateral neglect. *Neuropsychologia*, *34*, 493–508.

Werner, W., Hoffmann, K. P., & Dannenberg, S. (1997). Anatomical distribution of arm-movement-related neurons in the primate superior colliculus and underlying reticular formation in comparison with visual and saccadic cells. *Experimental Brain Research*, *115*(2), 206–16.

Wilson, B., Cockburn, J., & Halligan, P. (1987). Development of a behavioral test of visuospatial neglect. *Archives of Physical and Medical Rehabilitation*, *68*, 98–108.

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Queries

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Q1 Pavani, Làdavas, & Driver et al., 2004 – please add to reference list.

Q2 Guariglia & Antonucci, 1992 – please add to reference list.

Q3 Pisella et al., 2002 – please add to reference list.

Q4 Hemisoma – I am not familiar with this term – can you suggest an alternative.

Q5 Data were available for 20 up to 21 subjects. Are the figure in the sentence correct?

Q6 Bisiach & Vallar, 2000 – please add to reference list.

Q7 Physiatrist – do you mean physical or psychiatric?