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Prism Adaptation:
A Rehabilitation Technique for Spatial Neglect

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GENERAL DISCUSSION

Abstract

This doctoral thesis is divided in six chapters and presents the results of four experiments. It investigates the use of prism adaptation (PA) in the rehabilitation of spatial neglect, how PA may affect spatial cognition, and the specific mechanisms that are influenced by PA. Knowing more about the systems responsive to PA may help our understanding of which symptoms, and which patients, improve optimally after PA training.

The Introduction explains concepts and backgrounds useful for the understanding of the experimental projects. First, the definition and characteristics of Unilateral Spatial Neglect are introduced, followed by a review of the distinction in the variety of spatial neglect that separates “perceptual” versus “premotor” neglect and the anatomical and functional dissociation between brain areas associated with these two subtypes of neglect. The Introduction summarizes paradigms that have been used to disentangle the perceptual and premotor components of spatial neglect and the patterns of perceptual and premotor biases reported in neglect patients. A description of different methods that have previously been used in the rehabilitation of spatial neglect is also provided. Among them, the PA technique is described in detail, including the background in which PA has been used, measures to assess the presence of adaptation and aftereffects following the adaptation procedure, processes that have been proposed to be involved in the sensori-motor transformation that occurs during PA, the beneficial effects reported after PA paradigms in neglect patients, and the effects of PA in healthy individuals. Finally, the Introduction gives an overview of the cerebral circuits that appear to be involved in PA based on data derived from brain imaging studies, studies with brain-damaged patients, and studies with primates.

The next four chapters report the results of four experiments. These chapters are divided in two main parts. The first section focuses on the feasibility of using ecological visuo-motor activities, based on diverse and engaging visuo-motor tasks, during adaptation to prism.

In Experiment 1, 10 neglect patients were submitted to both a standard pointing adaptation training (Frassinetti et al., 2002) and a training involving diverse ecological visuo-motor tasks (Ecological procedure). The effect of the two treatments was compared in a large assessment including a variety of neuropsychological tests as well as functional scales.

In Experiment 2, the presence of adaptation and aftereffects was assessed during the ecological procedure, and these measures were compared with those obtained during the traditional pointing task.

In Experiment 3, we used a modified version of the paradigm of Schwartz et al. (1997) and Na et al., (1998) to decouple perceptual-attention “where” and motor-intention “aiming” components in visuo-motor tasks (line bisection). The effects of PA on where and aiming components were tested in a large group of neurologically healthy individuals.

In Experiment 4, the same effects were tested in a group of five neglect patients.

Lastly, the General Discussion summarizes and integrates the results of the four experiments, highlighting the implications for the rehabilitation of spatial neglect.

Results from these experiments show that PA training associated with varied visuomotor activities is an effective tool to ameliorate some aspects of spatial neglect as well as functional disabilities, being as effective as the more established pointing task.

In the four experiments, measures of adaptation and aftereffects were obtained using three different adaptation procedures: pointing, ecological, and line bisection tasks. It is argued that these measures, especially the aftereffect measures, may be important for establishing the effectiveness of adaptation procedures in neglect rehabilitation. It appears that the three adaptation procedures (pointing, ecological, line bisection) can all induce error correction during the exposure phase. However, the ecological and the pointing procedure seem to create strong and prolonged aftereffects, with the ecological task even better in inducing aftereffects than the pointing task. By contrast, the line bisection task appears to induce weaker aftereffects, suggesting that its use may not be optimal in prism paradigms. Reasons for such differences are explored, focusing on the motivations for the increased aftereffects during the ecological procedure. Indeed, exposure to prism decreased the aiming bias after PA in both studies. In the group of healthy individuals, the initial left aiming bias was reduced after exposure to left-shifting prisms (Experiment 3). In a similar way, in the group of neglect patients the initial right aiming bias improved after exposure to right-shifting prisms (Experiment 4). In addition, in the healthy participants no changes in the aiming bias were found after exposure to right-shifting prisms and control goggles, indicating that the effect of left-shifting prisms was not due to increased familiarity with the task (Experiment 3). These results are interpreted and integrated in light of recent findings.

Experiments 1 and 4 also showed the cortical areas associated with neglect in our patients and the responsiveness to the PA paradigm. Results confirmed that patients with right-sided brain lesions in the frontal-parietal cortical and subcortical areas are still able to adapt to the lateral shift induced by prism, and further suggested that adaption to prism and improvement in neglect symptoms can occur even in the presence of an occipital lesion.

Finally, the Discussion addresses the question of how to differentiate the effect of the experimental manipulation from spontaneous recovery while testing the efficacy of new rehabilitation methods in brain-damaged individuals. Therefore, evidence for the specificity of our intervention is provided. It is argued that spontaneous recovery cannot fully account for the present findings of improvement in neglect symptoms after PA treatment (Experiment 1 and 4). It is also suggested that performing studies employing neurologically healthy subjects can help in providing evidence for the effect of a treatment on cognitive function. In particular, testing healthy subjects to better understand the functioning of PA in neglect patients is facilitated by the fact that healthy individuals show biases in spatial cognition that mirror the biases in neglect patients.

INTRODUCTION

1.1 Unilateral spatial neglect

1.1.1 Definition and characteristics

Spatial neglect is a neuropsychological disorder whereby patients fail to report sensory events occurring in the portion of extra-personal space and of the body contralateral to the side of the hemispheric lesion, and to explore that part of space in the absence of primary sensory or motor impairments (Heilman, Watson, and Valenstein, 1979; Vallar, 1998; Husain, 2008; Driver and Mattingley, 1998; Halligan et al., 2003; Heilman et al., 2003).

Spatial neglect is more frequent and severe after damage to the right cerebral hemisphere, involving the left side of space (Bisiach and Vallar, 2000; Halligan, Fink, Marshall, and Vallar, 2003; Heilman, Watson, and Valenstein, 2003), but right neglect has also been reported after left-hemisphere lesions (Beis et al., 2004; Pia et al., 2009; Bultitude and Rafal, 2010). The rate of occurrence after stroke varies considerably across studies (from 13% to 82% with a median of 43% in the review of Bowen, McKenna, and Tallis, 1999), mainly depending on the test batteries adopted. Group studies indicate that left USN is a frequent deficit after right brain damage (moderate to severe in 36% of the patients reported by Azouivi et al., 2002, with some degree of neglect in 85% of the patients; 48% occurrence rate in the patients reported by Buxbaum et al., 2004).

In every daily life, patients with severe neglect following right hemisphere damage may behave as if the left side of the world no longer exists: they may forget to dress the left side of their body or ignore objects and people when located on their left. When walking or propelling the wheelchair, they may collide with furniture that is placed on the left side of the room.

In a similar way, when neglect patients are tested with paper and pencil diagnostic tests they may fail to cancel items on the contralesional side of the paper. Even when they mark all targets, the qualitative features of their performance may reveal spatial bias as patients with left spatial neglect typically begin to explore the visual display at the right side, contrary to the performance of healthy subjects or patients with left hemisphere damage (Gainotti, D'Erme, and Bartolomeo, 1991; Jalas, Lindell, Brunila, Tenovuo, & Hamalainen, 2002; Azouvi et al., 2002). Similarly, they tend to draw the right side of a scene and deviate rightward when bisecting a line. Spatial neglect is also frequently associated to phenomena such as "extinction", in which patients exhibit a preserved ability to detect a contralesional single stimuli but fail to report it when it is presented simultaneously with a second stimuli (Brozzoli et al., 2006; Driver et al., 1997), and to "anosognosia" defined as the unawareness of neglect symptoms (Bisiach and Gimiani, 1991; Marshall and Halligan, 1988; Berti, 2002).

Right-brain-damaged neglect patients typically present with a more severe sensorimotor impairment than right-brain-damaged patients without neglect (Buxbaum, et al., 2004; Paolucci, Antonucci, Grasso, and Pizzamglio, 2001). Although neglect symptoms tend to spontaneously improve during the acute phase of the disease, they may persist severe and chronic in many patients and become an obstacle for the outcome of rehabilitation training (Farnè et al., 2004; Sameulsson, Jensen, Ekholm, Naver, and Blomstrand, 1997; Katz, Hartmann-Maeir, Ring, and Soroker, 1999; Hier, Mondlock, and Caplan, 1983). Indeed, spatial neglect is associated with a more severe overall disability, and the presence of neglect is a predictor of poor functional outcome and loss of independence after right hemispheric stroke (Denes, Semenza, Stoppa, and Lis, 1982; Jehkonen, Laihosalo, Kettunen, 2006; Katz, et al., 1999; Paolucci, et al., 2001).

Spatial neglect itself is not generally considered a unitary condition (but see Corbetta and Shulman, 2011 and Karnath and Rorden, 2011). It may affect different sensory modalities, reference frames, or spatial domains to different degrees in different patients (Halligan, et al., 2003; Vallar, 1998; Vallar, Bottini, and Paulesu, 2003). Neglect symptoms may appear in visual, auditory and proprioceptive-somatosensory modalities (Cubelli, Nichelli, Bonito, De Tanti, and Inzaghi, 1991), and may be relative to egocentric frames, with reference to the mid-sagittal plane of the patients' body (for example eye-head, and trunk-centered) and/or to allocentric and stimulus-centered frames (for example, relative to the principal axes of objects) independent of the patient's body perspective (Marsh and Hillis, 2008; Bisiach, 1997; Farah and Buxbaum, 1997; see Walker, 1995 for a review). Selective neglect symptoms may be observed in the personal space, relative to the patients' body, or in the near and far extra-personal space, behaviourally defined as the space within and behind arms' reach (Bisiach, Perani, Vallar, and Berti, 1986; Guariglia and Antonucci, 1992; Halligan and Marshall, 1991; Vuilleumier, Valenza, Mayer, Reverdin, and Landis, 1998; Berti, Smania, and Allport, 2001, Vallar and Maravita, 2009).

The heterogeneity of the neglect manifestations suggests that spatial neglect does not derive from the impairment of a unitary monolithic supra-modal system and that multiple components are involved in spatial cognition. Spatial neglect may derive from unawareness of stimuli in contralesional space due to an inability to disengage attention from ipsilesional stimuli (Posner, Walker, Friedrich, and Rafal, 1987), from deficits in re-orienting attentional resources towards the contralesional space due to the asymmetric competence of the two hemispheres (Heilman and Van Den Abell, 1980), or from the rivalry between the two hemispheric attentional vectors (Kinsbourne, 1993). Neglect deficits may also be caused by defective directional motor programs (Heilman, Bowers, Coslett, Whelan, and Watson, 1985) or an impaired internal representation of space (Bisiach, 1993). The spatial-attentional, motor, and representational models are not mutually incompatible and the combination of their selectively damaged components may give rise to the behavioural dissociations that have been observed in neglect patients.

Finally, the severity of the neglect syndrome can be exacerbated by non-lateralized mechanisms impaired by nearby brain lesions (see Hussain and Rorden, 2003 for a comprehensive review). For example, impairments in temporal attention (i.e., attentional blink paradigm; Husain, Shapiro, Martin, and Kennard, 1997), sustained attention (Samuelsson, Hjelmquist, Jensen, Ekholm, and Blomstrand, 1998; Hjialtason, Tegner, Tham, Levander, and Ericson, 1996; Robertson et al., 1997), detection of the salience of stimuli among distractors, or trans-saccadic spatial working memory (Husain et al., 2001) may all increase the severity of spatial neglect.

1.1.2 Perceptual and premotor spatial neglect

Linked to the above chapter, a main distinction in the variety of spatial neglect separates “perceptual” vs “premotor” neglect (Bisiach, Geminiani, Berti, and Rusconi, 1990). This distinction may not be seen as a clear dichotomous division but more as a continuum of impairments that affect primarily the input versus output components of goal-directed visuo-motor responses. The “failure to perceive” contralateral events may be a consequence of reduced perceptual resources and unawareness of stimuli in contralesional space. On the other hand, the “failure to reach” objects located in the contralesional part of the space may depend on specific impairments in the planning, initiation and execution of actions toward the contralesional hemispace. In the literature, other terms have also been used such as “attentional” vs. “intentional”, or “where” vs. “aiming” types of neglect (Barrett, Beversdorf, Crucian, and Heilman, 1998; Barrett, Crucian, Beversdorf, and Heilman, 2001; Rapcsak, Verfaellie, Fleet, and Heilman, 1989).

Premotor/intentional/aiming disorders refer to impairments in actions toward the contralesional side of the space that cannot be ascribed to a primary motor impairment. In right-brain-damage patients, these deficits are related to movements performed with the right unimpaired arm when directed toward the left side of the space. Within this disorder, a distinction has been made between the slowness in the initiation of the actions, defined as "directional hypokinesia" (Watson, Miller, and Heilman, 1978; Heilman et al., 1979; Heilman, et al., 1985; Coslett, Bowers, Fitzpatrick, Haws, and Heilman, 1990), and the slowness in the execution of such movements, defined as "directional bradykinesia" (Mark, 1996; Heilman, 2004; Fink and Marshall, 2005). Selective premotor impairments have also been demonstrated in eye movements, with slowness in the initiation of saccades toward the left hemifield (Behrmann, Black, McKeeff, and Barton, 2002). Indeed, neglect patients may exhibit ipsilesional right gaze deviation (De Renzi, Colombo, Faglioni, and Gibertoni, 1982; Ringman, Saver, Woolson, and Adams, 2005; Karnath, 1997) and right ocular fixation (Barton et al., 1998) in association with fewer leftward fixation, fewer and smaller leftward saccades, and shorter inspection times on the contralesional left side of the space (Chedru, Leblanc, and Lhermitte, 1973; Girotti, Casazza, Musicco, and Avanzini, 1983; Ishiai, Sugishita, Mitani, Ishizawa, 1992; Behrmann, Watt, Black, and Barton, 1997; Ro, Rorden, Driver, and Rafal, 2001; Niemeier and Karnath, 2000; see Ishiai, 2006 for a review). Similarly, neglect patients can exhibit rightward deviation during navigation through locomotion, for example when asked to pass through a door, suggesting premotor impairments involving body movements (Robertson, Tegner, Goodrich, and Wilson, 1994; Tromp, Dinkla, and Mulder, 1995; Berti et al., 2002).

1.1.2.1 Anatomical dissociation

The presence of dissociated perceptual and premotor deficits in neglect patients has been suggested to reflect an anatomical and functional dissociation between brain areas (Vallar and Perani, 1986). For example, Mesulam (1981) proposed a model in which anatomically posterior brain lesions, located in the parietal lobe, are hypothesized to be more associated with perceptual-attentional impairments, while more anterior brain lesions, located in the frontal lobe, are more associated with motor impairments. Several studies involving different paradigms to disentangle the perceptual and premotor components in neglect patients have provided evidence in support of this hypothesis, suggesting an association with frontal-subcortical lesions in premotor types of neglect and posterior parietal-temporal-occipital lesions in perceptual-attentional types of neglect (Bisiach, et al., 1990: Coslett, et al., 1990; Tegner and Levander, 1991; Bottini, Sterzi, and Vallar, 1992; Ladavas, Umilta, Ziani, Brogi, and Minarini, 1993; Na et al., 1998; Bisiach et al., 1995; Daffner, Ahern, Weintraub, Mesulam, 1990; Liu, Bolton, Price, and Weintraub, 1992; Behrmann and Meegan, 1998). Further evidence was recently reported in a study by Sapir et al. (2007) in which neglect patients with damage in subcortical regions (caudate and putamen/basal ganglia), and in the white matter underlying the dorsal and ventral premotor cortex in the frontal lobe, showed premotor spatial impairments. Consistent with these findings, Bartolomeo et al. (1998) reported that 14 right-brain-damaged neglect patients who had no damage to frontal-subcortical areas all showed the perceptual-attentional type of neglect.

The premotor type of neglect may be relatively more frequent following left brain damage than following right brain damage, which may depend on the more frequent anterior location of left hemisphere lesions, whereas more frequent posterior lesions occur in right brain damage (Ogden, 1985). However, it is also possible that premotor factors may be more relevant for left brain damage than for right brain damage since the left hemisphere is dominant in programming actions (Schluter, Krams, Rushworth, and Passingham, 2001; Rushworth, Johansen-Berg, Gobel, and Devlin, 2003).

Although the neuro-anatomical distinction between perceptual and premotor types of neglect is well documented, it is not as clean-cut as one might like; conflicting evidence has also been reported (Bisiach, Ricci, Lualdi, and Colombo, 1998; Mattingley, Bradshaw, and Phillips,1992; Mattingley, Husain, Rorden, Kennard, and Driver, 1998; Husain, Mattingley, Rorden, Kennard, and Driver, 2000; Ishiai, Watabiki, Lee, Kanouchi, and Odajima, 1994; Vossel, Eschenbeck, Weiss, and Fink). Bisiach et al. (1998) for example, showed an association between the perceptual-attentional bias in a Landmark test (Milner, Harvey, Roberts, and Forster, 1993) and frontal damage, whereas the motor bias was more associated with subcortical damage. Other studies (Mattingley et al., 1998; Husain et al., 2000) have showed premotor impairments such as directional hypokinesia (slower initiation time) in neglect patients following selective parietal lesions, whereas selective frontal and subcortical lesions were more correlated with directional bradykinesia (slower movement time) or with a combination of directional bradykinesia and hypokinesia. Finally, some other authors failed to identify any clear anatomo-clinical correlation using the Landmark test (Harvey Milner, and Roberts, 1995a; Harvey, Milner, and Roberts, 1995b) or other clinical tests (McGlinchey-Berroth, et al., 1996) to differentiate subtypes of spatial neglect.

A possible interpretation of the presence of similar behavioural impairments following different brain lesion sites is related to the possible connections between brain areas, such that a lesion in one node of the network may affect other nodes of the same network. For example, the directional motor disorders recorded after selective parietal lesions as well as after selective frontal lesions may depend on the presence of visuo-motor streams connecting parietal (e.g., the superior parietal cortex) and premotor areas (in the frontal and subcortical areas; Bartolomeo et al., 1998). It is also possible that multiple brain areas may underlie similar tasks (e.g., motor exploration of the left side of the space) and may create similar behavioural deficits after selectively impairment.

1.1.2.2 Paradigms to identify perceptual and premotor biases

Several paradigms have been used to disentangle the perceptual and premotor components of spatial neglect (see Vallar and Mancini, 2010 for a comprehensive review).

In a first study, the side of the motor response was dissociated from the side to which visual attention was directed, asking neglect patients to control their line bisection movement through a TV video that was placed either in the right or left hemispace (Coslett et al., 1990). However, as Bisiach et al. (1990) pointed out, the authors did not uncouple the direction of the movement performed from the image projected on the screen so that the left side of each stimulus was always positioned on the left side of the screen. Therefore in successive experiments, the two spatial biases were assessed during the execution of clinical tests (e.g., line bisection and cancellation tasks) contrasting the subject’s performance in a standard natural view condition versus an incongruent reversed condition (Bisiach et al., 1990; Tegner and Lavander, 1991; Nico, 1996; Na et al., 1998; Adair, Na, Schwartz, and Heilman, 1998; Schwartz, Adair, Na, Williamson, and Heilman, 1997; Barrett and Burkholder, 2006; Garza, Eslinger, and Barrett, 2008). In the incongruent condition, the view of the movement was right-left reversed relative to the direction of the action performed, using devices such as a pulley, a mirror, an epidiascope, a video-mixer, and a computer program. In the study of Bisiach et al. (1990), a line bisection task was performed using a pointer to determine the midpoint of the line (Fig. 1). The pointer could be moved directly along the line or indirectly through a pulley device that moved the pointer in the opposite direction to that of the patient’s hand.

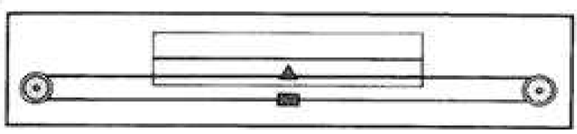


Fig. 1 - Pulley to separate the vision of the movement, “perceptual component”, from the direction of the movement performed, “motor component” (Bisiach et al., 1990). In the natural condition, the pointer is moved directly (performed with the triangle) and the perceptual and motor components are congruent. In the reversed condition, the pointer had to be indirectly moved through the rectangle, so that it is lateral displacement requires movement in the opposite direction.

Using a similar logic, Tegner and Levander (1991) and Bisiach et al. (1995) used a 90° angled mirror to reverse the image of the stimuli in the reversed condition, while Nico (1996) used an overhead projector (epidiascope) to present the mirror-reversed viewing condition. Finally, in the paradigm of Schwartz et al. (1997) subjects performed a line bisection task via a TV screen. The image of the stimuli was presented either in the natural or right-left reversed condition through a video camera (Fig. 2, from Na et al., 1998). The same paradigm was applied in other studies (Na et al., 1998; Adair et al., 1998; Barrett, Crucian, Schwartz, and Heilman, 1999; Barrett et al., 2001; Barrett and Burkholder, 2006; Garza et al., 2008).

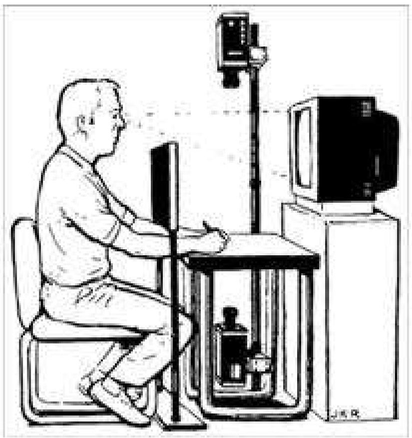


Fig. 2 - Video apparatus (from Barrett et al., 2006, based on Na et al., 1998) - The camera above records the work-space in a right-left natural condition. The camera below records the work-space in a left-right reversed condition. The black panel prevents subjects to look as their own hand during the line bisection task.

The logic of the natural-reversed paradigms lies in a separate, quantitative measurement of two different sources of error when subjects perform the same task under two different visual-motor conditions. In the natural condition, the visual feedback of the movement is congruent with the movement performed, so that rightward hand movements appear rightward, and leftward hand movements appear leftward. However, in the incongruent condition, the display is horizontally reversed so that visual feedback of rightward movements appeared leftward, and vice versa. If a participant errs toward the same side (for example, moving toward the right side of the workspace) under both natural and reversed viewing conditions, it suggests that the participant's bias is relatively insensitive to visual feedback and thus may be an output-related motor-intentional aiming bias. If a participant's error changes direction between the natural and reversed viewing conditions (e.g., the participant makes rightward responses under natural viewing, but leftward responses under the reversed viewing), it suggests that the bias is dependent on visual input, and thus may be a perceptual-attentional where spatial bias (Schwartz, et al., 1997). Directly comparing performance in natural and reversed viewing conditions allows one to determine whether spatial errors are primarily perceptual or premotor in nature (Bisiach et al., 1990; Na et al., 1998; Schwartz, et al., 1997). Furthermore, both perceptual-attentional where and premotor-intentional aiming biases may contribute to line bisection errors in the natural and reversed viewing conditions. Thus, Barrett and Burkholder (2006) quantified the two biases using Equations 1 and 2 reported below. In the Natural condition these biases are aligned and oriented in the same direction, and thus may contribute additively to performance (Equation 1). In the Reversed condition, the perceptual-attentional where bias acts in the direction opposite the premotor-intentional aiming bias, since the visual feedback is 180-degrees reversed (Equation 2).

Natural Error = Aiming Component + Where Component [Equation 1]

Reversed Error = Aiming Component – Where Component [Equation 2]

Algebraically solving these two equations using Equations 3 and 4 allows for the quantification of both bias components:

Where Component = (Natural Error – Reversed Error) / 2 [Equation 3]

Aiming Component = (Natural Error + Reversed Error) / 2 [Equation 4]

Several studies have supported the validity of this fractionation method by showing that perceptual-attentional and motor-intentional cueing conditions selectively affected the respective biases in healthy individuals (Garza, Eslinger, and Barrett, 2008). As predicted, visual distraction modified the perceptual-attentional where, but not the motor-intentional aiming bias. Conversely, motor cueing modified the motor-intentional aiming, but not the perceptual-attentional where bias components. The validity of the natural/reversed line bisection procedure was also supported by studies in neglect patients receiving interventions expected to affect primarily perceptual-attentional versus motor-intentional spatial bias (Barrett and Burkholder, 2006; Barrett et al., 1999; Barrett et al., 2001).

However, the use of paradigms with reversed-incongruent view conditions requires the ability to adjust to incompatible sources of information such as visual versus kinaesthetic inputs. Some authors have suggested that these paradigms may be too demanding for brain lesion patients who have difficulties with incompatible responses (Mattingley et al., 1998; Hussain et al., 2000). Therefore, other paradigms have attempted to dissociate the perceptual and premotor components of the spatial bias without using incompatible conditions. Some studies for example (Mattingley et al., 1992; Mattingley et al., 1998; Hussain et al., 2000; Sapir et al., 2007) have used a reaching task in which subjects responded to a target horizontally located in right, center and left positions with respect to the subject. The direction of the reaching movement towards the target was manipulated (rightward vs leftward) using different starting positions. The studies assessed the presence of premotor vs perceptual biases by comparing the latencies of movement initiation in the different directions. Thus, when the hand starts in a central position, perceptual and premotor biases are combined since left targets that appear in the left hemifield required leftward movement. The critical situation for evaluating the presence of motor vs perceptual impairment arises when subjects have to reach the target from the left starting position. In this situation, targets appear in the left visual field but require rightward movements. Performance can then be contrasted with conditions requiring leftward movements. However, also the reaching task is not immune to criticisms. In contrast to the natural-reversed paradigms, in the reaching task the execution of the movement is commanded by the appearance of the visual target that cues the initiation of the reaching movement. Therefore, the response time to initiate the movement may include both perceptual components (i.e., the detection of the target) and motor components (i.e., planning and motor execution) and thus, the perceptual and the motor response may not be entirely disentangled. To address this concern, a recent study has introduced a new paradigm based on a delayed-reaching task in which a memory-guided response to a target location was required (Shimodozono et al., 2006). In this paradigm, the detection time of the target (the perceptual-attentional component) was separated from the initiation time of the movement (the premotor-intentional component), and from the execution time of the movement.

Other studies have attempted at separating the perceptual-attentional and motor-intentional factors by comparing patterns of responses in multiple tasks. For example, some studies have directly compared the performance in tasks that require only a perceptual-attentional component and not a motor response (i.e. verbal response) versus the performance in tasks that required a motor manual response (i.e. paper and pencil tasks; Chiba, Yamaguchi, and Eto, 2005; Bottini et al., 1992).

Similarly, another study compared the performance (expressed in reaction time to the stimuli) in a perceptual task, characterized by lateralized visual stimuli and central motor responses versus a motor task based on a "traffic light" test consisting of central stimuli and lateralized motor responses (Bartolomeo et al., 1998). However, also this paradigm has possible problems, such that in the perceptual task a directional oculomotor deficit may also play a role in the response time to stimuli presented in the left hemifield, since subjects may be slower to move their eyes toward the left. In a similar way, in the motor task a deficit in the perceptual encoding of the left side may also impair the response time for leftward movements. Finally, other paradigms have contrasted patterns of responses in a line bisection task comparing the performance in the Landmark test (Milner et al., 1993), in which a perceptual verbal estimation of the length of pre-bisected lines is required, versus a line bisection task performed manually by the subject (i.e., marking the center of the line or pointing to the shorter-or-longer segment of the line; Harvey et al., 1995a; Harvey et al., 1995b; Harvey and Milner, 1999; Ishiai, Koyoma, Seki, and Nakayama, 1998; Bisiach, Ricci, Lualdi, et al., 1998; Bisiach, Ricci, and Modona, 1998).

1.1.2.3 Patterns of perceptual and premotor biases in neglect patients

From a review of the literature of the studies that dissociated the perceptual-attentional bias from the motor-intentional bias, assessed with different methodology and paradigms, it appears that spatial neglect may affect primarily perceptual-attentional bias, primarily motor-intentional bias, or a combination of the two components. By comparing the results obtained in group studies (N ≥ 10), it is evident that there is still not an agreement regarding the most common pattern of impairment in spatial neglect patients. Some studies reported the perceptual-attentional factors as more prevalent than the motor-intentional factors in neglect patients (Bisiach et al., 1990; Tegnèr and Levander, 1991; Sapir et al., 2007; Nico, 1996; Bartolomeo et al., 1998; Shimodozono et al., 2006). One study reported a predominance of motor-intentional impairments (Na et al., 1998, for the line bisection task), whereas other studies showed a mixed pattern of impairment (Chiba et al., 2005) or a comparable rate of occurrence of the two types of deficits (Adair et al., 1998; Na et al., 1998 for the target cancellation task; Bisiach et al., 1995).

However, the presence of different frequency distribution of subtypes of neglect may not be surprising. Indeed, some studies have shown that the same patient may present different patterns of biases (perceptual or premotor bias, or a combination of them) depending on the type of task performed (i.e., line bisection versus cancellation task: Na et al., 1998; Adair et al., 1998; Hamilton, Coslett, Buxbaum, Whyte, and Ferraro, 2008) or the type of response required (i.e., verbal versus manual in a Landmark test: Bisiach, Ricci, Lualdi, et al., 1998).

Similarly, some authors who have attempted to classify the same set of neglect patients into perceptual or premotor categories using multiple tasks have failed to find a consistent categorization across tasks (Harvey, Kramer-McCaffery, Dow, Murphy, and Gilchrist, 2002; Harvey and Olk, 2004). This result suggests that even apparently minor variations of the same task may involve different perceptual or premotor spatial components. For example, no consistent perceptual and premotor biases were found in neglect patients tested with two similar versions of the Landmark test, in which judgements of centrally pre-bisected lines or asymmetrically pre-bisected lines were required (Harvey and Olk, 2004). In this study, the subtype of neglect of only 3 out of 13 neglect patients was consistently classified across both tests. Similarly, in another study (Harvey et al., 2002) just 1 out of 12 neglect patients was consistently categorized as having a primarily perceptual bias across three tasks used to separate the perceptual and premotor components with different methods involving the pulley device (Bisiach et al., 1990), the epidiascope (Nico, 1996), and the Landmark test (Milner et al., 1993) previously described. These results support the idea that the perceptual and premotor subtypes of spatial neglect should not be considered as rigid categories. However, it is also possible that a robust and consistent bias in diverse tasks as well as a consistent performance in diverse time assessment procedures may reflect relatively selective dysfunction in the perceptual versus the motor spatial system. It may be useful in future investigation to test a large group of patients on a range of cognitive tasks over time to better understand whether perceptual versus motor spatial bias can be seen as a functionally constant state in individual subjects (Buxbaum et al., 2004).

1.1.3 Rehabilitation techniques: description of different methods

Several approaches have attempted to improve spatial neglect (Luaute, Halligan, Rode, Rossetti, and Boisson, 2006; Adair and Barrett, 2008; Parton, Malhotra, and Husain, 2004, Arene and Hillis, 2007). A main classification of rehabilitation treatments distinguishes top-down techniques, in which voluntary strategies are used, from bottom-up stimulus-based techniques. These different rehabilitation procedures will be briefly summarized below, together with the evidence for their efficacy reported in the literature. It should be noted, however, that a recent Cochrane review (Bowen and Lincoln, 2007) concluded that there is still insufficient evidence to either support or refute the efficacy of particular rehabilitation procedures in reducing disabilities or enhancing independence of neglect patients.

The *top-down* therapies require patients' active participation to learn strategies for compensating their deficits. Since neglect patients are often unaware of their impairments (anosognosia), the efficacy and applicability of these methods may be limited. The most widely used top-down method is based on visual scanning training (VST), in which explicit instructions are given to the patients to orient them toward the neglect side. The VST consists of long-term training for 40 sessions over 8 weeks. This therapy can include verbal, tactile, auditory and visual prompts and it has shown to improve some neglect disorders; one study reported generalization of improvements to every day living situations (Pizzamiglio, Guariglia, Antonucci, and Zoccolotti, 2006).

In the *bottom-up* therapies, instead, patients have a more passive role. The effects of these methods seem to depend on the enhancement of the processing of external stimuli through reconfiguration of correct spatial representations. A large group of bottom-up interventions is based on lateralized physiological stimulation. These methods have been shown to temporarily decrease neglect symptoms during and shortly after application (typically last not more than 30 min).

Examples include:

- Vestibular stimulation (Silberfenning, 1941; Rubens, 1985; Cappa, Sterzi, Vallar, and Bisiach, 1987; Bisiach, Rusconi, and Vallar, 1991; Rode and Perenin, 1984; Karnath,1994; Vallar, Papagno, Rusconi, and Bisiach, 1995)
- Optokinetic, TENS and neck muscle vibration (Pizzamiglio, Frasca, Guariglia, Incoccia, and Antonucci, 1990; Bisiach, Pizzamiglio, Nico, and Antonucci, 1996; Vallar, Guariglia, Magnotti, and Pizzamilgio, 1995; Vallar, Rusconi, et al., 1995; Vallar, Guariglia, Nico, and Pizzamiglio,1997; Karnath, Christ, and Hartje, 1993; Karnath, 1994; Karnath, 1995; Schindler, Kerkhoff, Karnath, Keller, and Goldenberg, 2002; Schröder, Wist, and Hömberg, 2008)
- Trunk rotation (Karnath et al, 1993)
- Repetitive Transcranial Magnetic Stimulation -- rTMS (Brighina, et al., 2003; Fierro, Brighina, and Bisiach, 2006)
- Direct current brain polarization (Ko, Han, Park, Seo, and Kim, 2008; Sparing et al., 2009; see also Kerkhoff, 2003 and Rossetti and Rode, 2002 for review).

Other bottom-up methods are:

- Eye-patching (Butter and Kirsch, 1992; Walker, Young, and Lincoln, 1996; Soroker, Cohen, Baratz, Glicksohn, and Myslobosky, 1994; Barrett et al., 2001; Beis, Andre, Baumgarten, and Challier, 1999; Zeloni, Farnè, and Baccini, 2002)
- Pharmacological treatment (Fleet, Valenstein, Watson, and Heilman, 1987 Hurford, Stringer, and Jann, 1998; Geminiani, Bottini, and Sterzi, 1998; Grujic et al., 1998; Barrett et al., 1999; Malhotra, Parton, Greenwood, and Husain, 2006; Husain and Rorden, 2003).
- Prism adaptation and Fresnel prisms lenses (described in detail in the next chapter).

The monocular patching technique is based on the Sprague effect (Sprague, 1991). Obstructing visual input to the ipsilesional eye (right) reduces the input to the contralesional superior colliculus (left), which increases the effectiveness of the ipsilesional superior colliculus (right), resulting in more eye movements into the neglected contralesional visual field (left; Rafal and Posner, 1987; Butter and Kirsch, 1992). Previous investigations have applied this therapy to neglect patients, but have reported contrasting finding. Some authors reported amelioration of neglect symptoms (Butter and Kirsch, 1992), whereas others have shown a decrease of them, and even provided evidence that eye-patching of the opposite left eye can produce similar results (Walker, Young, and Lincoln, 1996; Soroker et al., 1994; Barrett et al., 2001). A more promising approach seems the hemi-blinding technique, in which eye-patching occludes the ipsilesional (right) side of vision in each eye (Beis et al., 1999; Zeloni, Farnè, and Baccini, 2002). This method results in a suppression of visual inputs from the ipsilesional hemispace and appears to increase the occurrence of contralesional eye movements. Improvement in some neglect symptoms has been described using this technique (Beis et al., 1999; Zeloni et al., 2002).

Pharmacological interventions have also been used in the rehabilitation of spatial neglect, with conflicting results. Two main classes of drugs have been tested: dopamine agonists and noraepinefrine modulators. For dopamine agonists, such as bromocriptine, temporary improvements of neglect symptoms are reported in some cases (Fleet et al., 1987 Hurford, Stringer, and Jann, 1998; Geminiani, Bottini, and Sterzi, 1998), but also exacerbation of the symptoms has been reported (Grujic et al., 1998; Barrett et al., 1999). For the noradrenergic agonist (noraepinefrine modulators), such as Guanfancine, a positive result has been reported in increasing sustained attention and vigilance levels with improvement in leftward visual space exploration in some patients (Malhotra et al., 2006; Husain and Rorden, 2003).

Finally, other authors (e.g., Hussain and Rorden, 2003) have suggested that rehabilitation of spatial neglect should also include training of non-lateralized mechanisms (for example training of alertness or sustained attention) that are often impaired in conjunction with lateralized deficits in neglect patients. These methods are based on training in which attention to the task performed is increased by a periodic loud external noise, followed by training in which the prompt is shifted to the patient who has to verbally "self-alert" himself. These techniques have shown to lead to improvements, not only at the level of sustained attention, but also in lateralized spatial impairments (Robertson, Tegner, Tham, Lo, and Nimmo-Smith, 1995; Robertson, Mattingley, Rorden, and Driver, 1998; Thimm, Fink, Kust, Karbe, and Sturm, 2006).

1.2. Prism Adaptation

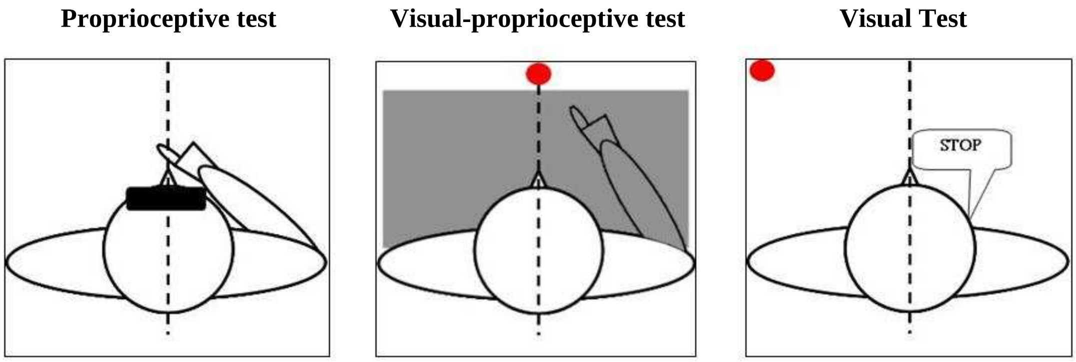
Fig. 3 - Rightward-shifting prism inducing a 10° lateral shift of the visual image

The human brain has a remarkable ability to quickly learn and adapt to environmental changes. One such change – perturbation of the visual field – has been studied using wedge prisms for the last two centuries (Stratton, 1896). Exposure to lateral shifting prisms induces an optical deviation that causes objects to appear laterally deviated from their actual location. Two types of lenses have been used in this kind of rehabilitation: the Fresnel lenses and the wedge prism lenses.

The Fresnel lenses are typically used for rehabilitation of visual deficits, such as hemianopia. This type of lens is very flexible since it is made of a static vinyl that allows the lenses to be directly attached to the spectacles (Fresnel press-on), and to be easily cut to custom shape. Fresnel lenses can also induce lateral deviation (Fresnel prism lenses) similar to the wedge prism. Two previous studies applied Fresnel prism lenses (both inducing a lateral deviation of 15 degrees to the right) for rehabilitation of neglect patients, demonstrating improvements of some neglect symptoms (Rossi, Kheyfets, and Reding, 1990; Keane, Turner, Sherrington, and Beard, 2006). The study of Rossi et al (1990) involved 39 patients affected either by hemianopia or spatial neglect. The Fresnel prism lenses were cut in half and applied only to the affected hemifield. In a second study involving 4 neglect patients, the Fresnel prism lenses were applied to the entire visual field and used with a similar paradigm that has been previously reported for prism adaptation techniques (Keane et al., 2006). A limitation of this kind of lenses, however, is that the flexibility of the material may reduce the contrast of objects viewed through the lens. By contrast, the wedge prism are made of rigid glass or plastic and do not alter the visual image.

Wedge prism typically used in interventions in neglect patients induce a lateral deviation of the visual field that ranges between 10-15 degrees among studies. The standard procedure employed in prism interventions in neglect patients comprises the repetition of pointing movements toward visual targets (Rossetti et al., 1998; Serino, Angeli, Frassinetti, and Ladavas, 2006; Serino, Bonifazi, Pierfederici, and Ladavas, 2007; Serino, Barbiani, Rinaldesi, and Ladavas, 2009; Frassinetti, Angeli, Meneghello, Avanzi, and Ladavas, 2002; Humphreys, Watelet, and Riddoch, 2006; Nijboer, Nys, van der Smagt, van der Stigchel, and Dijkerman, 2010; Ladavas, Bonifazi, Catena, and Serino, 2011; Mizuno et al., 2011).

The same procedure has been used in studies of prism adaptation (PA) in neurologically healthy individuals (see Redding, Rossetti, and Wallace, 2005 and Michel, 2006 for reviews, and Kornheiser, 1976 for older works). When a subject points to a target during exposure to prism, she initially performs a pointing error in the direction of the optical deviation (e.g., rightward deviation for rightward shifting prisms). *Adaptation* to prisms is demonstrated by a gradual error correction of the pointing movements during the exposure phase. *Aftereffects* refer to the appearance of contralateral pointing errors once prisms are removed (e.g., leftward deviation for rightward shifting prisms). In the literature (see Redding and Wallace, 2006 for a review and fig. 4 for an example of the test), such aftereffects have been assessed through the proprioceptive test, in which blindfolded subjects direct their pointing movements to the subjective straight ahead, and the visual-proprioceptive test, in which subjects direct their pointing movements toward visual targets in the absence of vision of their arm. An additional measure of aftereffects is assessed through the visual test, in which subjects verbally estimate the position of a visual target. Contrary to the shift induced in the pointing movements, the prism aftereffect observed in the visual test is oriented in the same direction as the optical displacement (e.g., rightward deviation for rightward shifting prisms; Redding and Wallace, 2010).



Proprioceptive test **Visual-proprioceptive test** **Visual Test**

Fig. 4 - Schematic of the 3 aftereffect measures: Proprioceptive test (left panel), subjects blindfolded have to point straight-ahead, Visual-proprioceptive test (middle panel), with the arm covered to view, subjects have to point to a visual stimulus (red dot); Visual test (right panel), subjects have to verbally stop the movement of the visual stimulus (red dot) when in front of them

Several factors can affect the size of the aftereffects. For example, aftereffects change with the amount of visible movement during the pointing task. Previous studies have demonstrated that minor changes in the adaptation procedure (i.e. exactly how much of the arm a person can see during the adaptation task) can influence the effectiveness of PA For example, concurrent exposure conditions, in which simultaneous visual and proprioceptive feedback of the pointing movement is available, have been shown to induce mostly proprioceptive aftereffects. By contrast, terminal exposure conditions, in which the vision of the limb is available only at the terminus of the pointing movement, induce mostly visual aftereffects (see Redding and Wallace, 1990; Redding and Wallace, 1997; Redding and Wallace, 2010; Ladavas et al., 2011).

1.2.1 Strategic recalibration and adaptive realignment processes

Two distinct processes have been proposed to be involved in the sensori-motor transformation that occurs during PA: a strategic re-calibration and a spatially adaptive realignment (Redding, et al., 2005; Redding and Wallace 2006; Newport and Jackson, 2006). The *strategic re-calibration* is responsible for the correction of the movements performed during the initial phase of prism exposure. During exposure to rightward shifting prism, the perceived location of the target is shifted towards the right of the true target location. The initial pointing movements result in lateral off-target endpoints deviated in the same direction as the prismatic shift. In order to reach the true target position subjects have to redirect the movement more leftward with respect to the perceived target location. Feedback signals generate a visuo-motor correction to the path of the movement, which is responsible for the gradual improvement of the performance. This process is based on plans that anticipate the error and minimize the perturbation (Weiner, Hallett, and Funkenstein, 1983; Welch, Choe and Heinrich, 1974; Redding and Wallace, 1993; Redding and Wallace, 1996). Due to the flexibility of the visuo-motor system, repetition of movements allows to establish new sensorimotor correlations. More recently, this process has been depicted as “recalibration” (Redding, et al., 2005, Rossetti and Wallace, 2006) meaning that the movements are recalibrated over subsequent trials. This mechanism was described as a temporary and local rearrangement of spatial representations that can occur quickly and can be observed within a few trials (5 to 15 trials, depending on the particular conditions employed).

When the visuo-motor interactions are further performed, an *adaptive realignment* of visual and proprioceptive spatial reference frames occurs (Rossetti, Koga, and Mano, 1993). When exposed to lateral shifting prism, the visual and proprioceptive reference frames are no longer aligned. For example, the eye-centered reference frame in which visual information is coded is shifted relative to the shoulder-centered reference frame that constrains the range of pointing movements. The perceived target location is specified by oculocentric coordinates. In order to reach the target the limb has to be moved away from the perceived deviated target location toward the real target location. Therefore, the motor program planned on the visual coordinates of the perceived target location has to be re-directed to an incorrect motor program that is planed in limb-based coordinate relative to the veridical target location. The redirection of the movement constitutes the spatial discrepancy signal required to update the visual and proprioceptive reference frame systems (Newport and Jackson, 2006). The discordance between the visual and proprioceptive information motivates the gradual sensory-motor adjustment of the two reference frames and is responsible for the appearance of the aftereffects during the post-exposure phase (Redding and Wallace, 1993; Redding et al., 2005). While the detection of pointing errors can occur in the first few trials of prism exposure, triggering strategic recalibration, the adaptive realignment takes much longer to occur. Reliable contralateral aftereffects are normally seen after 30 or more pointing trials (Newport and Jackson, 2006).

However, strategic recalibration and adaptive realignment are not necessarily serially dependent mechanisms. Indeed, these two components are thought to be interrelated and interactive (Michel, Pisella, Prablanc, Rode, and Rossetti, 2007; Newport and Jackson, 2006; Redding et al., 2005; Fernandez-Ruiz et al., 2007). Some studies have shown that when the role of one component is enhanced, the role of the other one is reduced or even cancelled. Strategic recalibration was enhanced in paradigms in which awareness of the presence of the optical distortion was increased, for example providing explicit information about the lateral deviation induced by prisms during the experiment (Jakobson and Goodale, 1989). Accordingly, the adaptive realignment was reduced, as shown by reduced aftereffects in the post-exposure condition. Similarly, reducing awareness of the optical displacement is associated with an increased adaptive realignment (more robust aftereffects), as shown in a study in which the detection of the prism deviation was reduced (Michel et al., 2007). A greater and longer-lasting aftereffect has also been shown in neglect patients compared to neurological healthy individuals (Rossetti et al., 1998; Farnè, Rossetti, Toniolo, and Ladavas, 2002; McIntosh, Rossetti, and Milner, 2002; Pisella, Rode, Farnè, Boisson, and Rossetti, 2002).

A possible explanation for the increased aftereffects in neglect patients derives from the fact that neglect patients are usually unaware of the visual perturbation generated by prism exposure. Indeed, when neglect patients are directly questioned about their performance during prism adaptation, they have the inclination to self-attribute prism-induced errors (e.g. “hypernosognosia”; Rode, Pisella, Rossetti, Farnè, and Boisson, 2003). Other authors demonstrated that neglect patients had reduced skin conductance modification when prisms were unexpectedly introduced during the pointing task, compared to healthy subjects or right-brain damaged patients without neglect (Calabria et al., 2004). Another possible explanation of the larger aftereffects observed in neglect patients may be related to differences in cerebral plasticity or brain asymmetry following brain damage, rather than to the mere reduction of the strategic component. Strategic recalibration has been shown to decrease with age, such that elderly people exhibits a slower error reduction during prism exposure (Weiner et al, 1983). Consistent with the idea that when one component decreases the other one increases, elderly people also demonstrated greater and longer-lasting aftereffects than young people (Weiner et al., 1983; Fernanedez-Ruiz, Hall, Vergara, and Diaz, 2000).

1.2.2 Effects of prism adaptation in neglect patients

Prism Adaptation (PA) appears to be a particularly promising technique for rehabilitating neglect. In the pioneering study of Rossetti et al. (1998), improvements in paper and pencil tests (drawing, cancellation and line bisection tests) were observed following just a few minutes (2-5 min.) of exposure to prism glasses inducing a rightward deviation of the visual field (10 degrees). The beneficial effect of PA on visuo-spatial tasks has subsequently been replicated (Farnè et al., 2002; Pisella et al., 2002; Saeversson, Kristjansson, Hildebrandt, and Halsband, 2009), and extended to other tasks involving mental imagery (Rode, Rossetti, Li, and Boisson, 1998; Rode, Rossetti, and Boisson, 2001; Rossetti et al., 2004), attentional orienting (Striemer, Sablatnig, and Danckert, 2006; Striemer and Danckert; 2007; Nijboer, McIntosh, Nys, Dijkerman, and Milner, 2008), and temporal order judgments (Berberovic, Pisella, Morris, and Mattingley, 2004). Improvement after PA has been reported in exploratory eye movements (Dijkerman et al., 2003; Ferber, Danckert, Joanisse, Goltz, and Goodale, 2003; Serino et al., 2006; Serino et al., 2007), postural control and balance (Tilikete et al., 2001; Shiraishi, Yamakawa, Itou, Muraki, and Asada, 2008), and wheelchair navigation (Michel, Rossetti, Rode, and Tilikete, 2003; Rossetti, Rode, Pisella, and Boisson, 1999).

Beneficial effects of PA have also been recorded in different sensory modalities including tactile (Maravita et al., 2003) and auditory extinction (Jacquin-Courtois et al., 2010), and somato-sensory (Dijkerman, Webeling, ter Wal, Groet, and van Zandvoort, 2004) and haptic perception (Girardi, McIntosh, Michel, Vallar, and Rossetti, 2004; McIntosh et al., 2002). In addition, prism adaptation may also reduce drawing perseveration (Vallar, Zilli, Gandola, and Bottini, 2006, nine right-brain-damaged patients with left neglect), a phenomenon frequently associated with neglect (Na et al., 1999; Rusconi, Maravita, Bottini, and Vallar, 2002), although in one right-brain-damaged patient neglect symptoms decreased, but perseveration increased after prism exposure (Nys, Seurinck, and Dijkerman, 2008).

Long-term benefits have frequently been shown hours and even days after a single PA session (Rossetti et al., 1998; Farnè et al., 2002; Pisella, et al., Dijkerman et al., 2004; Jacquin-Courtois, Rode, Pisella, Boisson, and Rossetti, 2008; Rode, Klos, Courtois-Jacquin, Rossetti, and Pisella, 2006), but also months and even one year after long-term training of multiple sessions (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Shiraishi et al., 2008; Humphreys et al., 2006; Ladavas et al., 2011; Nijboer et al., 2010; Mizuno et al., 2011).

One study, in right-brain-damaged stroke patients, reported that four consecutive days of pointing sessions during prism exposure improved left spatial neglect, as assessed by a cancellation task, although at a one month assessment no difference was found compared to a control group of patients who had worn neutral goggles (Nys et al., 2008). Other studies (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Serino et al., 2009; Ladavas et al., 2011) found that a two-week treatment with rightward shifting prisms decreased left spatial neglect, as assessed by visuo-spatial tests. The improvement involved both peripersonal (Frassinetti et al., 2002; Ladavas et al., 2011), and personal space (Serino et al. 2007), tactile extinction (Serino et al., 2006; Serino et al., 2007), and persisted up to six months (Serino et al., 2007). Spatial neglect was also decreased after ten pointing sessions in which right-brain-damaged patients wore neutral goggles. Importantly, however, the improvement was greater when patients pointed to visual targets while wearing prisms that produced a rightward shift (Serino et al., 2009; Mizuno et al., 2011). This suggests a specific role of prism adaptation, over and above the positive effects of visuomotor activity per se. Amelioration of the detection of contralesional stimuli (measured by visual field perimetry) was also reported in one patient with chronic neglect after right-brain lesion (patient LZ) that received a long-term rehabilitation training with PA for 3 months (Nijboer et al., 2010). Similarly, a group of 7 right-brain-damaged patients with a chronic left neglect showed improved in the leftward deviation of their eye movements and a standing task (measured as centre of pressure) after performing PA for a period of eight weeks, 50 minutes per day. The improvement was maintained for at least 6 weeks (Shiraishi et al., 2008).

1.2.2.1 Evidences of no amelioration after prism adaptation

Some studies have reported no significant amelioration in some visual-spatial tasks in neglect patients after prism exposure. For example, Rousseaux, Bernati, Saj, and Kozlowski (2006) showed no effect in a group of neglect patients in both cancellation and drawing tests after a single prism exposure. Luaute, Michel, et al. (2006) reported improvement after a single PA session in five neglect patients only in the cancellation tasks of the BIT (lines, stars and letters) whereas the figure and shape copying drawing tests remained unchanged. Another negative finding was recently reported in a group of 34 right-brain-damaged patients (16 with prisms, 18 sham) that participated in a single-blind randomized study; no different effects of the prism and the sham treatment on self care and left spatial neglect was found (Turton, O’Leary, Gabb, Woodward, and Gilchrist, 2010). However, this negative finding may reflect the use of prisms producing a minor rightward shift of the visual field (6 instead of 10 degrees rightward displacing prisms).

Some other studies revealed a relatively weak effect of PA particularly in perceptual tasks. For example, while eye movements were more leftward deviated after prism exposure in two neglect patients (patient RD in Dijkerman et al., 2003; one patient in Ferber, et al., 2003), the two patients did not show changes in perceptual-attentional tasks after PA involving, respectively, a perceptual size estimation of a geometric figure (Dijkerman, et al., 2003), and detection of chimeric faces (Ferber et al., 2003). A similar finding was reported in the study of Ferber and Murray (2005) involving 22 healthy subjects. The baseline leftward oculomotor bias decreased after PA, whereas the detection of chimeric faces remained leftward biased in the post-exposure condition. A lack of improvement on the perceptual bias after PA in neglect patients was also shown by Sarri and collaborators on two different tasks: detection of chimeric faces (Sarri, Kalra, Greenwood, and Driver, 2006; Sarri, Greenwood, Kalra, and Driver, 2010) as previously reported by Ferber et al. (2003), and a grayscale gradients task (Sarri et al., 2010).

However, in the same sample of patients, improvements in the detection of chimeric objects (Sarri et al., 2006) and in the *discrimination* of chimeric faces were also shown (Sarri et al., 2010). A null effect of PA on the attentional orienting bias was reported in the study of Morris and collaborators (2004) in three out of four neglect patients. The task required the detection of targets mixed with distracters and did not involve spatially directed motor responses. No improvements were found in the search time and number of left-side target omissions following adaptation. Interestingly, one subject (#3) showed a worsening of perceptual neglect symptoms after PA, as indicated by a reduction in search times for targets located on the (intact) right side of the display together with a bigger percentage of errors for targets located on the (neglected) left side of the display. Finally, another recent study, involving a group of neglect patients (Eramudugolla, Boyle, Irvine, and Mattingley, 2010), showed an improvement in the target detection efficiency in both visual and auditory dual tasks but not in the ipsilesional attentional bias of both conditions. These results suggest that PA may in some cases worsen the ipsilesional perceptual bias in neglect patients (but see Saeversson et al., 2009; Sarri et al., 2006; Sarri et al., 2010 for improvement in perceptual tasks post-PA).

1.2.3 Lateralized effects of prism adaptation in healthy individuals

Several studies have indicated that neurologically healthy individuals err subtly but systematically to the left in many spatial tasks. This phenomenon is commonly termed "*pseudoneglect*" because it mirrors the asymmetrical aspects of spatial neglect and it appears to stem from an overestimation of the stimulus properties located on the left relative to those on the right hemispace (Bowers and Heilman, 1980). In contrast to neglect patients, who neglect the left hemispace, healthy subjects show a subtle but systematic neglect of the right hemispace. Leftward errors have been recorded in tasks such as: 1) line bisection (Jewell and McCourt, 2000; Nicholls and Roberts, 2002; McCourt and Jewell 1999; Nicholls, Bradshaw, and Mattingley, 1999), even when performed in tactile and kinaesthetic modalities (Bowers and Heilman, 1980); 2) judgements of luminosity, size and numerosity (Nicholls, et al., 1999; Nicholls, Mattingley, Berberovic, Smith, and Bradshaw, 2004); 3) mental alphabet and mental number lines (Nicholls and Loftus, 2007; Longo and Lourenco, 2007); 4) recall of familiar scenes (McGeorge, Beschin, Colnaghi, Rusconi, and Della Sala, 2007).

Amongst the various mechanisms that have been proposed to explain pseudoneglect, one explanation suggests that the leftward bias derives from attentional biases due to a neurological asymmetry between the right and left hemisphere. In particular, the right hemisphere specialization for spatial attention (Heilman, Bowers, Valenstein, and Watson, 1987; Mattingley et al., 1992; Spiers et al., 1990; Nicholls et al., 2004; Bultitude and Aimola-Davies 2006) may explain the contralateral attentional bias, towards the left hemispace (see Kinsbourne, 1970). Consistent with this account, modulation of right hemisphere activation may reduce pseudoneglect (see Bultitude and Aimola-Davies 2006 for a review). Other authors (see Nicholls and Roberts, 2002 for a review) have suggested that an overestimation of the left side could derive from motor factors such as the limb used to perform the task or the starting point of the manual scanning (Heilman and Valenstein, 1979; Brodie and Pettigrew; 1996; Bradshaw, Bradshaw, Nathan, Nettleton, and Wilson, 1986; Sampaio and Chokron, 1992; McCourt, Freeman, Tahmahkera-Stevens, and Chausse, 2001; Halligan, Manning, and Marshall, 1991), or oculomotor direction of visual scanning, in which left to right eye movements may play a role in moving attention over the left starting position side (Halligan et al., 1991; Chokron, Bartolomeo, Perenin, Helft, and Imbert, 1998; Chokron and Bartolomeo, 1997; Brodie and Pettigrew, 1996; Chokron and Imbert, 1993; Chokron and De Agostini, 1995; Sakhuja., Gupta, Singh, and Vaid, 1996; Vaid and Singh, 1989).

While in neglect patients right- but not left-shifting prisms seems to improve a rightward spatial bias (Rossetti, et al., 1998; Rossetti et al., 2004), in unimpaired individuals left- but not right-shifting prisms appears to reduce a leftward spatial bias, thus mirroring the effects of PA in neglect patients. In the initial study of Colent and colleagues (2000), an asymmetrical effect of PA was found in a perceptual line bisection task. Participants showed post-adaptation effects only after training with left-shifting prisms, and failed to demonstrate any significant shift after training with right-shifting prisms. Berberovic and Mattingley (2003) replicated the same asymmetrical finding in the peri-personal space. However, they also found that both left- and right-shifting prisms induced a post-PA rightward shift on the perceptual task for stimuli appearing in extra-personal space. Effects of left- but not right-shifting prisms have also been demonstrated in several other tasks, including: 1) participants' body posture, measured as center of pressure while standing (Michel et al., 2003); 2) haptic and visual estimation of the center of a circle (Girardi et al., 2004); 3) perceptual greyscale task (Loftus, Vijayakumar, and Nicholls, 2009); 4) mental number line bisection task (Loftus, Nicholls, Mattingley, and Bradshaw, 2008); 5) mental alphabet bisection task (Nicholas and Loftus, 2007); and 6) global interference effect during local level identification (Bultitude and Woods, 2010).

1.2.4 Cerebral circuits involved in PA

Different brain areas are involved in prism adaptation. Current data derive from brain imaging studies, studies with brain-damaged patients, and studies with primates. These studies have revealed that the anatomical regions that are likely to be responsible for adaptation consist of a network of areas involving the parietal, the cerebellum, and the frontal cortex (Redding and Wallace, 1993; Redding and Wallace, 1996; Redding and Wallace, 2006; Michel, 2006; Michel, et al., 2007; Fernandez-Ruiz, et al., 2007; Newport and Jackson, 2006; Pisella, Rode, Farnè, Tilikete, and Rossetti, 2006). Studies with monkeys have revealed that these three broad areas (parietal, frontal and cerebellum) have numerous neuroanatomical interconnections. For example, the cerebellum projects to areas of the parietal lobe such as the posterior parietal cortex (PPC) via the dentate nuclei (Clower, West, Lynch, and Strick, 2001; Dum and Strick, 2003; Krienen and Buckner, 2009; Ramnani, 2006). The PPC is directly and indirectly connected to the primary motor areas (Johnson, Ferraina, Bianchi, and Caminiti, 1996; Rossetti, Pisella, and Pellisson, 2000; Wise, Boussaoud, Johnson, and Caminiti, 1997). The cerebellum has projections to frontal areas such as the ventral premotor cortex (PMv), via the thalamus (Dum and Strick, 2003; Middleton and Strick, 1997). In addition, the lateral cerebellar cortex receives input both from the PPC and the PMv via the cortico-ponto-cerebellar pathway (Brodal and Bjaalie, 1997; Glickstein, May, and Merciet, 1985). A speculative model of the connections and functions of these areas has recently been put forward by Newport and Jackson, 2006 (Fig. 5). The authors suggested that the cerebellum might be the principle region underlying the adaptive realignment process, creating a reconfiguration of the relationship between the hand and the target; this process may be started and triggered by the PMv area (magenta arrows). In addition, they hypothesized that the on-line correction of the pointing movement may be realized in a parieto-cerebellar loop (blue arrows) that allows continuously detecting and quickly correcting movements. Finally, a parieto-PMv loop (green arrows) may underlie the strategic component process of prism adaptation. Thus, the PMv area detects the discrepancy between the finger position and the target location, whereas the PPC provides the sensorimotor transformation necessary to realize the subsequent correct reaching movement after the error detection. Below follows a summary of currently available evidence for the role of parietal, cerebellar and frontal areas in prism adaptation.

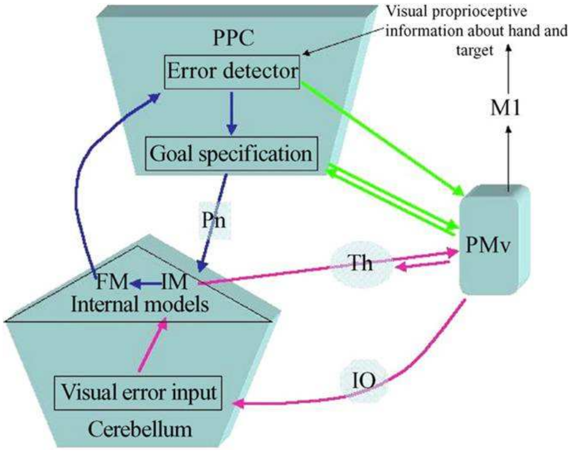


Fig. 5 - Areas involved in prism adaptation (model from Newport and Jackson, 2006).
PPC = posterior parietal cortex; M1= primary motor cortex; PMv = ventral premotor cortex; Th = thalamus; IO = inferior olive; Pn = pontine nuclei; IM = inverse models; FM= forward models

1.2.4.1 Parietal Areas

The parietal lobe and in particular the posterior parietal cortex (PPC) has been shown to be implicated in sensory-motor transformation and in the integration of multisensory inputs (Anderson, Snyder, Bradley, and Xing, 1997). PPC receives projections from areas that contain eye-, head- and body-centered representations of the space (Anderson et al., 1997; Xing and Andresen, 2000; Milner and Goodale, 1995) and it has been suggested to be an ideal area to trigger online modification of goal directed movements (Newport, Brown, Husain, Mort, and Jackson, 2006).

Several brain imaging studies have suggested the involvement of the parietal lobe, in particular the PPC, as mainly responsible for the strategic component of prism adaptation as shown by its selective activation in the first trials of prism exposure where the initial error correction takes place (Clower et al., 1996; Danckert, Ferber, and Goodale, 2008; Luaute et al., 2009).

In the early study of Clower et al. (1996), a selective activation of PPC was found during an ongoing adaptation task in which neurologically healthy subjects were exposed to alternated right- or left-shifting prism (one eye was exposed to rightward and one eye to leftward shifting prism). This procedure allows for a comparison with studies involving bilateral shifting prism paradigms since the same adaptation effect occurs with monocular and binocular vision (Redding and Wallace, 2005). When exposed to prism, subjects adapted in around 5-10 trials of pointing movements, and the prismatic displacement was regularly reversed in order to obtain an ongoing adaptation. The adaptation condition was compared to a control condition (without prism exposure) in which error detection was still present since the target was moved by an amount equivalent to the displacement induced by prism. The authors used positron emission tomography (PET) to localize changes in regional blood flow (rCBF). Irrespective of the prism direction, a selective activation of the *left* PPC (contralateral to the reaching limb) was found. The region of activation was located on the lateral bank of the intraparietal sulcus. The authors hypothesized that the PPC may be responsible for the detection of the mismatch between the seen and the felt positions of the hand rather than being involved in prism adaptation itself. Recently, Danckert et al. (2008) performed an fMRI study to explore the areas active during the initial phase of exposure to rightward shifting prism (first 3 pointing trials) in comparison with later trials of the exposure condition (10 trials). They confirmed that the parietal lobe was involved in the earlier phase of prism exposure in which a larger error correction took place. In particular, the authors reported a stronger activation of the left anterior intraparietal sulcus (IPS) and a concurrent activation of the vermis of the cerebellum during the first 3 trials of prism exposure. In addition, they registered activation in the left primary motor cortex and the anterior cingulate during the early and late trials. Similarly, another recent event-related fMRI study investigates the entire adaptation process (Luaute et al., 2009). The procedure was based on a trial-by-trial analysis to explore the neural activation over the time course of the adaptation process. Subjects were adapted to a leftward shifting prism. The authors again confirmed the role of the PPC in the initial phase of prism exposure as demonstrated by activation in the left anterior IPS. Moreover, they found activation in the left posterior occipital sulcus (POS) and suggested that IPS is involved in the error detection and POS in the error correction during the early adaptation process. Lastly, a recent study employed a blocked fMRI design to test brain activation during the strategic component associated with adaptation to left-shifting prisms (Chapman et al., 2010). Once again, the authors confirmed the role of the parietal lobe in the early stage of prism adaptation and defined two additional sites involved in the process: the right superior parietal lobule (SPL) and the right inferior parietal lobule (IPL). In addition, they found a concurrent activation in the posterior region of the left cerebellum and the anterior part of the right cerebellum.

Further evidence for the involvement of parietal areas in the strategic component of prism adaptation is provided by patients with bilateral lesions of the parietal lobe. In three case studies, patients exhibited impairment in on-line corrections of hand movements during PA (patient JJ, Newport and Jackson, 2006; patient IG, Pisella et al., 2004; Grea et al., 2002), while they still presented a contralateral aftereffect in the post-exposure phase. In addition, a study applying transcranial magnetic stimulation (TMS) over the PPC has provided evidence for its role in the on-line correction of hand movements during PA (Desmurget et al., 1999). Taken together, these studies indicate a critical involvement of the parietal lobe in detecting and correcting errors associated with the initial exposure to prismatic displacement.

Parietal areas have also been implicated in the spatial realignment component of prism adaptation (Michel, 2006; Luaute et al., 2009; Chapman et al., 2010). In particular, brain activation studies have shown activation in parietal areas during later stages of prism exposure. For example, Chapman et al. (2010) showed activation in the right inferior parietal lobe (IPL) and in the right angular gyrus concurrently with activation in the right cerebellum during the second half of prism exposure (see below for a full description of the putative role of the cerebellum in prism adaptation). The authors hypothesized that the right angular gyrus may be responsible for modulation of the activation of other areas involved in the later phase of prism adaptation, such as the cerebellum. Similarly, Luaute et al. (2009) showed activation in the left IPL during the de-adaptation phase (aftereffects), in which the spatial realignment component is thought to be involved. Moreover, a PET study in neglect patients exposed to one session of prism adaptation (Luaute, Michel, et al., 2006) suggested that the parietal cortex is involved in neglect improvement after prism adaptation (Pisella et al., 2006). The study showed activity in a network of areas including the right PPC and right cerebellar hemisphere as well as the thalamus, the temporo-occipital cortex, and the medial temporal cortex during the post-exposure condition, when improvement of neglect symptoms was recorded.

1.2.4.2 Cerebellum areas

The cerebellum has been implicated in several different tasks that are relevant for PA: 1) the initiation of movements toward visual targets (Bastian, Martin, Keating, and Thach, 1996; Stein, 1986); 2) eye-hand coordination (Miall, Imamizu, and Miyauchi, 2000); 3) visuo-motor learning tasks during short- and long-term learning processes (Gilbert and Thach, 1977; Ito 1989; Friston et al., 1992; Martin, Keating, Goodkin, Bastian, and Thach,1996; Imamizu et al., 2000); 4) correction of limb movements toward visual targets during perturbation of the visual field (Baizer and Glickstein, 1974; Weiner et al., 1983); 5) comparing the predicted consequence of an action with the actual sensory feedback from the movement performed (Held, 1961; Blakemore, Frith, and Wolpert, 2001). Some studies in patients with cerebellum lesions reported the inability of the patients to correct their limb movements during the whole phase of prism exposure (Thach, 1998; Morton and Bastian, 2004). Another study also reported impairment in the correction of the lateral deviation induced in a walking task after prism adaptation in subjects with cerebellar damage (Morton and Bastian, 2004). The lateral deviation persisted much longer in the patient group compared to a control group of neurological healthy subjects and never came back to the baseline level, as in the control group. Similarly, lack of error correction during prism adaptation was shown in studies with monkeys after a focal lesion in the vermal and paravermal region of the cerebellum (Baizer, Kralj-Hans, and Glickstein, 1999; Lewis and Tamago, 2001; Stein and Glickstein, 1992).

A recent event-related fMRI study also provided evidence for the involvement of the vermis of the cerebellum in the early stage of prism exposure in neurologically healthy subjects (Danckert et al., 2008). The cerebellum may also play a role in the later phase of prism exposure, when error corrections have already occurred and adaptive realignment components are predicted to happen. For example, patients with lesions in cerebellar areas did not exhibit contralateral aftereffects during the post-exposure phase (Martin et al., 1996). In the study of Luauté and collaborators (2009) activation of the lateral part of the right cerebellum (the culmen) was observed during later trials of leftward prism exposure. Similarly, Chapman and collaborators (2010) found increased activation during the last half of prism exposure in the posterior region of the right cerebellum.

1.2.4.3 Frontal areas

In the fMRI study of Danckert et al. (2008), activation of the left primary motor cortex (M1) was found during exposure to rightward shifting prism in the initial (3 trials) and late (10 trials) phase of prism exposure. In addition, the authors detected activation in the anterior cingulate cortex (AC). The AC region is known to be involved in conflicting monitoring tasks in which error detection, error correction and ongoing monitoring of performance is required to ensure continued accuracy (Van Veen and Carter, 2002a, 2002b). Another study has shown the involvement of associative motor areas, located in the frontal lobe, in sensory-motor adjustments during prism adaptation (Kurata and Hoshi, 1990). In this study, monkeys were exposed either to left- (left eye) or right- (right eye) shifting prism and they showed adaptation to the lateral displacement within 10-20 trials of visually guided reaching movements. The authors reported a selective role of the ventral premotor cortex (PMv) during adaptation to prism. In particular, monkeys lost the ability to correct the errors during the exposure condition when the PMv area (contralateral to the shift induced by prism) was blocked by a muscimol injection. By contrast, this deficit was not observed when the dorsal premotor cortex (PMd) or the ipsilateral PMv area were inactivated. Finally, activation in motor areas was also observed in a preliminary PET study in 6 normal subjects in which pointing movements performed under exposure to rightward or leftward prisms were contrasted with pointing movements performed without prisms (Zeffiro, 1995).

Table 1 A-B. Summary of brain regions implicated in PA paradigms during the early and late phase of prism exposure

1A. Early phase

Studies	Prisms	Method	Parietal lobe	Cerebellum	Frontal lobe	Others
Luaute et al., 2009	Lx	fMRI	Lx ant. IPS	Medial (vermis)	M1	Lx POS
Clower et al., 1996	Rx – Lx alternate	PET	Lx PPC lat. IPS			
Danckert et al., 2008	Rx	fMRI	Lx ant. IPS	Medial (vermis)	Lx M1, AC	
Chapman et al., 2010	Lx	fMRI	Rx ant. IPS, Rx SPL, Rx IPL	Lx post. areas, Rx ant. areas		

1B. Late phase

Studies	Prisms	Method	Parietal lobe	Cerebellum	Frontal lobe	Others
Luaute et al., 2009	Lx	fMRI	Lx IPL	Rx areas (culmen)		
Danckert et al., 2008	Rx	fMRI			Lx M1, AC	
Chapman et al., 2010	Lx	fMRI	Rx IPL, Rx angular gyrus	Rx post. areas		
Kurata and Hoshi, 1990	Rx – Lx alternate	Muscimol injection			Lx and Rx PMv (contraLat)	
Zeffiro, 1995	Rx – Lx alternate	PET		Lat. areas	preF	VL Th
Luaute et al., 2006	Rx	PET	Rx PPC	Rx areas (dentate nc, lobule V)		Lx Th, Lx TO

Prisms: direction of the deviation induced by the goggle; PPC: Posterior Parietal Cortex; IPS: Intra Parietal Sulcus; SPL: Superior Parietal Lobule; IPL: Inferior Parietal Lobule; M1: Primary Motor Cortex; AC: Anterior Cingulate cortex; preF: pre Frontal cortex; PMv: ventral Pre-Motor cortex; POS: Posterior Occipital Sulcus; Th: Thalamus; VL Th: VentroLateral Thalamus; TO: Temporo-Occipital cortex; post: posterior; ant: anterior; lat: lateral; contraLat: contralateral to the deviation induced by prism; Lx: Left; Rx: Right

FIRST PART

PRISM ADAPTATION AND ECOLOGICAL VISUO-MOTOR ACTIVITIES

Prism adaptation (PA) appears to be a particular promising technique since it has been shown to improve an extensive range of neglect deficits. The standard procedure employed in prism adaptation paradigm in neglect patients comprises a visuo-motor activity based on the repetition of pointing movements toward visual targets (Rossetti et al., 1998). Although this procedure is widely used in PA studies in neglect patients, it may not be optimal for long-term rehabilitation interventions due to the repetitive and tedious nature of the pointing movements. Various alternative tasks have been applied in studies investigating the effects of a single PA session. For example, activities involving line bisection movements, ball and dart throwing tasks, and walking trajectories have been used during PA in neglect patients and healthy neurological individuals (Goedert, Leblanc, Tsai, and Barrett, 2010; Micheal, Vernet, Courtine, Ballay, and Pozzo, 2008; Morton and Bastian, 2004; Fernandez-Ruiz and Diaz, 1999; Fernandez-Ruiz et al., 2000; Fernandez-Ruiz et al., 2003; Martin, Keating, Goodkin, Bastian, and Thach, 1996a; Martin, Keating, Goodkin, Bastian, and Thach, 1996b; see also the review of Kornheiser, 1976 for older works).

The first aim of this PhD work was to verify if more diverse and engaging visuo-motor tasks, performed during the exposure phase of the PA training, might be as effective as the traditional pointing task in ameliorating neglect symptoms. Therefore, in Experiment 1 we submitted 10 neglect patients to both a standard pointing adaptation training and a training involving diverse ecological visuo-motor tasks (ecological procedure). We compared the effect of the two treatments in a large assessment including a variety of neuropsychological tests as well as functional scales.

In Experiment 2 we assessed the presence of adaptation and aftereffects during the new ecological activities. Such measures are considered to be key indicators of the effectiveness of PA (Welch, 1978; Redding and Wallace, 1993). Errors performed during the exposure phase (adaptation effect) and after prisms were removed (aftereffects) were assessed when 48 neurologically healthy subjects performed the ecological adaptation procedure and the standard pointing procedure. We then compared the adaptation effect and aftereffects during the ecological procedure with those during the traditional pointing task. In the next two chapters we will present the methods and results of the two experiments.

EXPERIMENT 1

Rehabilitating patients with left spatial neglect by prism exposure during a visuo-motor activity

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Fortis, P., Maravita, A., Gallucci, M., Ronchi, R., Grassi, E., Senna, I., Olgiati, E., Perucca, L., Banco, E., Posteraro, L., Tesio, L., Vallar, G. (2010). Neuropsychology, 24(6), 681-97.

http://www.apa.org/pubs/journals/neu/index.aspx]

2.1 Aim of the study

The aim of the present study was to verify the efficacy of a new adaptation task in improving neglect symptoms. The new procedure was based on a series of visuo-motor activities, involving a variety of actions that are common in daily life and performed with different everyday objects. We compared the effect of one week of PA training with the traditional pointing task with the effect of one week of PA training with the novel ecological approach in a group of 10 neglect patients. We assessed whether ecological visuomotor training was at least as effective as the standard pointing training. We used a crossover design: the one-week pointing adaptation treatment served as the control condition and the one-week ecological visuomotor activities as the experimental condition, for a total of two weeks of treatment, following previous studies (Frassinetti et al., 2002; Serino et al., 2007). Recent studies have also provided evidence that PA intervention might have beneficial effects in behavioural and ecological tasks in neglect patients exposed to PA training (Vangkilde and Habekost, 2010; Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2009; Serino et al., 2007; Ladavas et al., 2011; Mizuno et al., 2011). Therefore, the efficacy of the two adaptation procedures was tested through an assessment based on traditional neuropsychological tests and through scales that measured the patients' ability and independence in daily-life activities (CBS and FIM scales).

Finally, some authors have suggested that the beneficial impact of PA on neglect symptoms might be related to the patients' ability to adapt to prism in terms of error correction during the exposure phase (Serino et al, 2006; Serino et al., 2007 Ladavas et al., 2011), or magnitude of aftereffect in the post-exposure phase (Sarri, 2008; Farnè et al., 2002). Therefore, we assessed whether the amount and duration of the adaptation and/or aftereffect could predict the improvement of patients' neglect symptoms. The adaptation effect and the aftereffect of the present study were recorded during the week in which patients received the pointing task procedure since the ecological task did not provide measures of error performance.

2.2 Materials and methods

Participants

A continuous series of ten right-hemisphere-damaged patients (seven females, and three males) with left USN entered this study. Patients were selected from the inpatient population of the Neurorehabilitation Unit of the Istituto Auxologico Italiano IRCCS, Milan, Italy, and the Neurorehabilitation Unit of the "Carlo Poma" Hospital, Bozzolo, Mantova, Italy. Patients gave informed consent to the study. The patients' mean age was 72.7 years (SD ±5.19, range 66-82), and their mean education was 9.1 years (SD ±4.48; range 5-17). Patients were recruited during an 18-months period (November 2006-May 2008). Twelve right-brain-damaged patients with left spatial neglect did not enter the study, being unable to complete the baseline assessment, due to the severity of their general medical condition. Four patients did not complete the study due to worsening of their general medical condition, and to incapacity to cooperate (one patient). The 10 patients' average length of illness was 3.4 months (SD± 3.13, range 1-10). All patients were right-handed, according to a standard interview (Oldfield, 1971), and had no history or evidence of previous neurological or psychiatric diseases. All patients had a normal or corrected-to-normal vision. The presence of visual field deficits was evaluated by a confrontation test (Bisiach et al., 1986), and, in four out of ten patients, also by computerized perimetry. The etiology of the lesion was vascular in nine patients (eight ischemic, one hemorrhagic stroke), and neoplastic in one patient (an operated benign tumor). The patients' lesions were assessed by CT scan in nine patients, and MRI scan in one patient. In patient FE the CT scan images, not available for mapping, showed an extensive cortico-subcortical ischemic fronto-temporo-parietal lesion, involving the basal ganglia and the insula. In nine out of ten patients, the extent and the location of the lesions were defined and visualized using MRIcro software (Rorden and Brett, 2000). Lesions were drawn manually on an MRI template, using the closest matching transverse slice for each patient. Combining all slices produced a 3D lesion ROI for each patient. Figure 6 shows the transverse sections of the ROIs. The patients' lesions overlapped in the anterior and central white matter, and in the basal ganglia (head of the caudate nucleus, and pallidal nucleus). The demographic and neurological features of the patients are summarized in Table 2.

Table 2. Demographic and neurological features of ten right-brain-damaged patients with left USN. M/F: male/female. I/H/N: ischemic/hemorrhagic/neoplastic. M/SS/VHF: motor/somatosensory/visual half-field deficit. -/+/++/+++/: absent/mild/moderate/severe deficit; e: extinction to double simultaneous stimulation.

Patient	Age/ Sex	Lesion Etiology	Education (years)	Duration of disease (months)	Neurological impairment			Group
					M	SS	VHF	
BA	71/F	H	13	2	+	-	-	CE
BG	79/M	I	5	1	-	++	+++	CE
TA	71/F	I	13	2	+++	++	++/e	CE
SG	82/F	I	13	2	+++	++	e	CE
PF	66/F	N	5	2*	-	e	e	CE
CF	75/M	I	17	7	+++	+++	+++	EC
FE	69/M	I	5	1	+++	++	++	EC
MF	71/F	I	7	10	+++	e	e	EC
RD	76/F	I	8	1	-	-	-	EC
GMT	67/F	I	5	6	+++	+++	e	EC

* After neurosurgery

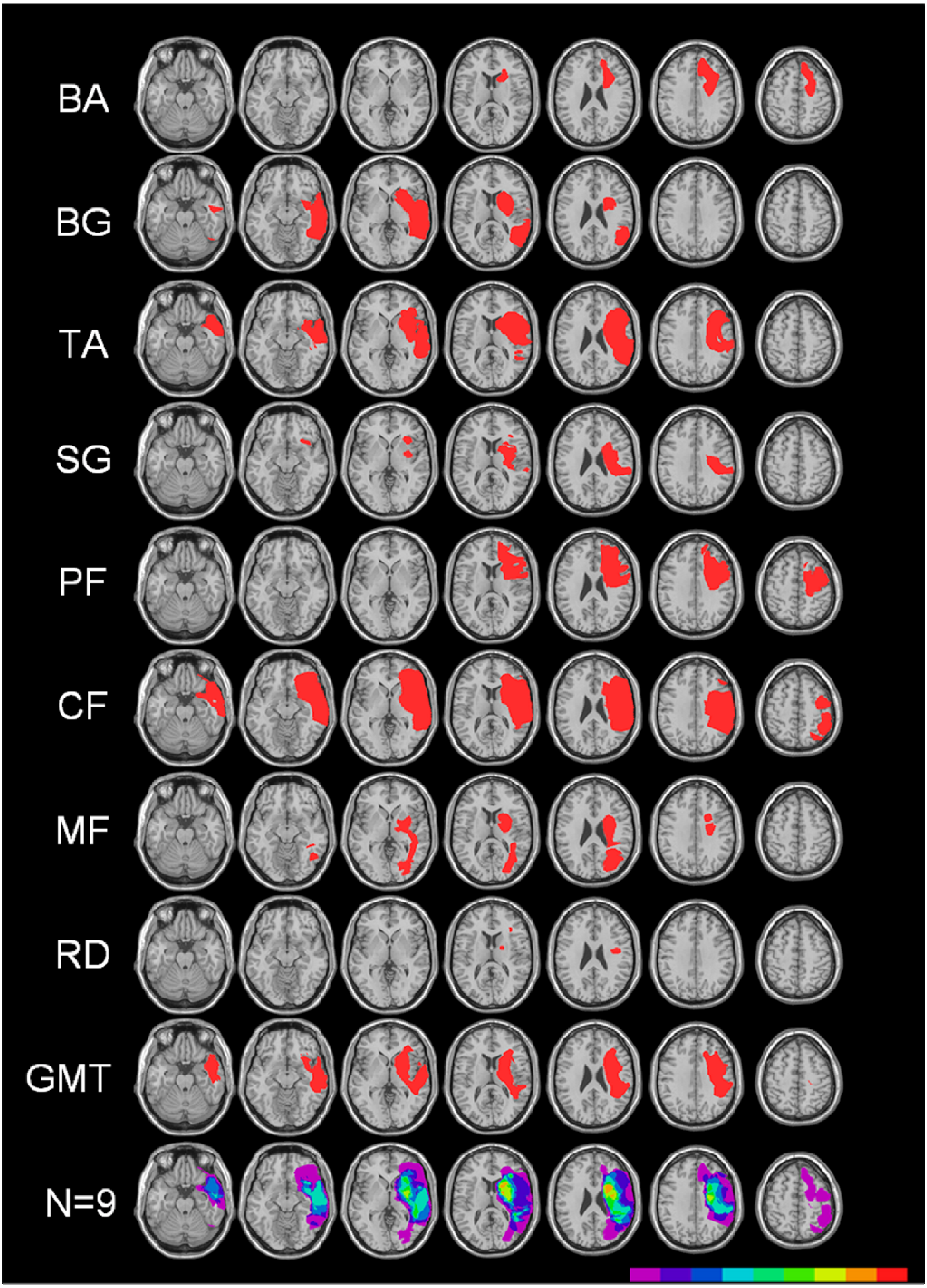

Figure 6. Lesion localization in nine right-hemisphere-damaged patients, and overlay lesion plots (bottom row: frequencies of overlapping lesions, from dark violet, n= 1, to orange, N=8).

Neuropsychological assessment and functional scales

Spatial neglect was assessed by standardized tests. All displays were presented with their centre aligned with the mid-sagittal plane of the trunk of participants, who used their right hand in the visuomotor tasks. Spatial neglect is a multi-component syndrome (Vallar, 1998), with the defective visuomotor exploration of near extra-personal space being its more frequently and extensively assessed manifestation, also in rehabilitation settings (Frassinetti et al., 2002; Pizzamiglio et al., 2006; Serino et al., 2007). Accordingly, patients were classified as showing left neglect, when a defective performance was observed in at least three out of the four tests of Cancellation, and Drawing. The neuropsychological battery included the following tests:

Cancellation tasks: Letter (Diller and Weinberg, 1977), Star (Wilson, Cockburn, and Halligan, 1987), and Bell (Gauthier, Dehaut, and Joanette, 1989). In the Letter task the score was the number of “H” letter targets crossed out by each participant (53 on the left-hand side, and 51 on the right-hand side of the sheet). Neurologically unimpaired participants made a mean of 0.13 (0.12%, SD ±0.45, range 0-4) omission errors out of 104 targets, with the maximum difference between omissions on the two sides of the sheet being two targets (Vallar, Rusconi, Fontana, and Musicco, 1994). In the Bell task the score was the number of ”bell” targets crossed out by each participant (18 on the left-hand side, and 17 on the right-hand side of the sheet). Neurologically unimpaired participants made a mean of 0.47 (1.3%, SD ±0.83, range 0-4) omission errors out of 35 targets, with the maximum difference between omissions on the two sides of the sheet being four targets (Vallar et al., 1994). In the Star task the score was the number of small “star” targets crossed out by each participant (30 on the left-hand side, and 26 on the right-hand side). Ten neurologically unimpaired participants (mean age 72.2, SD 5.27, range 67-82; mean years of schooling 9.2, SD ±6.21, range 3-18) scored 0.5 average omissions (0.9%, SD ±0.7, range 0-2), with the maximum difference between omission errors on the two sides of the sheet being one target.

Five-element complex drawing (Gainotti, Messerli, and Tissot, 1972). The patients' task was to copy a complex five-element figure: from left to right, two trees, a house, and two pine trees. Each element was scored 2 (flawless copy), 1.5 (partial omission of the left-hand side of an element), 1 (complete omission of the left-hand side of an element), 0.5 (complete omission of the left-hand side of an element, together with partial omission of the right-hand side of the same element), or 0 (no drawing, or no recognizable element). The total score ranged from 0 to 10. According to normative data from 148 neurologically unimpaired participants (age: range 40-79; education: range 5-13 years of schooling) a score lower than 10 indicated a defective performance (Valeria Corbetta, unpublished thesis).

Line Bisection. The patients' task was to mark with a pencil the mid-point of six horizontal black lines (two 10 cm, two 15 cm, and two 25 cm in length, all 2 mm in width), presented in a random fixed order. Each line was printed in the centre of an A4 sheet, aligned with the mid-sagittal plane of the participant's body. The length of the left-hand side of the line (i.e., from the left end of the line to the participant's mark) was measured to the nearest mm. This measure was converted into a standardized score (percent deviation), namely: measured left half minus objective half/objective half x 100 (Rode, Michel, Rossetti, Boisson, and Vallar, 2006). This transformation yields positive numbers for marks placed to the right of the physical centre, negative numbers for marks placed to the left of it. The mean percent deviation score of 65 neurologically unimpaired participants, matched for age (mean 72.2, SD ±5.16, range 65 – 83), and years of education (mean 9.5, SD ±4.48, range 5-18) was -1.21% (SD ±3.48, range -16.2% +6.2%; Valeria Corbetta, unpublished thesis).

Word non-word reading test. The test included two lists of 19 words (List-1: mean letter length 7.00, SD ±2.38; List-2: mean letter length 7.79, SD ±2.48), and 19 pronounceable non-words (List-1: mean letter length 7.47, SD ±2.61; List-2: mean letter length 7.37, SD ±2.36), taken from the set of Vallar, Guariglia, Nico and Tabossi (1996). Each stimulus was printed in 18-point Arial font, uppercase, on a 13 x 18 cm construction paper. For each list, the score was the number of incorrect responses (total range 0-38, for words and non-words). Errors were classified as neglect-related errors by a “neglect point” measure (Ellis, Flude, and Young, 1987), namely: errors in which target and error stimuli were identical to the right of an identifiable ”neglect” point in each item, but shared no letters in common to the left of that point. Errors which did not meet the criteria for the neglect category were classified as “other” errors. The two lists were alternately given to participants. Ten neurologically unimpaired participants, matched for age (mean 72.8 years, SD ±8.89, range 61-87), and education (mean 11.2 years, SD ±4.85, range 5-18) made no ”neglect” errors on this test, and 0.95 (SD ±1.43, range 0-5) ”other” errors.

Sentence reading test (Pizzamiglio et al., 1992). The test included six sentences. The score was the number of incorrectly read sentences (range 0-6). The “neglect point” score described above was used to classify reading errors as “neglect” and “other”. Ten control participants (see above, star cancellation) made no “neglect”, and 0.3 (5%, SD ±0.64, range 0-2) ”other” errors.

Personal Neglect Test (after Bisiach et al., 1986). In this test patients were asked to reach six left-sided body parts (ear, shoulder, elbow, wrist, waist, knee), using their right hand. Each response was scored 0 (“no movement”), 1 (“search without reaching”), 2 (“reaching with hesitation and search”), or 3 (“immediate reaching”), with a 0-18 score range. Ten control participants (see above, star cancellation) made no errors.

CBS scale. This sensitive and reliable 10-item scale (see Azouvi et al., 2003 for a description of the psychometric properties) included: a) the observation of the patients’ behavior in standardized daily-life tasks, and b) a parallel self-administered form, designed as a questionnaire for an auto-evaluation made by the patients themselves. The scale aimed at comparing activities in the right-hand and the left-hand sides of the patient’s body (e.g., “forgets to shave or groom the left part of his/her face”), and of extra-personal space (e.g., “collides with people or objects on the left side”). Each item was rated from 0 (“severe neglect") to 3 ("no neglect"), with a total maximum score of 30. The cumulative score was further classified as "severe" (score 1: 0-10), "moderate" (2: 11-20), and "mild" (3: 21-30) neglect. The difference between the scores recorded in the parallel versions should provide, according to the authors' suggestion, an index of anosognosia for USN (see Azouvi et al., 2003).

NIH stroke scale (Brott et al., 1989). This was a 15-item scale assessing sensory-motor and cognitive functions, with scores (items 1-13) ranging from 0 ("normal") – to 2 or 3 ("maximal impairment"), for a total maximum score of 36.

FIM™ scale (property of UB Foundation Inc., SUNY Buffalo NY). This scale rated the patient's independence in daily life (Tesio et al., 2002). The FIM scale included 13 "Motor" (e.g., dressing and walking), and five "Cognitive" (e.g., comprehension) items. Each item was rated from 1 ("requiring total assistance") to 7 ("completely independent"). The scale gives rise to three cumulative scores: a) the "total" score (18 items, range 18-126), b) the "motor" score, assessing mobility and locomotion (13 items, range 13-91), and c) the "cognitive" score, assessing communication and social cognition (5 items, score 5-35).

The NIH and the FIM scales were administered by a physician, the CBS by an occupational therapist, both blind to the purpose of the study. The neuropsychological assessments were performed by a psychologist, distinct from the therapist or psychologist who administered the treatments, and blind as to them. Throughout the time of the study all patients received a physical rehabilitation treatment.

Rehabilitation treatments

Pointing control treatment (Frassinetti et al., 2002)

The treatment consisted in repeated pointing movements towards a visual target (the top of a red pen), using the right upper limb, placed inside a 32 cm high wooden box (Figure 7). The lower and the upper surfaces of the box had a pentagonal shape (74 cm large on the patient's side, 19 cm high on the two sides, and 36 cm on the centre). The box was open on the patient's side (proximal). On the experimenter's side (distal) it could be made either open (visible) or closed by a removable Plexiglas (invisible condition).

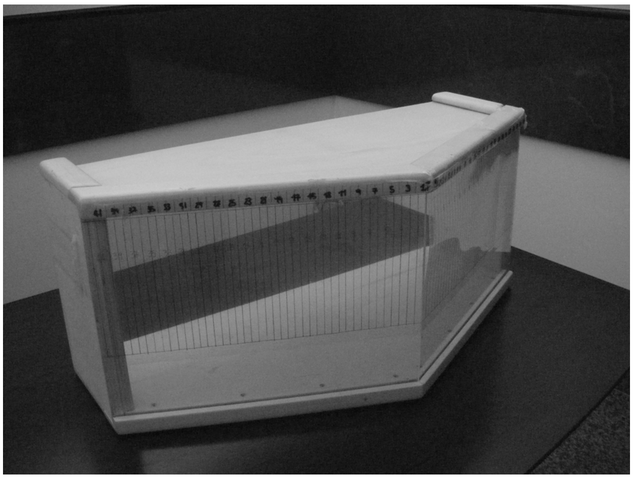

Figure 7 - The box used for the poinitng control treatment, closed by the removable Plexiglas, seen from the examiner's side. Marks for the recording of the patients' pointing errors are shown.

The target was presented in three positions on the distal side (straight-ahead, 21° rightwards, 21° leftwards). In all conditions, the three positions of the target were assessed in a random fixed order, with the same number of trials. The patients' task was to point to the target on the distal side of the box with their right index finger. Patients made a movement from the proximal side with their right upper limb inside the box, starting from the middle of their chest, with no visual feedback. Pointing was performed in two conditions. In the visible condition, the distal side of the box was open, and patients saw their index finger emerging from it. In the invisible condition, the distal side was closed, and the index finger did not show up. In both conditions, the vision of the proximal part of the patients' upper limb was prevented by a cloth attached from the patients' neck to the proximal side of the box. The distal edge of the box and the removable Plexiglas were marked, on the examiner's side, in order to measure the patients' pointing accuracy (angular degrees, °), namely the distance between their finger and the target. A positive score denoted a rightward displacement with respect to the position of the target, a negative score a leftward displacement.

On the first day only, patients made 30 visible pointing trials, before starting the treatment. The pointing treatment consisted of ten sessions (five in the morning, five in the afternoon, two per day), each including three conditions:

- *Pre-exposure*, immediately before wearing the prismatic goggles: 30 invisible pointing trials. The experimenter recorded the patient's performance during the beginning (1-3), and the end (28-30) three trials, each including one instance of the three target positions.
- *Exposure* (wearing the prismatic goggles): 90 visible pointing trials, while the patients wore base-left wedge prisms (Optique Peter, Lyon), that induced a 10° rightward shift of the visual field. The experimenter recorded the performance of each patient during the beginning (1-3), middle (44-46), and end (88-90) three trials.
- *Post-exposure* (immediately after the prismatic goggles had been removed): 30 invisible pointing trials. The experimenter recorded the patient's performance during the beginning (1-3) and the end (28-30) three trials.

The *adaptation effect* (the correction of the prism-induced lateral bias in pointing) was assessed comparing the errors in the beginning, middle, and end triplets of pointing trials in the exposure visible condition. The completeness of adaptation (whether or not, at the end of the exposure visible condition, the error score was comparable to that made in the pre-exposure baseline) was assessed comparing the pointing errors in the beginning three trials of the pre-exposure visible condition, and in the end three trials of the exposure visible condition. The *aftereffects* (namely, the error observed immediately after the rightward-displacing prisms were taken off) were assessed comparing the pointing error in three invisible conditions: the beginning three trials of the pre-exposure condition, the beginning and the end three trials of the post-exposure condition. The *persistence* of the aftereffects was the mean deviation in the beginning (1-3) post-exposure invisible trials minus the mean deviation in the end (28-30) post-exposure invisible trials.

In addition to the adaptation and aftereffects measures for each of the ten sessions, 10-session effects measures were computed, averaging the adaptation effect, the aftereffects, and the persistence of the aftereffects scores across the ten pointing sessions.

Finally, to assess the *long-term effects* of prism exposure, across sessions, the difference between the mean pointing error in the 1st session and in the last (10th) session of the pre-exposure invisible trials was computed for each patient. If the aftereffects of prism adaptation build up across sessions, the leftward pointing error should be greater in the 10th session, compared to the 1st ("long-term aftereffects").

The adaptation and aftereffects scores were recorded across the ten sessions of the control treatment with pointing, namely in the *Control-Experimental* (CE) group during the first week, and in the *Experimental-Control* (EC) group during the second week.

In order to investigate the relationships between the adaptation and the aftereffects scores and the changes in the scores in the tests and scales during the C (pointing) treatment, mediational analyses for repeated-measures designs were performed. These analyses were performed on the C treatment scores, since only for the pointing week complete adaptation and aftereffects measures were available. This method, based on regressing the change score of a test or scale, during the week in which patients received the C treatment, on the patients' adaptation or aftereffect scores (the mediator variable), allowed estimating the degree by which the effect of time (i.e., the improvement of the test or scale performance) was related to the size of the adaptation or aftereffects. Based on the mediation regression, the response to treatment (i.e., the score change during the treatment period) was considered as a mediator when the B coefficient associated with it was statistically significant; the constant term of the regression (a) estimated the amount of improvement for a treatment response equal to zero, namely, the amount of improvement not due to the treatment response (Judd, Kenny, and McClelland, 2001). The mediational analyses were performed on the tests where a change during the C treatment was found.

Experimental treatment

Patients sat at a table in front of the experimenter, and wore the base-left wedge prisms, while performing daily-life activities. The number of sessions (n= 10), and the time of exposure to the prismatic goggles for each session (20 min) were equal to those used in the pointing treatment. Patients were treated for one week, twice per day (morning and afternoon). Patients performed 12 activities, consisting in the manipulation of common objects, according to the following sequence: 1) collecting coins on the table and putting them in a money box, 2) dressing rings and bracelets, 3) opening and closing jars with the corresponding lids, 4) assembling three jigsaw puzzles, 5) assembling puzzles from the WAIS (Wechsler, 1997), 6) box and block, 7) sorting and playing cards, 8) threading a necklace with 12 spools and a rope, 9) copying a chessboard pattern on an empty chessboard, 10) serving a cup of tea, 11) WAIS Block Design, 12) composing a dictated word using letters printed on squares (see Figure 8 for some examples). Typically, not all of the 12 activities could be completed in one session. Accordingly, the next session started with the activity following the last performed in the sequence. The maximum time allotted to each task was five minutes, so that each patient performed at least four activities. If the patient completed the task in less than five minutes, the next activity was performed. When patients stopped performing the task, or were unable to complete one activity, the experimenter provided verbal and manual support for a maximum of three times each. If verbal prompts were ineffective, the examiner moved the patient’s hand close to the objects to-be-manipulated, but did not touch them.

Figure 8 - Some examples of the visuo-motor activities performed during the experimental ecological treatment.

Procedure

The neuropsychological and functional assessments were administered according to the following schedule:

- Assessments #1-3 (baseline, before the beginning of the treatment): #1 and #2 seven days before the study (one in the morning, and one in the afternoon), #3 seven days later, in the same day when the treatment was initiated; no scales were administered in #2.
- Assessment #4: at the end of the first week of treatment (week-1).
- Assessment #5: on the first day of the second week (week-2).
- Assessment #6: at the end of week-2.
- Assessment #7: at the beginning of the third week.
- Assessments #8, #9, and #10: one, two, and three months, after the end of the treatment.

Patients were assigned to two groups: the CE group received the pointing task (control) in the first week, and the experimental treatment in the second week, the EC group vice versa. Patients were alternately assigned to one of the two groups, starting with the EC condition. Before starting the experimental treatment, the five patients in the EC group received one half-session of the pointing task: 1) pre-exposure visible pointing (15 trials), 2) pre-exposure invisible pointing (15 trials), 3) exposure visible pointing (45 trials), and 4) post-exposure invisible pointing (15 trials). This session assessed the presence of prism adaptation and aftereffects in the week in which the EC patients received the experimental treatment. At the end of the two weeks patients were asked to communicate whether they had any preference concerning the two treatments.

Statistical design

In general, the effects of the two treatments over time were assessed by repeated-measures analyses of variance (ANOVAs). To normalize the distribution of the patients' scores in each test, percent correct responses were converted in the arcsin of the square root of the raw values. The transformation improved the normality of the score distribution, as evidenced by skewness and kurtosis values. For the NIH and the FIM scales the standard summary score was used (Millis, Straube, Iramaneerat, Smith, and Lyden, 2007). Nonparametric statistical analyses (Siegel and Castellan, 1988) were performed on the CBS scores due to the presence of ordinal scaling, and on the personal neglect test due to distributional concerns. For the ANOVAs, Group (CE, EC) was the main between-subjects factor, and Time (average baseline, week-1, and week-2) was the main within-subjects factor. The week-1 and week-2 scores were the means of the assessments performed at the end of each week (week-1: assessments #4-5; week-2: assessments #6-7). In each test and scale, significant differences were found neither in the week-1 (#4-5) nor in the week-2 (#6-7) assessments.

The adaptation and aftereffects were analyzed by ANOVAs, with the between-subjects main factor Group, and these within-subjects main factors: Pointing error [in the different exposure conditions, and in the different phases of the trial sequence (beginning, middle, end), averaged across the three positions of the target], Session (1-10).

Significant differences were explored by Newman-Keuls' post-hoc multiple comparisons. Effects were evaluated also according to their standardized effect size index. The partial eta-squared (pη2) was selected as the index (Cohen, 1973).

One-week stability of the deficit before treatment

The enrolment of the patients in the present study was pseudo-randomized, based on the alternate assignment to one of the two groups (Control-Experimental (CE), Experimental-Control (EC). A limited matching between the two groups, particularly for USN and stroke severity, is of concern. In order to assess the stability of USN before treatment, one-way repeated-measures ANOVAs were performed on the baseline scores (percent correct responses, converted into the arcsin of the square root of the raw values) of the diagnostic tests. No differences were found for the Letter [F(2,9)= 1.58,P= 0.23, pη2= 0.150], Star [F(2,5)= 0.51, P= 0.61), pη2= 0.16], and Bell [F(2,9)= 2.93, P= 0.08, pη2= 0.245] cancellation, as well as for the drawing [F(2,9)= 1.05, P= 0.37, pη2= 0.104] tests. No differences in the baseline scores were found for the NIH [F(1,9)= 1.00, P= 0.34, pη2= 0.100], FIM [F(1,9)= 1.01; P= 0.34, pη2= 0.100], and CBS scales (Wilcoxon matched pairs test, T= 0, P= 0.10).

However, differences between groups cannot be completely ruled out, because the limited number of participants in each group might provide insufficient power to detect a significant difference. In order to further control for possible effects of the baseline level of performance on the outcome of the treatment, the baseline score was used as a covariate variable. For each test and scale (summary scores), a one-way repeated-measures analysis of covariance (ANCOVA) was performed on Time (scores of week-1, and week-2), with the baseline score (the centered mean score of the three baselines) as a linear and interactive covariate. The interaction term was introduced to test for the applicability of the ANCOVA model (Cohen, West, Cohen, and Aiken, 2002; Rogosa, 1980). The covariate was centered to its mean to allow interpreting the treatment effect in the presence of the interaction term (Aiken and West, 1991). Finally, two ANCOVAs were performed on the scores obtained by the two patients' groups (EC, CE) in the two weeks of treatment (baseline, week-1, week-2), using the standardized NIH scale baseline score and the duration of disease as linear and interactive covariates. These analyses explored the possibility that baseline, neurological severity, and duration of disease influenced changes of the patients' scores in the tests and scales during the treatment.

2.3 Results

Neuropsychological tests and neurological and functional scales

Results of patients' performances in the three assessments, in the Cancellation tasks, in the Complex drawing, and Sentence reading tasks, and in the NIH and FIM scales are reported in Tables 3 and 4. Patients' performance improved during the two weeks of treatment (i.e., the Time main factor was significant in all analyses), independent of their assignment to the CE or EC group (i.e., the Group factor and the Time by Group interaction were not significant). In the Line bisection task the patients' performance did not change during the two weeks of treatment.

For the *reading test*, one out of ten patients showed left neglect dyslexia for single words and nonwords. FE made an average of 22 "neglect" errors out of the 38 word and non-word stimuli (57%) in the baseline sessions, five errors (12%) at the end of week-1 [$\chi2(1)= 14.71$, $P< 0.001$], and zero at the end of week-2 [$\chi2(1)= 28.21$, $P< 0.001$].

For the *personal neglect test*, four out of ten patients (three in the CE group, and one in the EC group) exhibited personal USN in the baseline, and in all of them the deficit had improved at the end of week-2. The scores of the ten patients were 17.32 (SD ±1.46) out of 18 (96.2%), 17.85 (SD ±0.33) (99.1%), and 17.95 (SD ±0.15) (99.7%), in the baseline, week-1 and week-2 assessments. A Friedman analysis of variance showed a difference among these assessments [$\chi2(2)= 9.5$, $P< 0.01$]. The scores of the four patients with personal USN were 15.74 (SD ±1.62) (87.4%), 17.63 (SD ±0.48) (97.94%), and 17.88 (SD ±0.25) (99.33%) in the baseline, week-1 and week-2 assessments.

The *CBS scale* was administered to nine out of ten patients. The patients' scores were 1.77 (SD ±0.83) in the baseline, 2.33 (SD ±0.87) at the week-1, and 2.55 (SD ±0.53) at the week-2 assessments. A Friedman analysis of variance revealed a significant difference among assessments [$\chi2$ (2)= 11.14, P< 0.01]. Multiple comparisons showed a significant difference between baseline and week-2 (P< 0.05). In the baseline, USN was severe in four patients, moderate in three, and mild in two. After one week of treatment, two patients showed a severe, two a moderate, and five a mild USN. After two weeks USN was mild in five patients, and moderate in four, with no patient showing a severe USN. In sum, in seven out of nine patients USN improved after the two weeks, being already mild in the baseline in two patients. The difference between the score of the CBS scale and the questionnaire of self-evaluation provided an index of the patients' awareness of USN. Two out of nine patients (MF, RD) proved to be aware of USN, as indexed by a score lower in the self-rated, compared to the observer-rated version of the test. The seven anosognosic patients scored 15.78 (SD ±9.17) in the baseline, 10.71 (SD ±8.12) at the week-1, and 8.64 (SD ±6.39) at the week-2 assessments. A Friedman analysis of variance showed a significant difference [$\chi2$ (2)= 6, P= 0.05]. Multiple comparisons revealed a significant difference between baseline and week-2 (P= 0.05). A perusal of the individual data showed that in six out of seven patients the anosognosia score diminished from the baseline to week-1, and from week-1 to week-2. One patient (CF) did not show any improvement of the anosognosia score.

Table 3. Neuropsychological scores (SEM in brackets) in the baseline (B) week-1 (W1), and week-2 (W2) assessments, by Group (CE, EC). LC/BC/SC (Letter/Bell/Star cancellation, percent correct), CD (Complex drawing, percent correct), SR (Sentence reading, percent error), LB (Line bisection, percent deviation). ANOVA: df (2, 16) for the Time main factor, and for the Time by Group interaction; (1, 8) for the Group main factor. For SC, df (2, 10; 1, 5). Post hoc Newman-Keuls comparisons: + *P*= 0.06; * *P*< 0.05; ** *P* ≤ 0.01; *** *P*< 0.001.

	Time			**ANOVA**			
TASK	**B**	**W1**	**W2**	**Time**	**Group**	**Time by Group**	**Post hoc**
LC				F= 14.82	F= 3.02	F= 1.77,	B-W1**
CE	0.65(0.04)	0.70(0.03)	0.86(0.03)	*P*< 0.001	*P*= 0.12	*P* = 0.20	B-W2***
EC	0.32(0.03)	0.56(0.05)	0.67(0.05)	$p\eta^2$= 0.65	$p\eta^2$= 0.27	$p\eta^2$= 0.18	W1-W2**
BC				F= 13.89	F= 0.37	F= 2.52	B-W1*
CE	0.45(0.07)	0.52(0.07)	0.59(0.06)	*P*< 0.001	*P*= 0.06	*P*= 0.11	B-W2***
EC	0.23(0.03)	0.41(0.04)	0.59(0.06)	$p\eta^2$= 0.63	$p\eta^2$= 0.04	$p\eta^2$= 0.24	W1-W2*
SC				F= 6.00	F= 0.02	F= 1.86	B-W2*
CE	0.55(0.08)	0.63(0.09)	0.66(0.07)	*P*< 0.05	*P*= 0.89	*P*= 0.21	
EC	0.57(0.13)	0.60(0.10)	0.74(0.13)	$p\eta^2$= 0.55	$p\eta^2$=0.003	$p\eta^2$= 0.27	
CD				F= 8.52	F= 3.99	F= 1.03	B-W2**
CE	0.92(0.01)	0.90(0.02)	0.98(0.004)	*P*< 0.01	*P*= 0.08	*P*= 0.38	W1-W2**
EC	0.55(0.07)	0.65(0.07)	0.76(0.05)	$p\eta^2$= 0.52	$p\eta^2$= 0.33	$p\eta^2$= 0.11	
SR				F= 5.00	F= 1.60	F= 2.10	B-W1+
CE	0.12(0.03)	0.02(0.01)	0.05(0.01)	*P*< 0.05	*P*= 0.24	*P*= 0.16	B-W2*
EC	0.34(0.08)	0.30(0.07)	0.18(0.07)	$p\eta^2$= 0.38	$p\eta^2$= 0.17	$p\eta^2$= 0.21	
LB				F= 0.48	F= 3.26	F= 0.82	
CE	0.057(0.025)	0.028(0.036)	0.031(0.016)	*P*= 0.63	*P*= 0.11	*P*= 0.46	
EC	0.098(0.046)	0.128(0.036)	0.085(0.021)	$p\eta^2$= 0.056	$p\eta^2$= 0.29	$p\eta^2$= 0.092	

Table 4. NIH and FIM summary scores. B, W1, and W2, see legend to Table 3.

	Time			**ANOVA**			
TASK	**B**	**W1**	**W2**	**Time**	**Group**	**Time by Group**	**Post hoc**
NIH				F= 5.00	F= 1.21	F= 0.89,	B-W1*
CE	14.51(1.57)	12.40(2.42)	10.60(2.18)	$P < 0.05$	$P = 0.30$	$P = 0.43$	B-W2*
EC	9.80(1.28)	8.60(1.83)	7.60(1.75)	$p\eta^2 = 0.35$	$p\eta^2 = 0.13$	$p\eta^2 = 0.10$	
FIM							
Motor				F= 15.31	F= 0.16	F= 0.75,	B-W1*
CE	32.60(8.91)	37.60(9.53)	39.20(9.93)	$P < 0.001$	$P = 0.70$	$P = 0.49$	B-W2***
EC	35.10(6.23)	38.34(8.06)	42.90(9.95)	$p\eta^2 = 0.66$	$p\eta^2 = 0.02$	$p\eta^2 = 0.09$	W1-W2*
Cognitive				F= 4.73	F= 3.90	F= 0.94,	B-W2*
CE	18.60(2.25)	20.21(2.27)	22.80(3.48)	$P < 0.05$	$P = 0.08$	$P = 0.41$	
EC	28.00(1.76)	28.54(1.92)	28.80(0.97)	$p\eta^2 = 0.37$	$p\eta^2 = 0.33$	$p\eta^2 = 0.11$	
Total				F= 14.45	F= 0.75	F= 0.38,	B-W1*
CE	51.20(7.52)	57.81(8.06)	62.00(7.39)	$P < 0.001$	$P = 0.41$	$P = 0.68$	B-W2***
EC	63.10(7.43)	66.88(9.12)	71.70(10.53)	$p\eta^2 = 0.65$	$p\eta^2 = 0.09$	$p\eta^2 = 0.05$	W1-W2**

Baseline performance and treatment effects

Table 5 shows the main effects of Time, and Group, the Time by Group interaction, the effect of Baseline, and the Time by Baseline interaction. For the Letter and Bell cancellations, and the Complex drawing tasks, and for the CBS and FIM scales, the main effect of Time was significant, while the Time by Group interaction and, crucially, the Baseline by Time interaction were not. The non-significant Baseline by Time interaction indicates that the improvement during the week 1-week 2 time period of treatment (i.e., the Time effect) was not dependent on the baseline level of performance. Therefore, any group difference present at the baseline time did not influence the improvement over the week 1-week 2 time period.

For the Sentence reading test not only the Time main factor, but also the Time by Group interaction was significant, while the Time by Baseline interaction was not. This result shows a differential improvement in the two groups (EC, CE) between week-1 and week-2. This may be traced back to differences in the performance levels of the two groups. The mean number of errors at the end of week-1 and week-2 were 2% and 5% for group CE, 30% and 18% for group EC (see Table 3). These scores, however, albeit different, were not affected by the baseline scores. For the Star cancellation task the main effect of Time, the Group by Time, and the Baseline by Time interactions were not significant. This test was given to only seven participants (four patients in the CE group, three in the EC group), possibly reducing the power to detect significant differences. For the Line bisection task, the ANCOVA confirmed the lack of improvement during the treatment.

For the NIH scale, the main effect of Time was not significant, while the Time by Baseline, and the Time by Group interactions were significant, or marginally significant. These findings indicate that the improvement of the NIH scale scores during the week 1-week 2 treatment period depended on the baseline level. A perusal of the data showed that the improvement was larger for the higher baseline NIH scores, namely in the patients with a more severe deficit. In sum, these findings show that the patients’ improvement in the NIH scale was dependent on the baseline level of performance, suggesting that the scores’ changes in the week 1-week 2 treatment period reflect factors different from the prism treatment, such as spontaneous recovery. This was not the case of the patients’ improvement in the neuropsychological tests and in the FIM and CBS scales, which were unaffected by the baseline level of performance.

Table 5. Repeated-measures ANCOVAs with a within-subjects factor, Time (scores W1, and W2), and a between-subjects factor, Group (CE and EC), with the standardized baseline mean score as a linear and interactive covariate. df : 1,7 for all analyses, but the Star test (1,4, Time main factor and the interactions; 1,3, Baseline covariate). Tests and scales: see legend to Table 3.

Test	Time	Group	Baseline	Time by Group	Time by Baseline
LC	F= 8.03, *P*< 0.05	F= 0.65, *P*= 0.45	F= 5.85, *P*< 0.05	F= 0.26, *P*= 0.88	F= 0.142, *P*= 0.72
BC	F= 7.59, *P*< 0.05	F= 2.21, *P*= 0.18	F= 20.98, *P*< 0.05	F= 0.93, *P*= 0.37	F= 0.04, *P*= 0.86
SC	F= 3.46, *P*= 0.136	F= 0.14, *P*= 0.91	F= 39.65, *P*< 0.05	F= 2.55, *P*= 0.19	F= 0.08, *P*= 0.79
CD	F= 7.75, *P*< 0.05	F= 0.11, *P*= 0.75	F= 22.85, *P*< 0.05	F= 0.36, *P*= 0.57	F=0.85, *P*= 0.39
SR	F= 5.95, *P*< 0.05	F= 0.78, *P*= 0.41	F= 35.12, *P*< 0.05	F= 23.1, *P*< 0.01	F= 0.24, *P*= 0.64
LB	F= 1.33, *P*= 0.29	F= 3.03, *P*= 0.12	F= 1.64, *P*= 0.24	F= 7.58, *P*= 0.41	F= 1.00, *P*= 0.35
CBS	F= 14.77, *P*< 0.05	F= 0.30, *P*= 0.60	F= 20.47, *P*< 0.05	F= 1.80, *P*= 0.22	F= 1.58, *P*= 0.25
FIM	F= 12.42, *P*< 0.05	F= 0.81, *P*= 0.40	F= 59.54, *P*< 0.001	F= 0.12, *P*= 0.74	F= 0.02, *P*= 0.88
NIH	F= 0.74, *P* =0.74	F= 2.80, *P*= 0.14	F= 16.33, *P*< 0.01	F= 5.13, *P*= 0.06	F= 6.65, *P*< 0.05

Neurological factors and recovery from USN after prism adaptation: NIH scale

To control whether the baseline level of neurologic severity may have influenced the outcome of the two-week prism adaptation treatment, the standardized baseline NIH score was used as a covariate variable. For each test and scale, repeated-measures ANCOVAs were performed, with Time (scores at baseline, week-1, and week-2) as a within-subjects factor, and Group (EC, CE) as a between-subjects factor. As Table 6 shows, for each test and scale the main effect of Time was significant, while the Group by Time, and the Time by NIH baseline score interactions were not significant. These results, particularly the lack of interaction between the Time and NIH baseline factors, show that both groups improved over time, independent of the patients' initial neurologic severity. This makes unlikely an interpretation of the recovery of USN during the prism adaptation treatment as an aspect of general neurologic recovery.

Table 6. Repeated-measures ANCOVAs with a within-subjects factor, Time (scores B, W1, and W2), and a between-subjects factor, Group (CE and EC), with the baseline NIH score as a linear and interactive covariate. df: 2,14 for the Time main factor, and the interactions; 1,7 for the Group main factor and the NIH covariate; for the Star test df 2,8, and 1,4. Tests and scales: see legend to Table 3.

Test	**Time**	**Group**	**NIH Score**	**Time by Group**	**Time by NIH Score**
LC	F= 14.49, *P*< 0.001	F= 5.75, *P*=0.05	F= 2.30, *P*= 0.17	F= 1.78, *P*= 0.20	F= 0.79, *P*= 0.47
BC	F= 12.55, *P*< 0.01	F= 5.38, *P*= 0.054	F= 7.07, *P*< 0.05	F= 0.73, *P*= 0.50	F= 0.36, *P*= 0.70
SC	F= 4.95, *P*< 0.05	F= 0.476, *P*= 0.53	F= 0.97, *P*= 0.38	F= 1.13, *P*= 0.37	F= 1.00, *P*= 0.41
CD	F= 9.27, *P*< 0.01	F= 2.41, *P*= 0.16	F= 0.03, *P*= 0.87	F= 2.59, *P*= 0.11	F= 0.25, *P*= 0.21
SR	F= 4.86, *P*< 0.05	F= 1.68, *P*= 0.24	F= 0.34, *P*= 0.58	F= 3.27, *P*= 0.07	F= 0.21, *P*= 0.81
LB	F= 0.45, *P*= 0.65	F= 1.13, *P*= 0.32	F= 0.17, *P*= 0.69	F= 0.59, *P*= 0.57	F= 0.56, *P*= 0.58
CBS	F= 24.89, *P*< 0.001	F= 0.12, *P*= 0.91	F= 0.20, *P*= 0.67	F= 2.23, *P*= 0.14	F= 2.95, *P*= 0.08
FIM	F= 15.73, *P*< 0.001	F= 0.44, *P*= 0.53	F= 5.70, *P*< 0.05	F= 1.54, *P* =0.25	F= 1.44, *P*= 0.27

Duration of disease

In order to control whether the distance from the onset of the neurological disease may have influenced the outcome of the two-week prism adaptation treatment, the standardized Duration of disease, expressed in months, was used as a covariate variable. For each test and scale, repeated-measures ANCOVAs were performed, with the Time and Group factors used in the ANCOVAs reported above. Table 7 shows that in the Letter and Star cancellation, Complex drawing, Sentence reading tasks, and in the scales, the main effect of Time was significant, while the Time by Group and the Time by Duration of disease interactions were not significant. For the Bell task, the main effect of Time, and the Time by Group interaction were significant, while the Time by Duration of disease interaction was not significant. This result suggests that Duration of disease did not influence the patients' improvement in the Bell task, while a different effect of Time was found in the two groups (CE and EC). This might have been caused by baseline differences between the two groups. To test for this hypothesis, a repeated-measures ANCOVA with Time (scores at week-1, and week-2) as a within-subjects factor, and Group as a between-subjects factor was performed, with the standardized Duration of disease and the standardized Baseline as covariate variables. The main effect of Time [F(1,7)=8.23, P= 0.05] was still significant, while the main effect of Group (F(1,6)= 5.27, P= 0.61) was not significant, as well as, crucially, the Group by Time interaction [F(1,7)= 1.59, P= 0.26]. These results show that also in the Bell test both groups improved over time, independent of the duration of disease.

Table 7. Repeated-measures ANCOVAs with Duration of disease as a linear and interactive covariate. Main factors and df as in Table 5. Tests and scales: see legend to Table 3.

Test	**Time**	**Group**	**Duration of disease**	**Time by Group**	**Time by Duration of disease**
LC	F= 14.22, P< 0.001	F= 1.43, P= 0.27	F= 0.10, P= 0.76	F= 9.82, P= 0.40	F= 0.64, P= 0.54
BC	F= 16.44, P< 0.001	F= 0.11, P= 0.75	F= 0.82, P= 0.78	F= 5.42, P< 0.05	F= 2.64, P= 0.11
SC	F= 8.17, P< 0.05	F= 0.60, P= 0.82	F= 0.50, P= 0.83	F= 2.99, P= 0.11	F= 1.94, P= 0.21
CD	F= 9.27, P< 0.01	F= 3.58, P= 0.10	F= 0.29, P= 0.61	F= 0.89, P= 0.43	F= 1.72, P= 0.21
SR	F= 4.75, P< 0.05	F= 3.12, P= 0.12	F= 1.61, P= 0.24	F= 2.45, P= 0.12	F= 0.05, P= 0.95
LB	F= 0.54, P= 0.60	F= 1.31, P= 0.29	F= 0.32, P= 0.59	F= 2.33, P= 0.13	F= 2.06, P= 0.16
CBS	F= 22.83, P< 0.001	F= 0.05, P= 0.94	F= 0.23, P= 0.65	F= 0.30, P= 0.75	F= 2.13 P= 0.16
FIM	F= 14.92, P< 0.001	F= 4.88, P= 0.06	F= 5.73, P= 0.05	F= 0.00, P= 0.10	F= 1.00, P= 0.39
NIH	F= 4.76, P< 0.05	F= 2.34, P= 0.17	F= 1.23, P =0.30	F= 0.23, P= 0.80	F= 0.69, P = 0.52

Control pointing task

Adaptation

Figure 9 shows that adaptation took place in the first 45 pointing trials of each session, with a reduction of the rightward error. An analysis of variance with the between-subjects factor Group, and two within-subjects factors [Session of treatment (1-10); Pointing error: beginning (1-3), middle (44-46), and end (88-90) trials] showed that the main effect of Pointing error was significant [F(2,16)= 17.74, P< 0.001, pη2= 0.680], while neither the Group [F(1,8)= 0.06, P= 0.81, pη2= 0.007], nor the Session [F(9,72)= 0.48, P= 0.88, pη2= 0.056] main effects were significant, as well as the Group by Session [F(9,72)= 0.86, P= 0.56, pη2= 0.097], the Group by Pointing error [F(2,16)= 0.33, P= 0.72, pη2= 0.039], the Pointing error by Session [F(18,144)= 0.59, P= 0.90, pη2= 0.068], and the Group by Session by Pointing Error [F(18,144)= 1.03, P= 0.42, pη2= 0.114] interactions. Multiple comparisons showed significant differences between the beginning and middle (P< 0.001), and the beginning and end (P< 0.001) trials. The difference between the middle and end trials was not significant (P= 0.68). The completeness of adaptation was assessed by analyzing whether the pointing error in the visible condition was comparable before adaptation, and at the end of it. The error scores in the beginning trials (1-3) of the pre-exposure visible condition, and in the end trials (88-90) of the exposure visible condition, averaged across the ten visible exposure sessions, were compared in the two groups. The main effects of Group [F(1,8)= 0.14, P= 0.71, pη2= 0.017], and of Pointing error [F(10,80)= 0.57, P= 0.83, pη2= 0.065], were not significant, as well as the Group by Pointing error interaction [F(10,80)= 1.38, P= 0.20, pη2= 0.147]. The scores in the beginning trials of the pre-exposure visible condition were -0.93° (SEM ±0.36) in group CE, and 2.73° (SEM ±0.80) in group EC. The scores in the end trials of the exposure visible condition were 2.02 (SEM ±0.06) in group CE, and 2.20 (SEM ±0.07) in group EC. No differences in prism adaptation related to the presence/absence of visual half-field deficits were found. An analysis of variance with the between-subjects factor Group [patients with

(N= 4) and without (N= 6) a left visual half-field deficit, see Table 2], and two within-subjects factors [Session of treatment (1-10); Pointing error (beginning, middle, and end trials of the exposure visible condition)] showed a significant main effect of Pointing error [F(2,16)= 16.20, P< 0.001, pη2= 0.669]. The main effects of Group [F(1,8)= 0.42, P= 0.52, pη2= 0.049], and of Session [F(9,72)= 0.50, P= 0.86, pη2= 0.058) were not significant, as well as the Group by Pointing error [F(2,16)= 0.48, P= 0.62, pη2= 0.056], the Pointing error by Session [F(18,144)= 0.70, P= 0.81, pη2= 0.086], the Group by Session [F(9,72)= 1.20, P= 0.30, pη2= 0.130], and the Group by Session by Pointing Error [F(18,144)= 1.61, P= 0.06, pη2= 0.167] interactions.

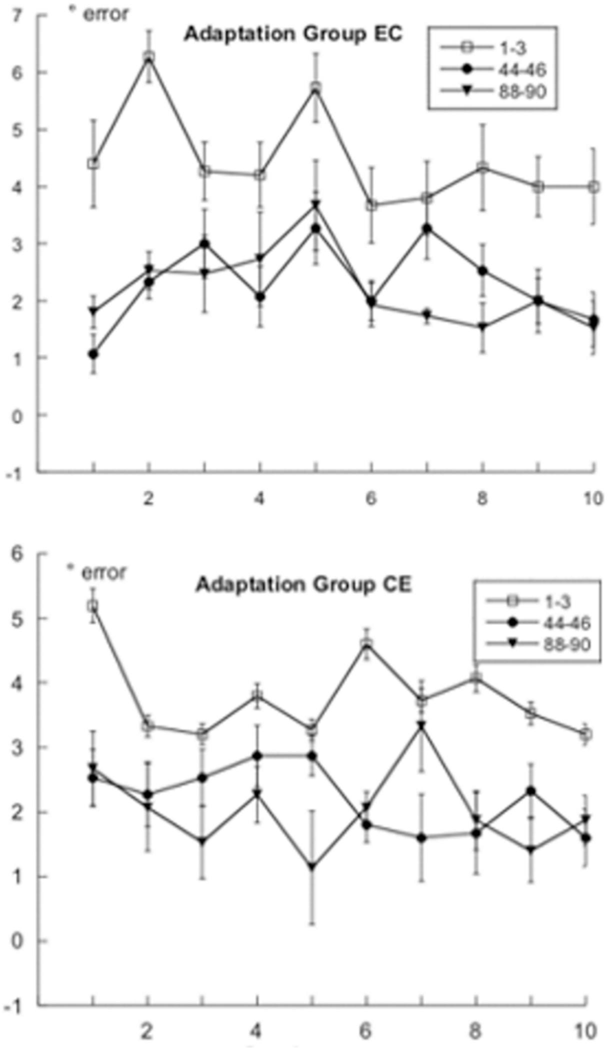

Figure 9. Adaptation effect: visible condition. Pointing error (°, SEM; positive/negative scores indicate rightward/leftward errors) in the beginning, middle, and end trials, by group (EC, CE).

Aftereffects

As Figure 10 shows, the aftereffects after the removal of the prisms (namely the difference between the pointing errors during invisible pointing, before and after adaptation) were comparable in the two groups. An analysis of variance with the between-subjects factor Group, and two within-subjects factors [Session (1-10); Pointing error: beginning (1-3) trials of the pre-exposure invisible condition, beginning (1-3) and end trials (28-30) of the post-exposure invisible condition] showed a significant main effect of Pointing error [F(2,16)= 26.20, P< 0.001, pη2= 0.766]. The main effects of Group [F(1,8)= 0.98, P= 0.35, pη2= 0.109], and of Session [F(9,72)= 1.96, P= 0.06, pη2= 0.196] were not significant. The Group by Session [F(9,72)= 1.27, P= 0.26, pη2= 0.137], the Group by Pointing error [F(2,16)= 0.80, P= 0.46, pη2= 0.090], the Pointing error by Session [F(1,8)= 0.14, P= 0.71, pη2= 0.017], and the Group by Session by Pointing Error [F(18,144)= 1.34, P= 0.17, pη2= 0.143] interactions were not significant. Multiple comparisons revealed that the mean error in the beginning trials of the post-exposure invisible condition (-4.54°, SEM ±0.95) differed from those of both the beginning trials of the pre-exposure invisible condition (-2.26°, SEM ±0.76; P< 0.001), and the end trials (-3.3°, SEM ±0.99) of the post-exposure invisible condition (P< 0.01). The difference between the beginning trials of the pre-exposure condition and the end trials of the post-exposure condition was also significant (P< 0.01). Exposure to prisms displacing the visual scene rightwards brought about aftereffects in the opposite leftward direction, which diminished in size during the post-exposure period. At variance with the present findings, Frassinetti et al. (2002) found no difference in the size of the aftereffects between the first three (-1.7°) and the last three (-1.8°) trials of the post-exposure invisible condition. The size of the leftward aftereffects was however larger in the present study (first three trials: -4.5°, last three trials: -3.3°). The aftereffects were not affected by the presence/absence of visual half-field deficits. An analysis of variance with the between-subjects factor Group (patients with and without a left visual half-field deficit), and two within-subjects factors [Session (1-10);

Pointing error: beginning trials of the pre-exposure invisible condition, beginning, and end trials of the post-exposure invisible condition] showed a significant main effect of Pointing error [F(2,16)= 23.62, P< 0.001, pη2= 0.747]. The main effects of Group [F(1,8)= 0.59, P= 0.46, pη2= 0.068], and of Session [F(9,72)= 1.62, P= 0.13, pη2= 0.168] were not significant. The Group by Session [F(9,72)= 0.93, P= 0.50, pη2= 0.104], the Group by Pointing error [F(2,16)= 0.80, P= 0.47, pη2= 0.090], and the Pointing error by Session [F(18,144)= 0.76, P= 0.74, pη2= 0.086], as well as the Group by Session by Pointing Error [F(18,184)= 1.36, P= 0.16, pη2= 0.117] interactions were not significant. As for the long-term aftereffects, the error in the invisible pre-exposure pointing trials was -0.43° (SEM ±0.46) in the 1st session, and -2.73 (SEM ±0.27), more leftward, in the 10th session [paired t test: t(9)= 2.66, P< 0.05].

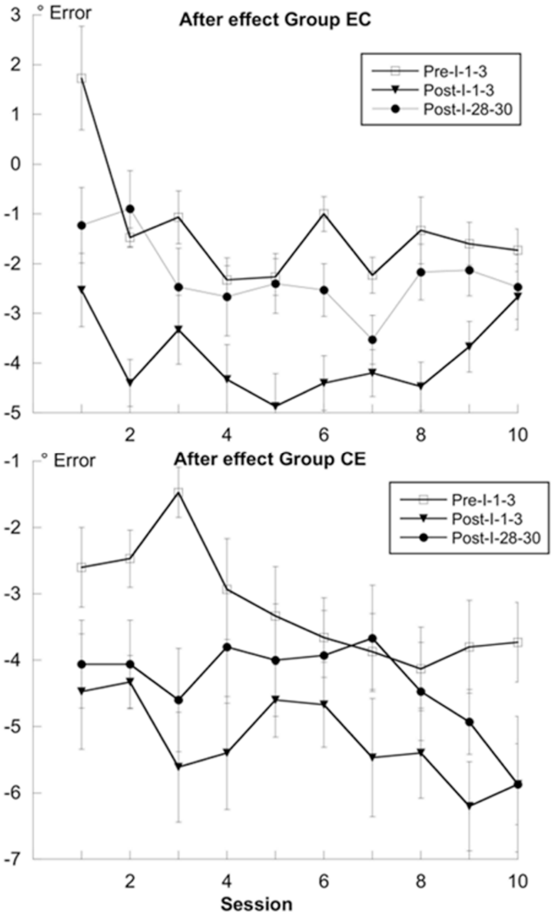

Figure 10. Aftereffects: invisible condition. Pointing error (see Figure 9) in the pre-adaptation beginning trials, and in the post-adaptation beginning and end trials, by group (EC, CE).

Group EC: single pointing half-session

Adaptation

The patients' average scores in the beginning (1-3) trials of the pre-exposure visible condition, in the beginning (1-3) and in the end (43-45) trials of the exposure visible condition were 0.47° (SEM= ±0.38), 7.13° (SEM= ±0.64), and 1.80° (SEM= ±0.37), respectively, showing adaptation. A one-way analysis of variance showed a significant difference among conditions [$F(2,8)= 13.05$, $P< 0.01$, $p\eta 2= 0.765$]. Post-hoc multiple comparison revealed significant differences between the beginning and the end trials of the exposure condition ($P< 0.01$), and between the beginning trials of the pre-exposure condition and the beginning trials of the exposure condition ($P< 0.01$). The difference between the beginning trials of the pre-exposure condition and the end trials of the exposure condition was not significant ($P= 0.36$).

Aftereffects

The patients' average scores in the beginning (1-3) trials of the pre-exposure invisible condition, in the beginning (1-3) and in the end (13-15) trials of the post-exposure invisible condition were 0.40° (SEM= ±0.81), -3.00° (SEM= ±1.43), and -1.40° (SEM= ±1.17), respectively, showing leftward aftereffects. A one-way analysis of variance showed a significant difference among conditions [$F(2,8)= 6.21$, $P< 0.05$, $p\eta 2= 0.608$]. Post-hoc multiple comparison revealed a significant difference between the beginning trials of the pre-exposure invisible condition and the beginning trials of the post-exposure condition ($P< 0.05$).

Patients' reports

All patients reported that the ecological treatment was more varied and less repetitive. During the pointing treatment, all patients spontaneously complained of some minor stiffness or numbness in the right upper limb, particularly at the end of the daily session. The examiners consistently reported that it was generally easier to have the patients go through the whole of the ecological than the pointing treatment.

Mediational analyses

For these analyses, an Overall cancellation score (average of the scores in the Letter, Bell, and Star cancellation tasks), the Complex drawing scores, the Sentence reading scores, and the FIM and NIH scale scores were used. The mediators were: a) the average 10-session aftereffects, b) the average 10-session persistence of the aftereffects, c) the long-term aftereffects, and d) the average 10-session adaptation effect.

A preliminary analysis by paired t-tests assessed whether the patients' performance had improved in the week in which the pointing treatment was administered, comparing their scores before and after this treatment: overall Cancellation score [t(9)= -2.68, P< 0.05]; Complex drawing test [t(9)= -1.003, P= 0.34]; Sentence reading test [t(9)= -3.05, P< 0.05]; NIH scale [t(9)= 2.86, P< 0.05]; FIM scale [t(9)= -4.71, P< 0.01]. Accordingly, the mediational analyses were performed on the Overall cancellation, the Sentence reading test, the NIH and the FIM scale scores.

For the overall *Cancellation score*, the effect of the aftereffects on the patients' improvement was significant [B= 0.08, t(8)= 2.65, P< 0.05], whereas the non-mediated improvement resulted not significant [a= 0.08, t(8)= 1.19, P= 0.27]. The mediational role of prism exposure was replicated using the persistence of the aftereffects [B= 0.15, t(8)= 3.12, P< 0.05; a= 0.08, t(8)= 1.35, P= 0.21], and the long-term aftereffects [B= 0.03, t(8)= -3.58, P< 0.01; a= -0.02, t(8)= -0.54, P= 0.60]. These results indicate a full mediational effect (Baron and Kenny, 1986) of prism exposure, as indexed by the aftereffects, on the improvement of cancellation performance, with larger aftereffects predicting a greater improvement. By contrast, no mediational effect was found for adaptation [B= 0.01, t(8)= 0.42, P= 0.69; a= -0.07, t(8)=-1.14, P= 0.29].

For the *Sentence reading test*, no mediational effects were found: aftereffects [B= 0.04, t(8)= 0.69, P= 0.51; a= -0.06, t(8)= -0.44, P= 0.15], persistence of the aftereffects [B= -0.06, t(8)= -0.61, P= 0.56; a= -0.23, t(8)= -1.74, P= 0.12], long-term aftereffects [B= -0.01, t(8)= -0.60, P=

0.57; a= -0.18, t(8)= -2.56, P= 0.03], and adaptation [B= 0.05, t(8)= 1.44, P= 0.19; a= -0.06, t(8)=- 0.70, P= 0.50].

For the *NIH scale* no significant mediational effects were found: aftereffects [B= 0.01, t(8)= 0.44, P= 0.67; a= 0.08, t(8)= 1.41, P= 0.20], persistence of the aftereffects [B= 0.04, t(8)= 1.14, P= 0.29; a= 0.11, t(8)= 2.21, P= 0.06], long-term aftereffects [B= 0.01, t(8)= 1.22, P= 0.26; a= 0.08, t(8)= 2.99, P= 0.02], and adaptation [B= -0.001, t(8)= -0.08, P= 0.94; a= 0.05, t(8)= 1.50, P= 0.17].

For the *FIM scale*, the mediational role of the aftereffects measures resulted weaker than those found for the Overall cancellation score. No mediational effect of the aftereffects was found [B= 0.001, t(8)= 0.47, P= 0.96; a= -0.051, t(8)= -1.59, P= 0.15]. The average 10-session persistence of the aftereffects mediated weakly the FIM improvement [B= 0.41, t(8)= 2.22, P= 0.06; a= -0.005, t(8)= -0.229, P= 0.82]. Finally, the mediational effect of the long-term aftereffects on the FIM improvement score was significant [B= 0.010, t(8)= 2.502, P< 0.05], even though also the not-mediated improvement remained significant [a= -.032, t(8)= -2.64, P< 0.05]. No mediational effect was found for the adaptation effect [B= -0.002, t(8)= -0.25, P= 0.81; a= -0.06, t(8)= - 2,79, P= 0.02]. In sum, some measures of aftereffects exerted a significant mediational effect on the improvement of the FIM score.

Follow up

Seven patients were examined at month-1, and four at the end of the 2nd and 3rd month (respectively, assessments #8, #9, and #10). Three patients (BA, BG, and GMT) did not enter the follow up.

Visuomotor exploratory tasks. The Cancellation score (average of the patients’ scores in the Letter, Bell, and Star cancellation tasks) was used. The percent average scores of the seven patients at the month-1 (0.74, SD ±0.26) were comparable to those at the week-2 assessment (0.67, SD ±0.25) [F(1,6)= 2.16, P= 0.19, pη2= 0.26]. The scores of the four patients at the month-1 (0.76, SD ±0.30), month-2 (0.69, SD ±0.30), and month-3 (0.73, SD ±0.32) assessments were also comparable [F(2,6)= 0.59, P= 0.58, pη2= 0.16].

Functional scales. For the CBS scale, the patients' average scores were 2.55 (SD ±0.53) at the week-2, and 2.80 (SD ±0.33) at the month-1 assessment (Wilcoxon matched pairs test, T= 0, P= 0.10). The scores of four patients assessed at month-2 and month-3 did not change. In five patients the anosognosia CBS scores were 6.10 (SD ±5.00) at the week-2, and 4.60 (SD ±4.20) at the month-1 assessment (Wilcoxon matched pairs test: z= 0.73, P= 0.46). The CBS and anosognosia scores did not change in the follow up. For the NIH scale, the patients' average scores were 9.84 (SD ±5.34) at the week-2, and 9.84 (SD ±5.08) at the month-1 assessment [F(1,5)= 0.02, P= 0.87, pη2= 0.004]. For the FIM scale, the patients' average "total" scores were 63.58 (SD ±25.15) at week-2, and 68.49 (SD ±29.39) at month-1 [F(1,5)=2.19, P= 0.20, pη2 = 0.30]. The NIH and FIM scores of the four patients assessed at month-2 and month-3 did not change.

2.1 Conclusion

Experiment 1 provided evidence that the ecological adaptation procedure is equally effective in ameliorating neglect symptoms as the more traditional pointing adaptation procedure. Patients received 20 sessions of PA during a period of two weeks in which they performed the pointing task (one week) and the ecological procedure (the other week). Improvement of patients' visuo-spatial deficits took place after the first week and continued in the second week of treatment, with no difference between the ecological and the pointing procedure. The Effect-size indices supported this conclusion. With the exception of the line bisection task, which showed no changes, the patients' improvement in the tasks assessing spatial neglect was testified by the large effect-size indices associated with time (average effect size 0.55, range 0.38-0.65). By contrast, group differences were never significant or remarkable (average effect size 0.16, range 0.003-0.33), and groups did not show a differential improvement over time (the average effect size of the Group by Time interaction equals to 0.20, range 0.11-0.27). The patients' improvement was unrelated to baseline level of performance, neurological impairment, as assessed by the NIH scale, and duration of disease (see tables 6-7).

In this experiment, we did not find positive effects of the prism adaptation treatment on line bisection performance. While prism adaptation has overall positive effects on the patients' performance, as assessed by different tasks, there are differences among studies as for the specific tasks affected by the procedure. Cancellation performance, however, appears to be consistently improved. The lack of effects on line bisection, as well as the absence of mediational effects of aftereffects on sentence reading performance, suggests some specificity of the effects of prism adaptation in a rehabilitation setting.

Since a cross-over design was used, the data from the second week of treatment might be biased by a carryover effect from the first week, making it difficult to disentangle the specific contribution of each treatment. The results, however, did not indicate a carryover effect. First, across the different tasks and indicators, the statistical interaction between the Group and Time main factors was not significant (see Tables 3 and 4), showing that the improvement of the patients' performances was not affected by the particular treatment in the first session (Jones and Kenward, 2003). Secondly, the improvement after the first week (Bowen and Lincoln, 2007), with no differences between the two groups, indicated an equivalence of the treatments even before any possible carryover effect might take place. The decrease of spatial neglect during the second week was shown both by the ANOVAs using the three time intervals (Baseline, Week-1, and Week-2) as a within-subjects main factor (see Tables 3 and 4), and by the ANCOVAs using as covariate the mean scores of the three baselines (see Table 5). Taken together, these results strongly suggest that the experimental treatment is as effective as the control treatment in ameliorating spatial neglect symptoms.

One limitation of the present study is that the design did not compare the effects of the ecological treatment with a control group receiving no treatment. However, in a previous controlled study it was already established that prism adaptation with the pointing task is effective (Frassinetti et al., 2002). Similarly, an early study using Fresnel prisms found that patients wearing the prisms showed a greater improvement of USN and hemianopia, as compared with a control untreated group (Rossi et al., 1990). Furthermore, recent reports show that ten sessions of visuomotor pointing activity alone decrease left USN, yet the improvement is lower than the one achievable by prism adaptation through repeated pointing (Serino et al., 2009; Mizuno et al., 2011). Our experiment also provided evidence for the presence of adaptation and aftereffects (see reviews in Redding et al., 2005; Redding and Wallace, 2006; Redding and Wallace, 2010) during the week of the pointing task, as expected from previous studies (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Ladavas et al., 2011). In every session, we recorded the expected rightward bias that was corrected during the exposure condition (see figure 9, adaptation effect), followed by the leftward deviation in each post-exposure condition (see figure 10, aftereffect). The current study also showed, for the first time, the presence of long-term aftereffect as demonstrated by the increasing error recorded in the pre-exposure condition that became more leftward in each session.

In the present study, the improvement of the patients’ neurological impairment, as assessed by the NIH scale, was unrelated to the effects of prism adaptation, as suggested by both the ANCOVA using the baseline NIH score as a covariate (see Table 6), and the mediational analysis. Conversely, the improvement of the patients’ scores in a widely used measure of independence in everyday activities (i.e., the FIM scale) was partly accounted for by the aftereffects, as indicated by the mediational analyses. Thus, the benefit of a prism adaptation treatment did not extend to neurologic severity but its effect appears to be specific to neglect symptoms. Improvement following prism adaptation may also generalize to whole-person activities and independence in daily life, as assessed in an inpatient setting. A similar result was recently replicated in a controlled study, in which the group of neglect patients that was submitted to ten sessions of PA pointing treatment improved significantly more than the control group who received neutral goggle. The improvement was recorded both in the CBS and in the FIM scales (Mizuno et al., 2011).

Results from the mediational analysis also supported the hypothesis (Sarri et al., 2008; Farnè et al., 2002) that the beneficial impact of prism adaptation on neglect symptoms might be related to the magnitude of the aftereffect in the post-exposure phase. Indeed, on the different mediators that we tested (adaptation and aftereffect indexes), only the aftereffect measures could predict the improvement. Larger and more prolonged aftereffects were related to greater improvements in the cancellation tasks and in part the FIM scores. By contrast, we did not find any evidence that improvement was related to the patients' ability to adapt to prism in terms of error correction during the exposure phase, as previously reported by other authors (Serino et al, 2006; Serino et al, 2007 Ladavas et al., 2011). The mediational analyses provided evidence both for positive effects of a prism adaptation treatment, and for an advantage of at least ten repeated sessions.

Finally, and importantly for rehabilitation purposes, patients reported a preference for the ecological activities, which could be better tolerated, allowing a higher number of brain-damaged participants to go through the whole training.

EXPERIMENT 2

Ecological activities during prism exposure induce larger aftereffects than pointing task in healthy individuals

[Fortis P, Ronchi R, Calzolari E, and Vallar G. (In preparation)]

3.1. Aim of the study

In the first study (Experiment 1), we demonstrated the effectiveness of the new ecological procedure in ameliorating a wide range of visuo-spatial disorders in neglect patients. Since we did not provide measurements of adaptation and aftereffects during the ecological task, in this second experiment we tested if the ecological adaptation procedure results in adaptation and aftereffects that are comparable to those previously demonstrated in the traditional pointing task (e.g., Redding and Wallace, 2010). If results from our study show adaptation and aftereffects following the ecological task, this would increase our confidence in the effectiveness of this procedure and make it a viable option for long-term neglect rehabilitation. We submitted 48 neurologically healthy subjects to two consecutive days of exposure to rightward shifting prisms in which subjects performed the ecological task and the pointing task in separate days. In order to record if error correction occurred during the adaptation phase we modified the ecological procedure previously employed in the neglect study (Experiment 1). We added 4 pointing movements before and after the execution of the visuo-motor activities. In addition, we tested the presence of aftereffects in each day through three tests that are widely used in literature of prism adaptation: the proprioceptive, visual and visual-proprioceptive tests. We tested subjects of different ages, representative of young and aged populations. The young participants were selected to allow for comparisons with studies of PA in healthy subjects, typically involving young individuals (see for example Berberovic and Mattingley, 2003; Michel, Pisella, et al., 2003; Loftus et al., 2008; Loftus et al., 2009, Michel et al., 2008). To make our result comparable with studies of PA in neglect patients, often involving older individuals, we included a group of elderly subjects. Similar to Experiment 1, we also administered a questionnaire at the end of each adaptation task to assess participants' level of satisfaction in performing the adaptation procedures and the possible difficulties they encountered in executing them.

3.2 Materials and methods

Participants

Two groups of healthy right-handed subjects (young and aged) were tested. The young group consisted of twenty-four undergraduate students (12 females, mean age: 24 years, SD: 2.67, range 19-30; mean education: 15 years, SD: 1.37, range 13-17), enrolled in the Department of Psychology, University of Milano-Bicocca, Italy. The aged group consisted of twenty-four elder subjects (12 females, mean age: 68 years, SD: 5.74, range 57-79; mean education: 13 years, SD: 5.60, range 5-18), recruited from the inpatient population of the Neurorehabilitation Unit of the Istituto Auxologico Italiano IRCCS, Milan, Italy, with no history or evidence of neurological or psychiatric disease. Each subject had normal or corrected to normal vision and was naive to the purpose of the study. All subjects gave their informed consent prior to participating in the study and the students received course credits. The study was approved by the university and the hospital ethics committee.

Prism adaptation procedure

Subjects received two sessions of prism exposure on two consecutive days in which they completed a paradigm including 1) a pre-exposure evaluation; 2) exposure to a base-left wedge prisms (Optique Peter, Lyon, France) displacing the visual field horizontally by 10° to the right; 3) a post-exposure evaluation identical to the pre-exposure one.

During the exposure condition, subjects performed the pointing adaptation task on one day, and the ecological adaptation tasks on the other day. The order of the two adaptation procedures was counterbalanced: twenty-four subjects (12 young and 12 aged) performed the pointing adaptation task in the first day and the ecological task on the following day; the other twenty-four participants (12 young and 12 aged) performed the adaptation tasks in the reverse order. Each adaptation task was carried out with the right arm. The exposure phase lasted about 20 minutes.

Exposure condition: Pointing adaptation task

Participants sat at a table and positioned their right upper limb inside a two-layer wooden box (32 cm high, 74 cm wide). The lower and upper surface of the box had a pentagonal shape with the base facing the participants' side (see Figure 7, Experiment 1). The pentagon's depth at the center (distance between the base and the vertex of the box) was 32 cm, and 19 cm at the lateral sides. Participants were asked to point with their right index finger to a target (the top of a red pen) presented by the examiner at the distal side of the box. They were instructed to perform one quick out-and-back motion. After each movement, the participant returned her hand to the starting position at body center. A black cloth attached from the participant's neck to the upper surface of the box occluded the vision of the starting position of the arm. The pentagonal shape of the box occluded the view of the arm's movement until the terminal part, such that only the right index finger emerging from the distal side of the box was visible. Ninety pointing movements were made. The target was presented in a pseudorandom fixed order 10° to the right or left of the participants' mid-sagittal plane (MSP). The same number of trials was presented for each of the two target positions. The initial and last four pointing trials included two instances of the right and left target positions. The distal edge of the box was marked with angular gradations (degrees, °), attached on the upper side of the box on the examiner's side, which was not visible to the participants. The distance between the target and the participants' finger was measured. A positive score denoted a rightward displacement with respect to the position of the target, a negative score a leftward displacement.

Exposure condition: Ecological adaptation task

During the ecological adaptation task participants performed 10 of the 12 visuo-motor activities used in Experiment 1. Two activities were excluded since they required material from a neuropsychological test (WAIS; Wechsler, 1997) that was not available in the present study. The instructions how to perform each task were standardized and the activities were presented in the following order: 1) collecting coins on the table and putting them in a money box, 2) dressing rings and bracelets, 3) closing jars with the corresponding lids, 4) assembling jigsaw puzzles, 5) box and block, 6) sorting cards, 7) threading a necklace with 12 spools and rope, 8) copying a chessboard pattern on an empty chessboard, 9) serving a cup of tea, 10) composing a dictated word using letter printed on a square. During the ecological procedure the vision of the arm was available for the entire movement path. Prior to and after the execution of the ecological activities, participants performed four pointing movements that were administered with an identical procedure as the one employed during the pointing adaptation task.

Pre and Post-exposure evaluation: aftereffect measures

Participants sat at a table with their head aligned with the body's MPS and stabilised by a chin-rest attached to the table. A transparent square panel (50 cm side) marked with a goniometry with lines radiating from -90° to + 90° was placed on the table centered with participants' MPS (see Fig. 11). During the pre- and post-exposure evaluation, three aftereffect measures were administered: proprioceptive, visual, and visual-proprioceptive tests. The three tests were presented in counterbalanced order across participants. For the proprioceptive and the visual-proprioceptive tests participants were asked to perform fast and accurate pointing movements with their right upper limb. Participant's arm was positioned at the center of the panel with the right hand resting on a starting location near their body. This served as a starting point for all movements.

1. Proprioceptive Test. Participants were blindfolded and instructed to indicate the subjectively estimated position of their body midline on the panel surface. They performed 10 straight-ahead pointing movements. On each trial, the experimenter recorded the deviation of the finger position from the true objective body midline (°, degrees of visual angle).

2. Visual Test. A red LED was mounted on a pulley (120 cm length, 1.5 cm deep) placed horizontally at the top of a black wooden box (35 cm high, 75 cm wide, and 20 cm deep, see Fig. 11). The box was positioned in a darkened room at the distance of 85 cm from participants' MPS. Two strings placed on both LED sides were used to move the LED on the pulley. The speed of the LED movement was varied between trials in order to avoid counting strategies. The visual test did not involve arm movements: participants were instructed to verbally stop the movement of the LED, when its position corresponded to their MPS. The LED was moved ten times: 5 times from right to left and 5 times in the opposite direction, starting with the right to left movement first, in respect to participants' view. A centimetre attached to the pulley on the experimenter's side allowed for the recording of the deviation of the LED position from the center of the pulley corresponding to the true objective participants' MPS (cm). Each measurement was then transformed in degrees of visual angle (°).

3. Visual-Proprioceptive Test. The same pulley-mounted LED box of the visual test was used. With eyes open, participants performed 10 pointing movements on the panel surface to indicate the downward projected position of the LED. On each trial, the LED was placed in front of the participants' MPS but participants were unaware of its position. The movement of the arm was occluded from vision by a two-layer wooden box (30 cm high, 75 cm wide, and 50 cm deep) and by a black cloth attached from the participant's neck to the upper surface of the box. Participants were instructed to close their eyes between each trial to allow the experimenter to re-position the light.

To minimize the de-adaptation effect participants were asked to close their eyes at the end of the adaptation phase and between each test performed in the post-exposure evaluation.

The difference between the deviation on the initial and last four trials of the exposure condition was used to evaluate the extent to which participants were able to correct the lateral deviation induced by the prismatic displacement (adaptation effect). The difference between post- and pre- exposure measures was computed to express the relative shift in estimate for each test and quantify the presence of aftereffects: proprioceptive shift, visual shift, and visual-proprioceptive shift.

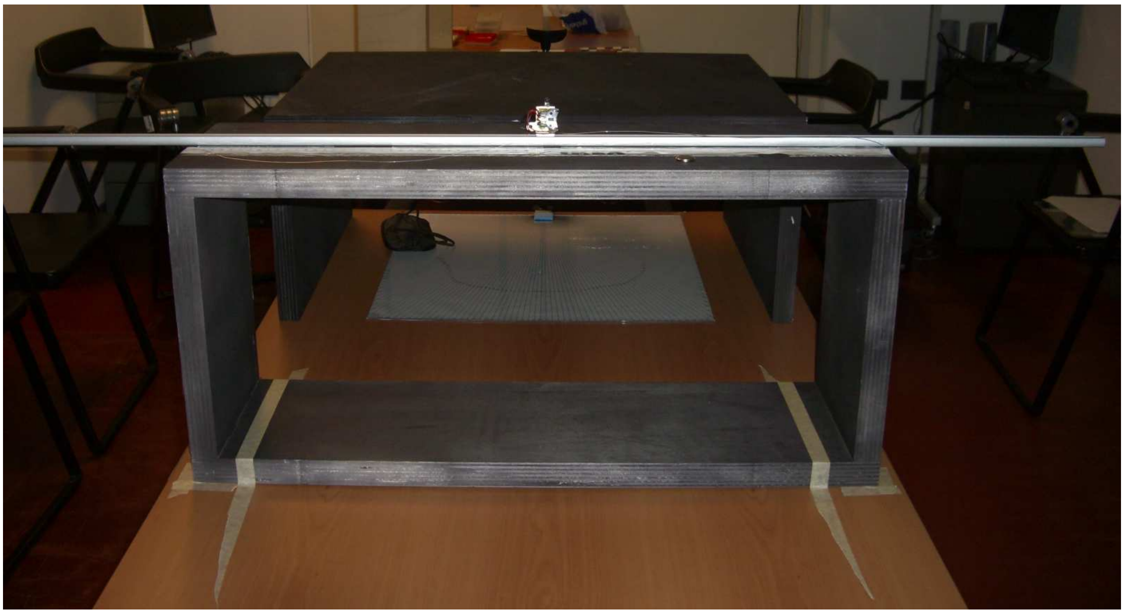

Figure 11. Box used in the Visual and Visual-proprioceptive tests. On the table, the goniometry board to record the error of the pointing movement

Questionnaire

A Likert-scale questionnaire was administered at the end of each day of the experiment and assessed how participants subjectively experienced performing the adaptation tasks (see Appendix at the end of the chapter). Participants were required to indicate their level of agreement with each of the thirteen questionnaire statements. The scale ranged from 1 (“totally disagree”) to 7 (“totally agree”).

Statistical analysis

The adaptation effect, the proprioceptive, visual and visual-proprioceptive aftereffects and the participants' responses in the questionnaire were assessed through parametric statistical analyses (ANOVAs). Significant differences were explored by Newman-Keuls' post-hoc multiple comparisons.

3.3 Results

Adaptation as error correction effect

The difference between the initial and last four pointing trials of the exposure condition (shift) was examined to assess whether participants were able to correct the lateral deviation induced by the prisms. A mixed-design ANOVA with Day (day1/day2) as the within-subjects factor and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Age (Young/Aged) as the between-subjects factors was performed. The effect of the Intercept [F(1,46)= 51.94, p< 0.001] was significant revealing that a significant shift was induced by prisms during prism exposure. The main effect of Day [F(1,44)= 7.34, p< 0.01] was also significant showing that a larger shift was present in the first day compared to the second day of prism exposure. No other significance differences were found in the analysis. As can be seen in Figure 12, participants showed an initial rightward pointing error deviated in the same direction as the lateral shift induced by prisms. The error was reduced at the end of the exposure phase with a same amount of error correction following the ecological and the pointing tasks. This result was consistent in the young and aged group of subjects.

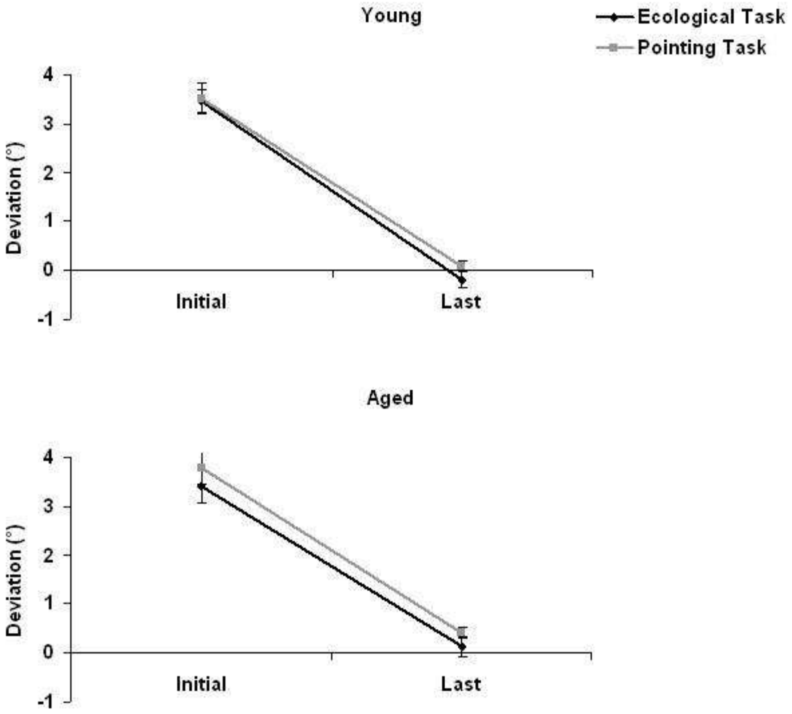

Figure 12. Adaptation effect in the young group (above panel) and in the aged group (below panel) of participants. Values represent the mean pointing errors (°, error bars are 1 SEM) in the first and last 4 trials of the exposure condition during the ecological (black line) and the pointing (grey line) adaptation procedures. Positive/negative scores indicate rightward/leftward errors.

A subsequent analysis was performed to investigate the different magnitude of the lateral shift induced in the two days of prism exposure. A two-way ANOVA with Time (mean first 4 trials/ mean last 4 trials) and Day (day1/day2) as the within-subjects factors revealed that the main effect of Time [F(1,47)= 561,21 p< 0.001], the main effect of Day [F(1,47)= 44.21, p<0.001], and the interaction of Time by Day [F(1,44)= 7.74, p< 0.01] were significant. Post-hoc comparisons revealed that subjects were able to adapt to the lateral deviation induced by prism in both days as shown by a reduced lateral deviation in the last pointing trials of the exposure condition (p's <0.001 for day1 and day2; see Table 8). In addition, the comparison between the errors performed in the initial pointing trials of the two days of prism exposure was significant (p<0.001). Participants' initial pointing errors of the second day were less rightward deviated than the initial pointing errors of the first day of prism exposure. Similarly, the comparison between the errors performed in the last pointing trials of the two days of prism exposure was significant (p<0.01). Participants' final pointing movements of the first day of PA was still rightward deviated from the true target position (M = 0.34°, SD = 0.74; t test against zero = 3.22, p = 0.002) whereas the final pointing movements of the second day were closer to the target position (M =-0.11°, SD = 0.68; t test against zero = -1.12, p = 0.27; see Table 8).

Table 8. Mean deviation of the Initial and Last four trials of the exposure condition in each day of prism exposure. Values represent the deviation (expressed in degree) from the target: positive values indicate rightward deviation, and negative values indicate leftward deviation. Values in parentheses are standard deviations.

	Day 1	**Day 2**
Initial 4 trials	4.09 (1.39)	3.00 (1.34)
Last 4 trials	0.34 (0.74)	-0.11 (0.68)

Pre-post test differences: aftereffect measures

Analysis of the proprioceptive shift, visual shift, and visual-proprioceptive shift were assessed to test the presence and magnitude of the aftereffects following the ecological and the pointing adaptation tasks. Mixed-design ANOVAs with Task (ecological/pointing) as the within-subjects factor and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Age (Young/Aged) as the between-subjects factors were performed. Furthermore, because the effects of prisms may wear off as a participant performs multiple post-test assessments, all analyses of shift differences were initially carried out with the inclusion of Test-order (first, second, or third) as a factor. For the proprioceptive and visual tests there were no main effects or interactions involving Test-order (all ps > 0.22). Thus, for simplicity, the order factor was dropped from these analyses. Effect of order occurred in the visual-proprioceptive test and is reported below.

Proprioceptive Test

A mixed-design ANOVA on the proprioceptive shift showed a significant effect of the Intercept [F(1,46)= 51.94, $p < 0.001$], revealing that exposure to rightward shifting prisms induced a significant leftward deviation in the proprioceptive measures (M = -2.35°; SD = 2.26). In addition, the main effect of Task was significant [F(1,46)= 4.84, p= 0.03] showing that the amount of aftereffect varied according to the task performed during the adaptation phase. Inspection of the means revealed a greater leftward deviation after the ecological adaptation tasks (M = -2.93°; SD = 3.32) than the pointing adaptation task (M = -1.77°; SD = 2.43). The main effect of Age [F(1,46)= 1.68, p= 0.20] and the interaction of Task and Age [F(1,46)= 0.56, p= 0.46] were not significant. As can be seen in Figure 13, the ecological adaptation task created a greater leftward deviation both in the young and aged group of subjects.

Visual Test

A mixed-design ANOVA on the visual shift showed a significant effect of the Intercept [F(1,46)= 28.45, $p < 0.001$], revealing that exposure to rightward shifting prisms induced a significant rightward deviation in the visual measures (M = 1.08°; SD = 1.83). In addition, the main effect of Task approached significance [F(1,46)= 3.91, p= 0.05], suggesting that the amount of aftereffect varied according to the task performed during the adaptation phase. Inspection of the means (Figure 13) revealed greater rightward deviation after the ecological adaptation tasks (M = 1.41°; ES = 0.27) than the pointing adaptation task (M = 0.76°; ES=0.26). The main effect of Age [F(1,46)= 0.00, p= 1.00] and the interaction of Task and Age [F(1,46)= 0.96, p= 0.33] were not significant.

Visual-Proprioceptive test

A mixed-design ANOVA on the visual-proprioceptive shift including the factor of Test-order revealed a significant interaction of Task by Age [F(1,36)= 4.99, $p < 0.05$], and an interaction of Task by Age by Test-Order [F(2,36)= 3.74, p= 0.03]. The Intercept [F(1,46)= 120.39, p<

0.001] was also significant, showing that exposure to rightward shifting prisms induced a significant leftward deviation in the visual-proprioceptive measures (M = -3.78°; SD = 3.52). No other significance differences were found in this analysis. To follow up on the three-way interaction, two separate analyses were performed in the young and aged group of participants using mixed-design ANOVAs on the visual-proprioceptive shift with Task (ecological/pointing) as the within-subjects factor and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Test-order (first, second and third) as the between-subjects factors. For the young group, analysis revealed a significant effect of the Intercept [F(1,18)= 63.00, $p< 0.001$], and of the main effect of Task [F(1,18)= 8.67, $p< 0.01$]. No other significance differences were found in this analysis, showing that the amount of leftward deviation in the visuo-proprioceptive test varied according to the task performed during the adaptation phase. As can be seen in Figure 13, a greater leftward deviation was recorded after the ecological adaptation task (M = -5.48°; SD = 4.06) than the pointing adaptation task (M = -2.93°; SD = 2.44) for young participants.

For the aged group, analysis revealed a significant effect of the Intercept [F(1,18)= 59.38, $p< 0.001$], and of the interaction of Task by Test-Order [F(2,18)= 3.90, $p< 0.05$]. No other significance differences were found in this analysis. As can be seen in Figure 13, the main effect of Task [F(1,18)= 0.20, $p< 0.66$] was not significant and the same amount of leftward deviation was recorded after both the ecological and the pointing adaptation tasks. Post-hoc comparisons revealed no order effect during the pointing adaptation task: a mean leftward shift of -3.31°, -4.48°, and -2.96° was recorded for those performing the visual-proprioceptive test as first, second and third, respectively. During the ecological adaptation task a mean leftward shift of -3.14°, -0.36°, and -5.87° was recorded for those performing the test as first, second and third, respectively. Post-hoc comparisons revealed a reduced leftward deviation for those performing the test in the second position compared to those who performed the task in the third position (p< 0.02). The other pair wise comparisons were not significant.

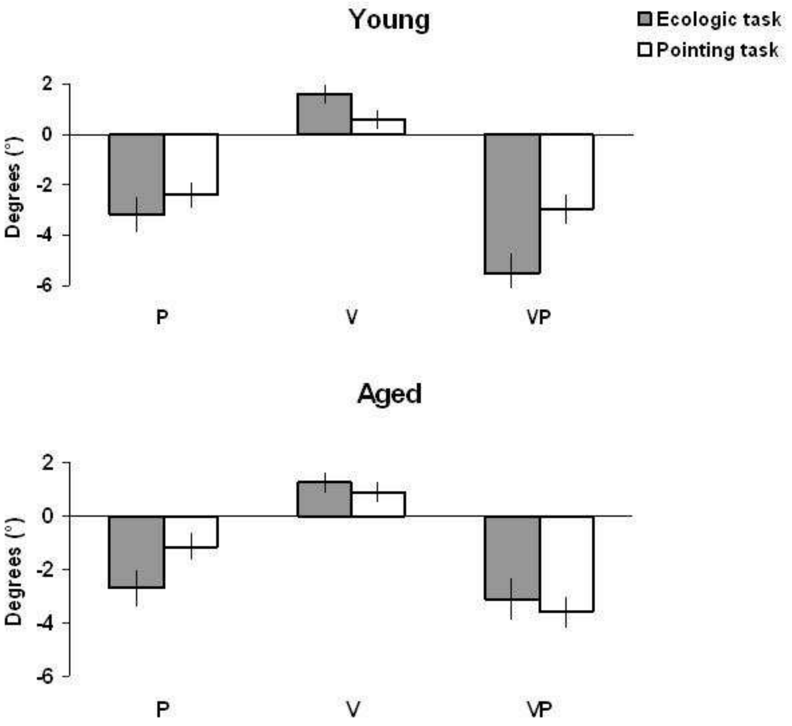

Figure 13. Aftereffects in the young group (above panel) and in the aged group (below panel) of participants, in the proprioceptive test (P, left panel), visual test (V, middle panel), and visual-proprioceptive test (VP, right panel). Results refer to the shift (mean values of the post-exposure condition – mean values of the pre-exposure condition) induced by prism in the 3 aftereffect tests during the ecological (grey column) and the pointing (white column) adaptation procedures. Positive/negative scores indicate rightward/leftward errors (°, error bars are 1 SEM).

Questionnaire

The 13 items of the questionnaire (see Appendix) were grouped into 5 topics to assess how participants experienced performing the adaptation task. The topics referred to the pleasantness (items 1-3) or monotony (items 4-5) of the task and to the presence of side effects potentially caused by the motor activities (items 6-7) or the prism (items 8-12). The last topic tested how participants could experience to repeat or extend the adaptation procedure over time (items 13 -14). The results in the 5 topics are presented in Figure 14.

Participants' mean responses for each topic were analyzed by mixed-design ANOVAs with Task (ecological/pointing) as the within-subjects factor and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Age (Young/Aged) as the between-subjects factors.

For the pleasantness of the task, the main effect of Task was significant [$F(1,44)= 34.32$, $p< 0.001$] showing that the ecological task (mean level of agreement = 6.04, SD = 0.90) was considered more pleasant than the pointing a task (mean level of agreement = 5.20, SD = 1.18). No other significance differences were found in the analysis.

For the monotony of the task, the main effect of task [$F(1,44)= 20.71$, $p< 0.001$], and the interaction of Task by Order of adaptation task [$F(1,44)= 4.43$, $p< 0.05$] were significant. Post-hoc comparisons revealed that the ecological adaptation task was considered less repetitive than the pointing adaptation task in the group who performed the pointing task in the first day followed by the ecological task in the second day ($p < 0.001$). A similar trend was found in the group who performed the task in the opposite order ($p = 0.09$). This suggests that the pointing task was considered more tedious than the ecological tasks.

For the side effects due to the motor activities, no significant main effects or interactions were found. Young and aged participants did not experience pain in the arm or in the body neither after the ecological (mean level of agreement = 1.79, SD = 1.30) nor after the pointing adaptation task (mean level of agreement = 1.70, SD = 1.28).

For the side effects due to the prism, the main effect of Task [$F(1,44)= 16.02$, $p< 0.001$], the main effect of Age [$F(1,44)= 7.00$, $p< 0.05$], and the interaction of Task by Age [$F(1,44)= 4.90$, $p< 0.05$] were significant. Post-hoc comparisons revealed that young participants experienced more side effects of prism after the ecological adaptation task (mean level of agreement = 2.72, SD = 1.63) than the pointing adaptation task (mean level of agreement = 2.23, SD = 1.34). This difference was not found in the aged group of subjects (mean level of agreement ecological task = 1.76, SD = 1.13; mean level of agreement pointing task = 1.62, SD = 0.93). However, the responses remained at the disagreement level suggesting that the execution of both adaptation procedures was well tolerated in the young and aged group of subjects.

Lastly, for the items that assessed how participants would experience the extension of the adaptation procedure over time, the main effect of Task [F(1,44)= 9.62, p< 0.001] was significant. No other significance difference were found in the analysis, showing that participants would prefer to perform the ecological tasks (mean level of agreement = 4.07, SD = 1.48) than the pointing task (mean level of agreement = 3.43, SD = 1.38) for a longer period of time.

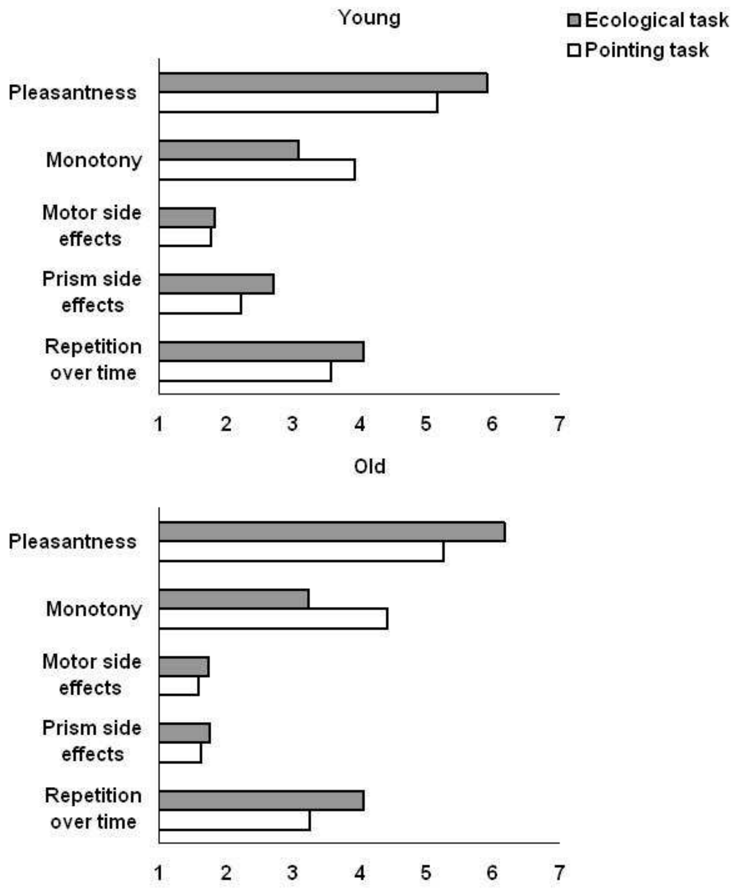

Figure 14 - The mean scores of the ecological and the pointing adaptation procedures on the 5 topics of the questionnaire in the young group (above panel) and in the aged group (below panel) of participants. The scale ranged from 1 (“totally disagree”) to 7 (“totally agree”).

3.4 Conclusion

In this experiment, we showed that performing the ecological tasks during the prism exposure phase induces the same error correction as performing the pointing adaptation task, both in the young and old group of subjects. Indeed, in the initial trials of the exposure condition, participants made pointing errors that were rightward deviated from the target location as a consequence of the optical displacement. The errors were similarly reduced at the end of the exposure phase following both adaptation tasks and this result was recorded consistently in the young and aged subjects. The mean deviation in the initial trials was about 40% of the optical displacement in the first day and 30% in the second day, whereas the final trials of both days were closer to the target.

In addition, we also demonstrated that the last trials of the exposure condition of the first day, although more correct than the initial trials, were still relatively rightward deviated from the true target position (mean pointing errors = 0.34°). On the contrary, a complete accuracy was achieved in the final trials of the second day in which the pointing movements were centred on the target (M= -0.11°). This result is consistent with recent findings in a group study of 20 neglect patients exposed to 10 consecutive sessions of prism adaptation (Ladavas et al., 2011). In that study, patients performed a pointing adaptation task during the exposure condition and the pointing errors diminished progressively over the ten sessions. It is possible that the correction of the error induced by prism becomes more efficient in consecutive sessions of PA. Therefore, the more accurate performance recorded in the pointing movements of the second day of our experiment may derive from a faster and more efficient correction of the deviation induced by prism. It is also possible that the result reflects a carry-over effect of the contralateral deviation induced by prism during the first day of PA. Indeed, in the post-exposure phase of the first day, subjects performed pointing movements that were leftward deviated from the target (see below the aftereffect in the visual-proprioceptive test). The leftward deviation of the pointing movements may still be present during the exposure condition of the second day and may have reduced the rightward shift induced by prism. In support of this hypothesis, several studies in healthy neurological individuals and in primates have demonstrated long-lasting aftereffects that persisted for several days and even weeks following a single day of prism exposure (Hatada, Miall, and Rossetti, 2006; Lackner and Lobovits, 1977; Klapp, Nordell, Hoekenga, and Patton, 1974; Yin and Kitazawa, 2001). A similar persistence of aftereffect over time was also recorded in Experiment 1, when patients were exposed to ten consecutive sessions of PA with the pointing adaptation task. During the pre-exposure condition of each PA session, patients performed pointing movements to a visual target without vision of their arm (as in the visual-proprioceptive test of the second experiment). As we previously reported (Experiment 1), the errors recorded in the pre-exposure condition were progressively increased toward the left side over the 10 sessions suggesting a persistent and additive effect of the contralateral deviation induced by prism.

In sum, performing ecological or pointing adaptation tasks can similarly induce correction of the movements during prism exposure that results in spatially accurate performance at the end of the exposure phase (adaptation effect). Additionally, our result further suggests that the duration of the aftereffects can be increased if multiple sessions of pointing or ecological tasks during PA are performed.

Results from the second experiment also provided evidence that the ecological and the pointing procedures both induced a significant deviation in three aftereffects measures recorded in the young and aged group of participants. After exposure to prism with both adaptation procedures, the pointing movements of the proprioceptive and visual-proprioceptive tests were leftward deviated, and the perceptual judgments of the visual test were rightward deviated. Thus, the visually-guided movements performed by participants during the ecological tasks induced a deviation in the three aftereffects measures in the same direction that has previously been reported after exposure to rightward shifting prism through the pointing task (see Redding and Wallace 2010 for a review).

Strikingly, when we compared the magnitude of the shift generated by the two adaptation procedures we recorded even stronger aftereffects following the ecological procedure. In particular, in the proprioceptive test, the ecological tasks induced a larger leftward deviation than the pointing task in both the young and aged subjects. Similarly, in the visual test a trend toward a greater rightward deviation was found after the ecological procedure in both the young and aged subjects. Finally, in the visual-proprioceptive test, a greater leftward deviation was recorded for the young group after the ecological task than the pointing task. In the aged group a similar amount of shift was found after the two adaptation procedures but the magnitude was dependent on the order in which the tests were administered. These results may have implications for neglect interventions since results from Experiment 1 and previous reports (Sarri et al., 2008; Farnè et al., 2002) have shown that the magnitude and duration of the aftereffects can, at least in some cases, predict the neglect recovery.

Finally, results from the questionnaire indicated that the ecological procedure was preferred over the pointing task, as it was considered as more enjoyable, interesting, easy to perform, and less repetitive than the pointing task. In a rehabilitation setting, this difference can be expected to translate in a greater compliance with the therapy.

Taking together these results suggest that the ecological procedure is a good tool to induce adaptation and aftereffects to prism in healthy individuals. The presence of stronger aftereffects and a subjective preference for the ecological procedure suggest that this procedure is preferable for rehabilitating neglect patients.

3.5 Appendix

Questionnaires performed after the ecological procedure (version A) and after the pointing procedure (version B).

A: *How did you experience wearing the goggles while you were manipulating the objects?*

B: *How did you experience wearing the goggles while you were pointing to the pen?*

1. It was enjoyable
2. It was interesting
3. It was easy to perform
4. It was boring
5. It was repetitive
6. It was painful for my arm
7. It was tiring to maintain the posture
8. My eyes were getting tired
9. It made me dizzy
10. It made me sick
11. I visually perceived objects distorted
13. I would have liked to continue the activity
14. I would like to participate in future experiments with the same procedure

SECOND PART

PRISM ADAPTATION AND SPATIAL BIAS

The second aim of my PhD work was to clarify how prism adaptation may affect spatial cognition and which are the mechanisms that are primarily influenced by the exposure to the goggle. Knowing more about the systems responsive to prism adaptation may help our understanding of which symptoms, or which patients, improve optimally after prism adaptation training. As reported in the Introduction of this thesis, not all neglect-related symptoms, nor treated patients, improve (e.g. Rousseaux et al., 2006; Dijkerman, et al., 2003; Ferber et al., 2003; Ferber and Murray, 2005; Morris et al., 2004; Sarri et al., 2006; Sarri et al., 2010), and the mechanism through which PA ameliorates spatial neglect still remains unclear. A main distinction within spatial cognition is the separation between the ability to perceive and allocate attention to stimuli versus the ability to respond and orient to stimuli. An interesting question is whether prism adaptation differentially modifies these two processes. As reviewed in the Introduction, different methods have been used to decouple perceptual-attention where and motor-intention aiming components in visuo-motor tasks, such as with video (Adair et al., 1998; Coslett et al., 1990; Na et al., 1998; Schwartz et al., 1997; Barrett, et al., 2001; Barrett, et al., 1999; Barrett and Burkholder, 2006), mirrors (Tegner and Levander, 1991), and an epidiascope (Nico, 1996). All of these methods reverse the orientation of visually-viewed hand movements relative to the direction of actual hand movement in the workspace. In our experiments, we used a modified version of the paradigm of Schwartz et al. (1997) and Na et al., (1998) in which participants performed a line bisection task while viewing their hand and the line via a TV screen, rather than directly (see the Introduction paragraph 1.1.2.2 for a full explanation). In a pilot study (Fortis et al., 2009 - Abstract presentation), we submitted 3 neglect patients to the TV line bisection task before and after a single session of prism adaptation with right-shifting prism. We found a selective reduction of the motor-intention aiming component in 2 out of 3 patients (in 1 patient there was no change of the aiming component), whereas the perceptual-attention where bias got worse for all the patients, increasing toward the right-side after the prism exposure session. A functional improvement of neglect deficits (tested with the CBS scale) was observed only in those two patients who showed the reduction in the aiming bias component. In addition, a recent study from Striemer and Danckert (2010a) similarly showed that 3 neglect patients improved in a manual line bisection task (consisting of both motor-intentional and perceptual components), whereas the performance on a purely perceptual landmark test remained unchanged after rightward prism exposure. In *Experiment 3* and *Experiment 4* we further investigated the effects of prism adaptation on where and aiming components of spatial cognition, both in a large group of neurologically healthy individuals (Experiment 3) and in a group of neglect patients (Experiment 4). We hypothesized that the beneficial effect of prism adaptation in neglect patients may be at least partly due to an influence on motor-intentional aiming errors (i.e., planning and executing actions towards the contralesional hemispace), rather than on perceptual-attentional where errors.

EXPERIMENT 3

Prism adaptation differently affects motor-intentional and perceptual-attentional bias in healthy individuals

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[**Fortis P.**, Goedert, K.M., and Barrett, A.M. (2011). Neuropsychologia, 49 (9) 2718-27. w*ww.elsevier.com/locate/neuropsychologia*]

4.1 Aim of the study

In Experiment 3, we wished to learn whether a primary effect of PA on spatial motor-intentional aiming component could be observed in a group of healthy young subjects. In addition, we tested the effect of both left- and right-shifting prisms. Several studies have detected an asymmetric effect of adaptation to left- and right-shifting prisms in healthy young adults mirroring that of neglect patients, with healthy young adults showing greater generalization of aftereffects after exposure to left-, as opposed to right-shifting prisms (Berberovic and Mattingley, 2003; Michel, et al., 2003; Loftus et al., 2008; Loftus et al., 2009, but see Michel et al., 2008; Morton and Bastian, 2004). Because these effects may be mediated in part by the a priori leftward baseline bias of young healthy individuals on visuomotor tasks (Goedert et al., 2010), they are similar to PA effects in neglect patients who have an a priori rightward baseline bias on visuomotor tasks, and show adaptation to right-, but not left-, shifting prisms (Rossetti et al., 1998). Therefore, in the present study, we exposed healthy participants to right- or leftward-shifting prisms or control goggles fitted with plain glass lenses. We used a computerized line bisection task to decouple the perceptual-attentional where and motor-intentional aiming components of their line bisection errors. If the aiming hypothesis of the therapeutic effects of PA were correct, we would expect to see dissociable effects on motor-intentional aiming and perceptual-attentional performance. In addition, consistent with previous findings, we expected that adaptation to leftward shifting prisms would affect the motor-intentional "aiming" component of the computerized line bisection task, whereas no change was expected for the right-shifting group.

4.2 Materials and methods

Participants

Eighty-four right-handed participants (35 males, 49 females, mean age: 19 years; SD: 2.11; range 18-31), naive to the purpose of the study, were enrolled from the Department of Psychology of Seton Hall University, South Orange, New Jersey and gave their informed consent prior to participating in the study. Twenty-eight participants were exposed to right-shifting prisms (13 male, mean age: 19 years, SD: 1.15, range 18-23), 28 to left-shifting prisms (11 male, mean age: 20 years, SD: 3.18, range 18-31), and 28 to control goggles fitted with plain glass lenses (11 male, mean age: 19 years, SD: 1.36, range 18-25). All participants were right handed and had normal or corrected to normal vision.

Prism Adaptation Procedure

Participants completed the following tasks in this order: 1) a pre-exposure evaluation; 2) exposure condition to either rightward or leftward lateral shift, or to control goggles fitted with plain glass lenses, and 3) a post-exposure evaluation identical to the pre-adaptation one. During prism adaptation with right- or left-lateral shift, participants wore Bernell^{TM} Deluxe Prism Training Glasses fitted with optical wedge prisms shifting participants' vision 12.4° laterally. During adaptation with control goggles, and during pre- and post-adaptation evaluation, participants wore Bernell^{TM} frames fitted with plain glass lenses. The glasses were inserted into a light-proof goggle that prevented participants from seeing any undistorted portion of the peripheral visual field.

Exposure condition

Participants sat at a table with their right hand positioned on top of the table near the center of their body. This served as a starting point for all movements. A narrow shelf (19 cm high X 14 cm wide) occluded the participant’s view of the early part of any arm movements and a black cloth attached from the participant’s neck to the shelf blocked the view of the starting position of the arm. The adaptation procedure consisted of a line bisection task. The arm’s movement remained occluded to vision for most of its path and became available in the last part of the trajectory. Depending on the length of the individual participants’ arms, participants could see the distal third of their handpath (approximately 20 to 22 cm including the hand, wrist, and early part of the arm). Participants were asked to mark the perceived center of a horizontal line by performing one quick out-and-back motion. They were also instructed to not correct the movement trajectory in the last part, when the hand became visible. After each movement, the participant returned her hand to the starting position at body center. Sixty horizontal lines (240 mm length, 2.0 mm thick) were presented one at a time on sheets of standard letter size paper. The lines were placed in the right, center, or left position relative to the participant’s midsagittal plane. The right/left position deviated from center by 21 cm. The lines were presented twenty times in each position in a pseudorandom order, such that each group of 6 trials included two instances of the three positions (right, center, and left). The exposure phase lasted about 10 minutes. The difference between the deviation on the initial and last six trials was used to index the extent to which participants were able to correct the lateral deviation induced by the prismatic displacement.

Pre- and Post-exposure evaluation

During the pre- and post-exposure evaluation, two aftereffect measurements (visual-proprioceptive and proprioceptive tests), and a computerized line bisection fractionation task were administered.

Proprioceptive Test

Participants were blindfolded and used their right index finger to point straight ahead 5 times to indicate the subjectively estimated position of their body midline. After each movement, the experimenter prompted them to return to the starting position in the middle of their chest. A transparent panel (1.0 m long, 0.5 m high) marked with a ruler was placed at the distance of 55 cm, aligned with the center of participants' body (Mark and Heilman, 1990), allowing the experimenter to record the deviation of the finger position from the true objective body midline. Rightward errors were recorded as positive and leftward errors as negative (in degrees).

Visual-Proprioceptive Test

Participants sat at a table in front of a wooden box (35 cm high, 100 cm width, and 28 cm deep). A black cloth attached from the participant's neck to the upper side of the box blocked the initial view of arm movements and the shelf prohibited participants from viewing the remainder of their pointing movement. With eyes open, participants performed six pointing movements toward a visual target (pen) presented by the experimenter at the distal edge of the top face of the box. The target was presented two times in each of three positions (straight-ahead, 21° rightwards, and 21° leftwards), in a pseudorandom order. After each movement, the experimenter prompted participants to return to the starting position in the middle of their chest. The distal side of the box was closed by a transparent panel marked with a ruler visible only from the experimenter's side, such that pointing error could be recorded. Pointing errors were measured in degrees of distance between the finger and the target: a positive score denoted a rightward displacement with respect to the position of the target, a negative score a leftward error.

Computerized line bisection task

Participants were seated at a table in front of a computer screen (set to 640 X 480 pixel resolution). The screen was positioned at the distance of 50 cm and aligned with the center of the participant’s body. The participants’ task was to mark the center of twenty horizontal lines (265 mm length, 3 mm thick). Each line was presented alone and displayed at the center of the screen at participants’ eye level. Between each line bisection trial a random-dot visual mask appeared for 500 ms. Participants used a computer mouse to click on the location that they believed to be the center of the line. The right arm and hand movement was occluded from view via a wooden box covering the arm and hand (25 cm high, 80 cm wide, and 25 cm deep) and via a black cloth attached from the participants’ neck to the proximal side of the box. During the first half of the trials (10 lines, natural condition), the movement of the mouse and the pointer on the video screen was congruent: rightward movement of the mouse moved the pointer rightward and leftward movement, leftward. In the other half of the trials (10 lines, reversed condition) the right-left video feedback of the pointer movement was reversed. Thus, in the reversed condition, rightward movement of the mouse moved the pointer leftward on the video screen and vice versa.

The deviation from the objective midpoint of the line presented in the natural and reversed conditions was scored by transforming from pixels to the nearest mm: a positive value denoted a rightward error, a negative value, a leftward error. Using Equations 1 and 2 and their algebraic equivalents (Equation 3 and 4), we fractioned individual participants’ error in the natural and reversed conditions into its where and aiming spatial bias components (Barrett et al., 2001; Barrett and Burkholder, 2006; Chen, Erdahl, and Barrett, 2009; Garza et al., 2008; see Introduction for a full explanation).

Natural Error = Aiming Component + Where Component [Equation 1]

Reversed Error = Aiming Component – Where Component [Equation 2]

Where Component = (Natural Error – Reversed Error) / 2 [Equation 3]

Aiming Component = (Natural Error + Reversed Error) / 2 [Equation 4]

4.3 Results

We adopted an alpha (α) of 0.05. We followed up all significant interactions with orthogonal, single degree-of-freedom, simple main effects tests after Keppel and Wickens (2004, p. 520) and used a Bonferroni-corrected alpha when making multiple means comparisons with t tests. Where appropriate, we reported the partial eta-squared (η_p^2) measure of effect size.

Pre-test / Baseline

Separate one-way ANOVAs with group (right- and left-shifting prisms, and control goggles) as a factor revealed that the groups were similar at baseline for all tests: proprioceptive test, F(2,81) = 0.57, p = 0.566, $\eta_p^2 =$ 0.01; visual-proprioceptive test, F(2,81) = 0.16, p = 0.851, $\eta_p^2 =$ 0.01]; natural, F(2,81) = 2.12, p = 0.124, $\eta_p^2 =$ 0.05, and reversed, F(2,81) = 1.10, p = 0.332, $\eta_p^2 =$ 0.03, computerized line bisection tasks; "where", F(2,81) = 1.71, p = 0.209, $\eta_p^2 =$ 0.04, and "aiming", F(2, 81) = 1.40, p = 0.260, $\eta_p^2 =$ 0.03, fractionated bias components.

We performed separate single-sample t tests versus zero on the measures to determine the accuracy of performance at baseline using the Bonferroni-corrected α of 0.01. For the proprioceptive and visual-proprioceptive tests, participants' baseline performance was accurate (ts < 1.3, ps ≥ 0.200). Consistent with the leftward bias of healthy young participants observed in previous studies, the natural line bisection performance (M = -2.69, SD = 3.6), and the fractionated "where" (M = -2.16, SD = 3.6) and "aiming" biases (M = -0.52, SD = 1.4) were significantly leftward biased at baseline (ts ≥ 3.4 and ps ≤ 0.001, for all tests; all errors in mm).

Prism Exposure

The difference between the initial and last six trials of the exposure condition was examined to assess whether participants were able to correct the lateral deviation induced by the prisms. As can be seen in Table 9, participants exposed to right- or left-shifting prisms showed an initial line bisection error deviated in the direction of the lateral shift induced by prisms, but this error was reduced at the end of adaptation. A 3x2 mixed ANOVA with Prisms (left, right or control) and Time (first six trials, last six trials) as factors revealed a main effect of Prisms, F(2,81)= 28.9, p< 0.001, η_p^2= 0.42 and a Prisms by Time interaction, F(2,81)= 23.4, p< 0.001, η_p^2= 0.37. Simple main effects tests on the effect of Time at each level of Prism revealed that both the left-shifting, F(1,81) = 25.1, p < 0.001, η_p^2= 0.24, and right-shifting, F(1, 81) = 20.5, p < 0.001, η_p^2= 0.20, prism groups reduced their prism-induced error between the first and last six trials of adaptation. The leftward deviation of the control group, however, did not significantly change between the first and last trials of the exposure condition, F(1, 81) = 2.9, p = 0.092, η_p^2= 0.04.

Table 9 Adaptation effect. Mean deviation of the Initial and Last six trials of the exposure condition across the three groups: right- and left-shifting prisms, and control plain goggle. Values represent the deviation (expressed in mm) from the objective center of the line: positive values indicate rightward deviation, and negative values indicate leftward deviation. Shift represents the difference between the first and last six trials of the exposure condition. Values in parentheses are standard deviations. Asterisks denote a significant reduction (*p*s < 0.001) in error from the first to the last six trials.

	Initial 6 trials	**Last 6 trials**	**Error Reduction**
Right-shifting Prism	3.71 (4.95)	0.96 (4.64)	2.75* (2.86)
left-shifting prism	-6.57 (3.56)	-3.52 (3.17)	3.04* (3.88)
Control goggle	-1.93 (3.67)	-0.89 (3.54)	1.04 (2.84)

Pre-Post Test Differences

Analyses of pre- versus post-test differences were performed using mixed ANOVAs with Prisms (left, right and control) and Pre/Post (pre, post) as factors. Furthermore, because the effects of prisms may wear off as a participant performs multiple post-test assessments, all analyses of pre-post differences were initially carried out with the inclusion of Test-order (first, second, or third) as a factor. For the proprioceptive, visual-proprioceptive, natural line bisection, and "aiming" bias there were no main effects nor interactions involving Test-order (all ps > 0.09). Thus, for simplicity of reporting, the order factor was dropped from these analyses. Effects of order on "where" bias and reversed line bisection are discussed below.

Proprioceptive test

Pointing movement deviations in the proprioceptive and visual-proprioceptive tests before and after exposure to the prisms were examined to assess whether participants adapted to the prisms. As can be seen in Figure 15a, accurate pre-prism proprioceptive pointing performance moved in the direction opposite the prism shift after training with the prism. Analyses revealed a significant main effect of Prisms, F(2,81)= 3.89, p = 0.02, η_p^2= 0.09, and a Prisms by Pre/Post interaction, F(2,81)= 5.85, p = 0.004, η_p^2= 0.13. Simple main effects tests of pre-post differences at each level of Prism revealed that proprioceptive straight-ahead was shifted significantly rightward after left prism adaptation, F(1, 81) = 4.4, p = .039, η_p^2= 0.05, and significantly leftward after right prism adaptation, F(1, 81) = 6.6, p = 0.012, η_p^2= 0.08. However, there was no significant change in proprioceptive straight-ahead for the control group, F(1, 81) = 1.8, p = 0.184, η_p^2= 0.02.

Visual-proprioceptive test

Pre-post performance on the visual-proprioceptive test is depicted in Figure 15b. As can be seen in the figure, both left and right-shifting prisms induced aftereffects in the direction opposite the prism shift. Analyses revealed a significant main effect of Prisms, F(2,81)= 30.85, p < 0.001, η_p^2= 0.45, and a Prisms by Pre/Post interaction, F(2,81)= 69.39, p < 0.001, η_p^2= 0.62. Simple main effects tests revealed that for the right-prism group, the initial pre-exposure error in the pointing movements was more left-deviated in the post-exposure condition, F(1, 81) = 51.2, $p < 0.001$, $\eta_p^2 = 0.39$. Similarly, for the left-prism group, the initial pre-exposure error was more rightward deviated in the post-exposure condition, F(1, 81) = 77.4, $p < .002$, $\eta_p^2 = 0.49$. The amount of error in the pointing movements of the control group did not change from pre to post, F(1, 81) = 1.9, $p = 0.167$, $\eta_p^2 = 0.02$.

Taken together, these results demonstrate that both right- and left-shifting prisms induced contralateral aftereffects in the proprioceptive and visual-proprioceptive tests, showing that participants adapted to the lateral displacement induced by both prisms. Inspection of the effect sizes suggests these effects were of similar magnitude for the left and right prisms (0.49 and 0.39 on the visual-proprioceptive and 0.05 and 0.08 on the proprioceptive for the left and right groups, respectively).

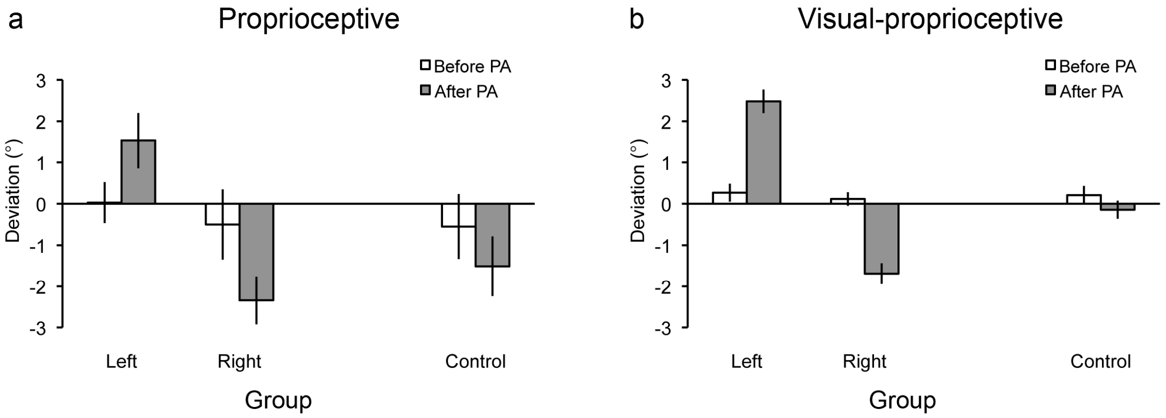

Figure 15 a: Proprioceptive test and **b**: visual-proprioceptive test. Values represent the pointing errors (°, error bars are 1 SEM): in the proprioceptive test from the true objective body midline; in the visual-proprioceptive test from the visual target. Results refer to the average of the group of participants before (white column) and after (grey column) exposure to left-shifting prisms (left panel), right-shifting prisms (middle panel), or control plain goggles (right panel). Positive/negative scores indicate rightward/leftward errors.

Fractionated Where and Aiming Components of Computerized Line Bisection

The fractionated where and aiming biases were our measures of primary interest as these represent a quantification of motor-intentional and perceptual-attentional errors assessed while a person is performing a visually-guided action. Participants' average aiming bias is depicted in Figure 16a. Consistent with our hypothesis, we observed a significant interaction between Prisms and Pre/Post for the “aiming” bias, $F(2,81)= 5.35$, $p = 0.007$, $\eta_p^2 = 0.12$, and no other effects ps ≥ 0.23. Simple main effects tests of Pre/Post at each level of Prism revealed a significant rightward shift only for the left prism group, $F(1, 81) = 9.6$, $p = 0.003$, $\eta_p^2 = 0.11$. By contrast, no pre-post difference was found for the right-shifting prism, $F(1, 81) = 1.5$, $p = 0.222$, $\eta_p^2 = 0.02$, and control groups, $F < 1$, $\eta_p^2 = 0.00$. Thus, a motor-intentional aiming bias was significantly affected only in the group exposed to left-shifting prisms.

Preliminary analyses of the where bias including the factor of Test-order revealed a Pre/Post by Prism by Test-order interaction, $F(4, 75) = 4.4$, $p = 0.003$, $\eta_p^2 = 0.19$. Inspection of the means revealed that for both left and right-shifting prisms, a general rightward pre-post shift was observable for those performing the computerized line bisection task first or second, but was absent in those who performed the task last. For the left prism, there was a mean rightward shift of 1.53, 1.62, and 0.09 mm for those performing the task first, second and third, respectively. For the right prism there was a mean rightward shift of 0.68 and 2.73 for those performing the task first and second, but a mean leftward shift of 0.50 for those performing the task third. Due to this order effect, remaining analyses of the where bias were performed on the subset of participants who performed the task either first or second (N = 43)[1], as the effects of the prism may have worn off for participants performing the task last.

The where bias for those who performed the task first or second appears in Figure 16b. Analyses revealed a significant main effect of Pre/Post, $F(1,40) = 12.69$, $p = 0.001$, $\eta_p^2 = 0.24$ and a significant Pre/Post by Prisms interaction, $F(2, 40) = 7.5$, $p = 0.002$, $\eta_p^2 = 0.27$. Simple main effects tests of Pre/Post at each level of Prism revealed a significant rightward shift for

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[1] An error in assignment to the conditions led to 43 participants performing the line bisection task last and 43 participants performing it either first or second.

both the left, F(1, 40) = 10.9, p = 0.002, η_p^2 = 0.21, and right prism groups, F(1, 40) = 13.6, p = 0.001, η_p^2 = 0.26. There was no pre-post difference observed in the control group, F(1, 40) = 1.1, p = 0.294, η_p^2 = 0.03.

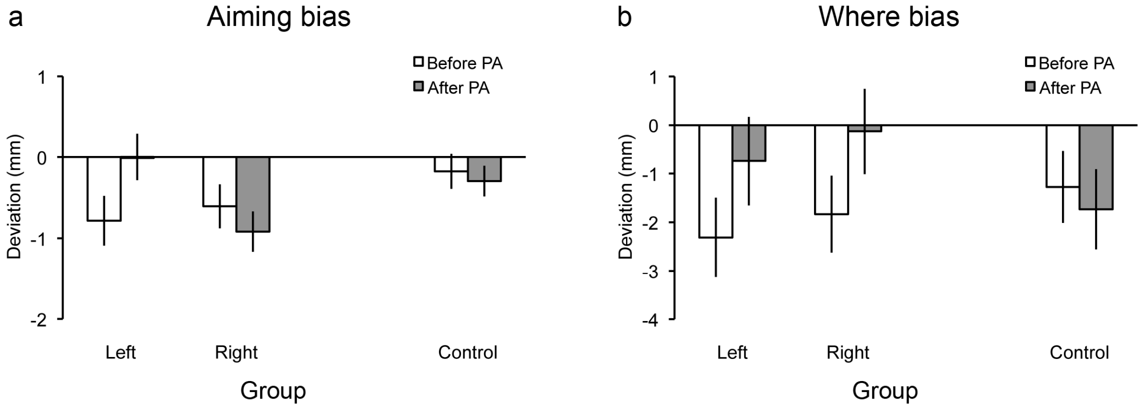

Figure 16 a: Motor-intentional "aiming" bias and **b**: perceptual-attentional "where" bias. "Where" and "aiming" biases were derived from the fragmentation of the natural and reversed line bisection errors (mm, positive/negative scores indicate rightward/leftward errors, error bars are 1 SEM). Results refer to the average of the group of participants before (white column) and after (grey column) exposure to left-shifting prisms (left panel), right-shifting prisms (middle panel), or control plain goggles (right panel). Note that for the "where" bias, these averages exclude participants who performed the computerized line bisection last.

Computerized Line bisection Performance in Natural and Reversed Condition

Performance in the natural and reversed line bisection conditions, by themselves, do not indicate the extent of participants' where and aiming biases, but they do give a picture of the resultant performance when these biases are working together, as is the case in a visually-guided movement. Table 10 contains the mean error for the natural and reversed conditions before and after prism exposure. Analysis of the natural condition revealed a main effect of Pre/Post, F(1,81)= 5.31, p = 0.024, η_p^2 = 0.06, and a Prisms by Pre/Post interaction, F(2,81)= 3.04, p = 0.050, η_p^2 = 0.07. Simple main effects tests revealed a significant rightward deviation after exposure to left-shifting prisms, F(1, 81) = 11.0, p = 0.001, η_p^2 = 0.12. By contrast, there was no significant change in the line bisection performance of the right-shifting prisms, F < 1,

η_p^2 = 0.01, and control groups, F < 1, η_p^2 = 0.00. Thus, only the left-shifting prisms significantly affected the line bisection performance under natural viewing conditions.

Preliminary analysis of the performance in the reversed condition revealed a Prisms by Pre/Post by Test-order interaction, F(4, 75) = 4.1, p = 0.005, η_p^2= 0.18. Inspection of the means revealed that for both left and right-shifting prisms, a general leftward pre-post shift was observable for those performing the computerized line bisection task first or second, but this shift deviated rightward for those who performed the task last. For the left prism, there were mean leftward shifts of 0.998 and 0.84 for those performing the task first and second, and a 0.858 mean rightward shift for those performing it third. Similarly for the right prism, there were mean leftward shifts of 0.585 and 3.572 for those performing the task first and second, but a mean rightward shift of 0.260 for those performing the task third. Thus, the effect of the prisms on reversed line bisection performance seems to wear off for those who performed the computerized line bisection task last. Limiting the analyses of the reversed line bisection condition to those who performed the computerized bisection task either first or second, revealed a main effect of Pre/Post, F(1, 40) = 6.2, p = 0.017, η_p^2= 0.18 and a Pre/Post by Prisms interaction, F(2, 40) = 4.0, p = 0.027, η_p^2= 0.17. Simple main effects tests revealed a significant leftward pre-post shift in reversed bisection errors for the right prism group, F(1, 40) = 11.0, p = 0.002, η_p^2= 0.22 and no significant pre-post change in the errors of the left prism, F(1,40) = 2.0, p = 0.162, η_p^2= 0.05 and control groups, F < 1, η_p^2= 0.01.

Table 10. Computerized Line Bisection. Mean error in the Natural and Reversed conditions of the computerized line bisection task pre and post prism exposure. Values represent the mean deviation (expressed in mm) from the objective center of the line: positive values indicate rightward deviation, and negative values indicate leftward deviation. Shift represents the difference between the pre and post exposure errors. Standard deviations appear in parentheses. Note that for the reversed condition, these averages exclude participants who performed the computerized line bisection last. Asterisks denote significant pre-post shifts in performance (*ps* < 0.01).

		Pre	**Post**	**Shift**
Line bisection - Natural condition	**Right-shifting prism**	-3.75 (3.62)	-3.46 (3.99)	0.29 (2.55)
	Left-shifting prism	-2.51 (3.84)	-0.97 (4.84)	1.54* (2.19)
	Control goggle	-1.79 (3.24)	-1.77 (3.64)	0.03 (2.61)
Line bisection - Reversed condition	**Right-shifting prism**	1.18 (3.99)	-0.90 (4.22)	-2.08* (3.30)
	Left-shifting prism	1.76 (3.18)	0.83 (3.23)	-0.93 (1.56)
	Control goggle	1.09 (2.97)	1.42 (3.39)	0.33 (1.80)

Correlation analysis

To test whether the change in the aiming motor-intentional bias was related to the degree of adaptation, we computed Pearsons' correlations between the mean lateral deviation (post exposure – pre exposure) in the aiming bias and the proprioceptive and visual-proprioceptive measures of participants exposed to left-shifting prisms. Neither the correlation between the deviation in the aiming bias and the visual-proprioceptive shift (r = -0.24, p= 0.22), nor the correlation between the deviation in the "aiming" bias and the proprioceptive shift (r = 0.05, p= 0.80) approached significance.

4.4 Conclusion

In this experiment, we showed that exposure to left-shifting prisms decreased the leftward aiming bias in a group of healthy young subjects, as demonstrated by a more central bisection performance in the post-exposure condition. In contrast to the effects of PA on the aiming bias, the effect of PA on the where bias was not prism-specific: both participants who adapted to left-shifting prisms and participants who adapted to right-shifting prisms showed a more rightward deviated where bias after prism exposure. Our results support the idea that, at least in this experimental design, prism adaptation primarily affects motor-intentional aiming spatial systems.

Many studies have shown that healthy individuals have a leftward bias in the line bisection task (Bowers and Heilman, 1980; Jewell and McCourt, 2000; McCourt and Jewell, 1999; McCourt et al., 2001), and also in a variety of other tasks (Nicholls et al., 1999; Nicholls and Loftus, 2007; Longo and Lourenco, 2007; McGeorge et al., 2007). Our sample of participants confirmed the presence of an a priori leftward bias in the line bisection task as well as in both the perceptual-attentional where and motor intentional aiming component. We also replicated previous findings (Schwarz et al., 1997; Barrett, Crosson, Crucian, and Heilman, 2002; Garza et al., 2008) of the presence of a primarily perceptual-attentional bias in the line bisection error in young to middle-aged adults, as shown by a larger magnitude of where than aiming bias in the error recorded in the group of our participants. Finally, our study supports the idea of the asymmetrical effect of prism adaptation in healthy subjects, since left-shifting but not right-shifting prisms induced a significant change in the participants’ performance (Berberovic and Mattingley, 2003; Michel, Pisella et al., 2003; Michel et al., 2008; Colent et al., 2000; Loftus et al., 2008; Loftus et al., 2009; Nicholls and Loftus, 2007).

EXPERIMENT 4

Effects of prism adaptation on motor-intentional spatial bias in neglect

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Fortis P., Chen P., Goedert, K.M., and Barrett, A.M. (2011). Neuroreport, 22 (14): 700-705]

5.1 Aim of the study

In the fourth study, we wished to learn whether a primary effect of PA on spatial motor-intentional aiming component could be observed in a group of neglect patients. The procedure employed in this study was similar to the procedure used in Experiment 3. Participants were submitted to a modified version of the paradigm of Schwartz et al. (1997) and Na et al. (1998) in order to separate the perceptual-attentional where versus motor-intentional aiming bias of their line bisection performance. The line bisection test was assessed before and after two sessions of exposure to rightward shifting prism.

5.2 Material and methods

Participants

Five consecutive neglect patients with right hemisphere strokes were enrolled from the inpatient rehabilitation hospital (Kessler Institute for rehabilitation, NJ, USA) after providing written consent. See Table 11 for patient characteristics. Participants were right-handed, with normal or corrected-to-normal vision and no history of other neurological or psychiatric disorders. All participants showed neglect symptoms either on the Behavioural Inattention Test (Wilson et al., 1987) or the Catherine Bergego Scale (Azouvi, Marchal, and Samuel, 1991). The presence of deficits in vision, somato-sensation, and audition was evaluated by a double-stimuli confrontation test (Bisiach et al., 1986). All participants had ischemic (N=4) or hemorrhagic (N=1) stroke, confirmed by CT (N=3) or MR images (N=2). We visualized lesion locations using MRIcro software (Rorden and Brett, 2000), drawing manually on an MRI template, and using the closest matching transverse slice for each patient. Figure 17 shows the regions of interest (ROIs) for each patient. The areas of greatest lesion overlap were in the frontal-parietal, and frontal-subcortical regions.

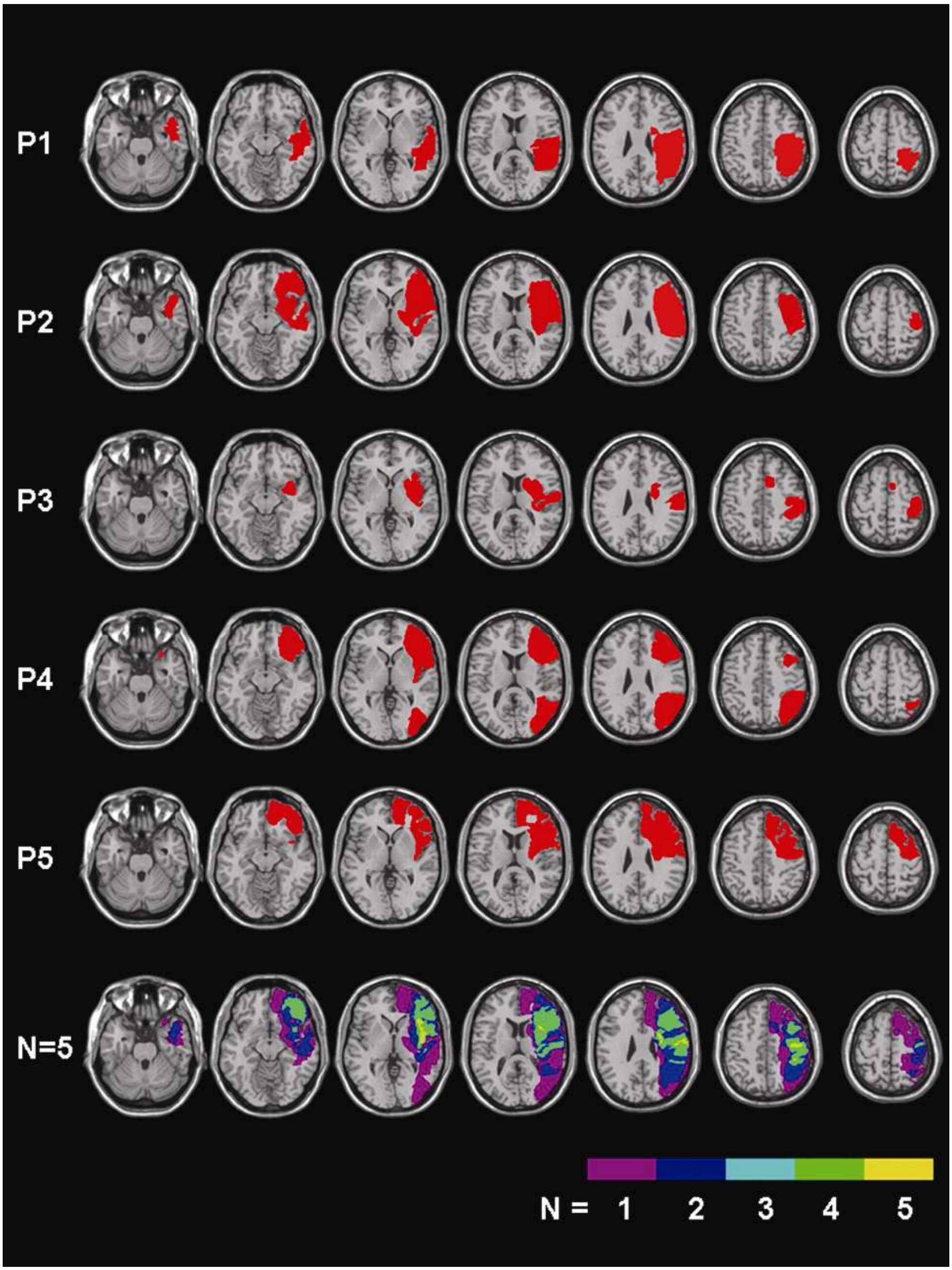

Figure 17. Lesion mapping in five right-hemisphere-damaged patients, and lesion overlay plots (bottom row: frequency of overlapping lesions, from violet, N= 1, to yellow, N=5.

Table 11. Patients' demographic and clinical data. +/- = presence or absence of deficits. For *Visual Field*: + = left homonymous hemianopia; for *Tactile Perception* + = hemianestesia at the left hand; for *Auditory Sensation* + = auditory loss at the left ear; e: presence of extinction at double stimuli. The BIT (Behavioural Inattention Test), range 0-146, is rated from 0 (maximum deficit) to 146 (no impairment); cut-off 129. The CBS (Catherine Bergego Scale), range 0-30; each item is rated from 0 (no deficit) to 3 (severe neglect impairment); the cumulative score is rated as "mild" (score 0-10), "moderate" (score 11-20), and "severe" (21-30) neglect. I/H: Ischemic/Hemorraegic lesion; F: Frontal, P: Parietal, T: Temporal, O: Occipital, Bg: Basal ganglia.

Patient	Age (Years)	Gender	Education (Years)	Duration of Disease (Weeks)	Visual Field	Tactile Perception	Auditory Sensation	BIT	CBS	Etiology, Lesion Site
P1	67	M	12	2	+	e	e	109	24	H, P-T
P2	52	F	13	5	e	e	e	31	26	I, F-P-T
P3	78	F	12	2	+	+	+	57	28	I, F-P-Bg
P4	68	M	12	2	+	e	e	14	27	I, F-P-T-O
P5	51	M	12	5	-	+	-	128	25	I, F-P-Bg

Procedure

Assessment of Spatial Where versus Aiming Bias. We assessed participants' where and aiming biases and prism adaptation aftereffects before and after the two consecutive days of prism adaptation. Participants marked the center of 16 horizontal lines (240 mm length, 3 mm thick), each printed alone on a 278 X 216 mm sheet and presented centrally on a table in front of the participants (see Figure 18). Similar to the paradigm of Na et al. (1998), participants' ability to view the line and their arm's movement directly was prevented by a black cloth. A camera (Sanyo, VCC-5884) positioned 37 cm above the table transferred the image of the line onto a video screen centered 80 cm in front of the participant. Therefore, to bisect lines, participants monitored their hands and the line indirectly via the video screen. Participants first bisected 8 lines in the Natural condition, in which visual information displayed on the video screen was congruent with actual arm movements: rightward movements appeared rightward and leftward movements, leftward. Participants then bisected 8 lines in the Reversed condition, in which a video mixer right-left reversed video feedback such that rightward movements appeared leftward on the video screen, and vice versa. In both conditions, we recorded deviation from the objective midpoint of the line in millimetres (mm), with positive values denoting rightward errors and negative values denoting leftward errors.

We derived participants' where and aiming biases by separating Natural and Reversed errors using Equations 1 and 2 (Garza et al., 2008).

Natural Error = Aiming Component + Where Component [Equation 1]

Reversed Error = Aiming Component – Where Component [Equation 2]

Both perceptual-attentional where and motor-intentional aiming biases contribute to line bisection errors in the Natural and Reversed viewing conditions. However, in the Natural condition these biases are aligned and oriented in the same direction, and thus may contribute additively to performance (Equation 1). In the Reversed condition, the where bias acts in the direction opposite the aiming bias, since the visual feedback is 180-degrees reversed (Equation 2). Algebraically solving these two equations allows quantification of both where and aiming bias components for each participant. Previous work supported the validity of where and aiming spatial error fractionation in stroke survivors and controls (see review and data in Garza et al., 2008).

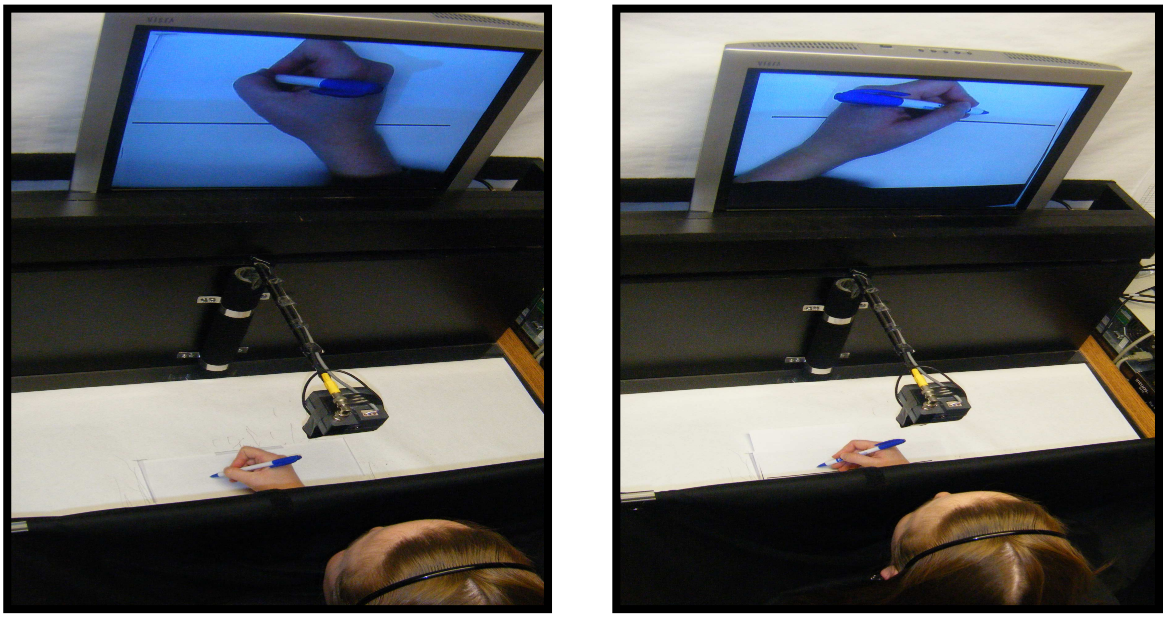

Figure 18. Line bisection task performed in the Natural (Left image) and Reversed (Right image) condition. The camera, positioned above the table, transferred the image to the video screen located at 80 cm in front of the participant. A black cloth prevented participants to directly view the line and their arm's movement. Participants' error in the Natural and Reversed condition was used to decouple the where and aiming spatial biases.

Prism Adaptation. During prism exposure, participants wore wedge prisms (Bernell^{TM} Deluxe Prism Training Glasses, 20-diopter), displacing the visual field horizontally rightward 12.4°. They performed 60 pointing movements to a visual target located at 0° or 21° to the right or left distal side of a board aligned with the participant's midsagittal plane. The three target positions (center, right, and left) were presented in a pseudorandom order. During target pointing, a shelf blocked the view of most of the arm's path, allowing participants to see only the distal part of the movement - i.e. the finger emerging to point to the target. The distal side of the board was marked with a ruler visible only from the experimenter's side, and pointing error was recorded (in degrees).

We assessed prism adaptation aftereffects with two tests. The visual-proprioceptive test consisted of 6 pointing movements to a visual target presented two times in each of the three positions (0°, 21° right, 21° left) in a pseudorandom order. Although the target was in view, participants could not see their pointing movement, hidden under an occluding shelf. For the proprioceptive test, blindfolded participants pointed 10 times to the position they felt was straight ahead of their body's center. A transparent panel marked with a ruler and aligned with the participants' body center allowed the experimenter to measure the distance (in degrees) between indicated and actual target/body center position to determine error in the two tasks, respectively. Rightward errors were recorded as positive, and leftward errors as negative.

5.3 Results

Given the small sample size, we used nonparametric statistical analyses to account for anticipated non-normal data distribution.

Error reduction. The presence of error reduction during prism exposure was assessed by comparing pointing errors in the initial and last six trials of prism exposure. Participants made a rightward error in the first six trials (day 1: M = 8.43°, SD = 2.88; day 2: M = 4.67°, SD = 2.34), which was reduced in the last six trials of exposure, on both days (day 1: M = 0.80°, SD = 0.55; day 2: M = 0.65°, SD = 0.43; z = 2.02, p = .043 for both days).

Aftereffects. Participants experienced a significant leftward shift in visual-proprioceptive error after 2 days of prism adaptation (before prism adaptation: M = -0.80°, SD = 1.57; after prism adaptation: M = -7.27°, SD = 1.47; z = 2.02, p = 0.043). Although not significant, the group also experienced a leftward proprioceptive error shift after 2 days of prism adaptation (before prism adaptation: M = 5.07°; SD = 3.30; after prism adaptation: M = -0.60°; SD = 6.76; z = 1.75, p = 0.080). Exploration of individual scores revealed that 4 of 5 participants experienced a leftward shift in proprioceptive error post prism adaptation.

Where versus Aiming Bias. Errors in the Natural and Reversed line bisection conditions appear in Table 12, and fractionated where and aiming biases are depicted in Figure 19. Critically, the motor-intentional aiming bias improved after prism adaptation in all participants. The initial rightward aiming spatial error (M = 19.37; SD = 10.27) was reduced after two days of prism adaptation (M = 2.30; SD = 14.03; z = 2.02, p = 0.043). In contrast, no change was detected in pre- (M = 0.53, SD = 14.63) versus post-prism adaptation (M = 9.58, SD = 17.11) perceptual-attentional where spatial bias (z = 0.40, p = 0.69).

Table 12. Patients' performance on the Natural and Reversed line bisection conditions before and after two days of prism adaptation. Positive value means rightward deviation, and negative value means leftward deviation (mm).

	Natural		**Reversed**	
Patient	**Before**	**After**	**Before**	**After**
P1	41.9	17.4	21.0	14.9
P2	-1.8	41.0	23.4	-33.9
P3	17.1	14.5	3.8	-2.4
P4	30.3	16.3	-0.9	-2.1
P5	12.0	-29.8	46.9	-12.9
Mean	19.9	11.9	18.8	-7.3

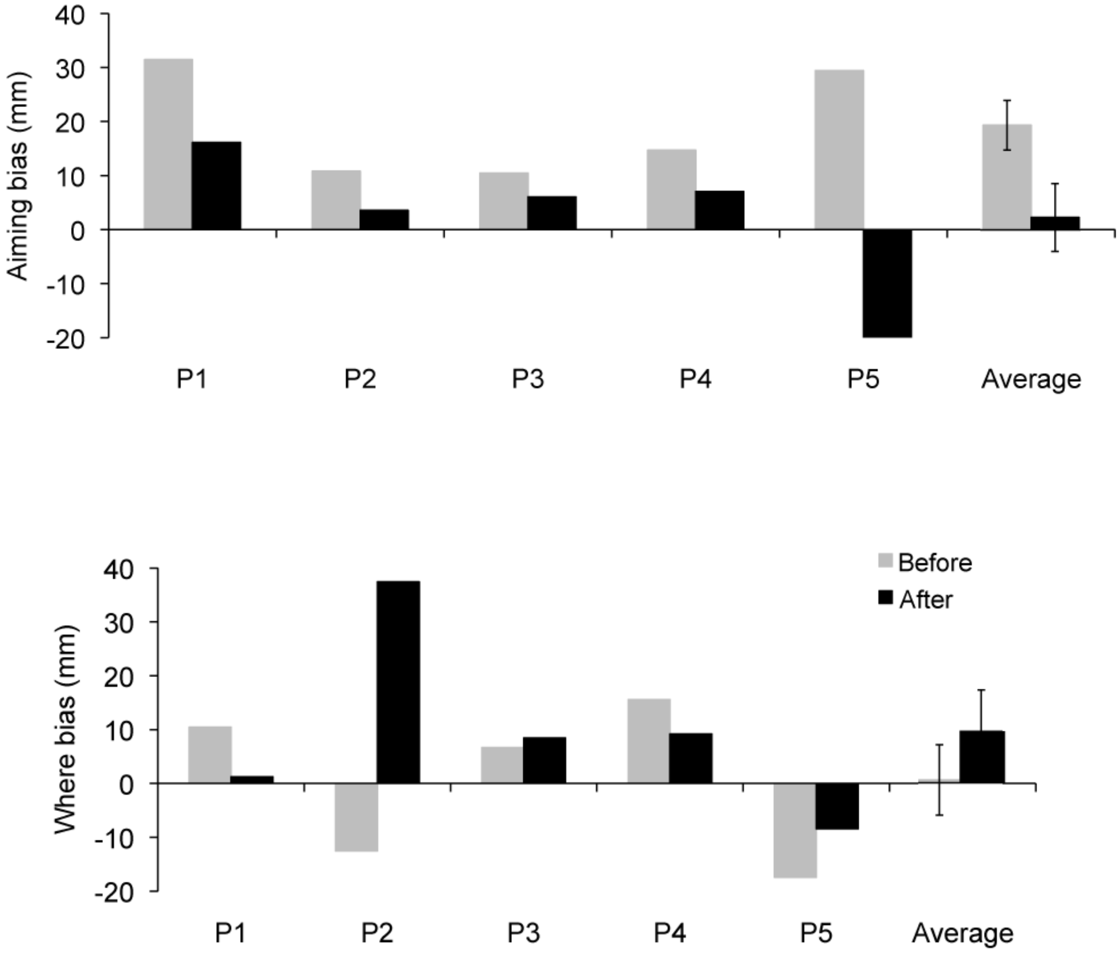

Figure 19. Motor-intentional "aiming" bias (above panel) and perceptual-attentional where bias (below panel). Where and aiming biases were derived from the fragmentation of the Natural and Reversed line bisection errors (mm, positive/negative scores indicate rightward/leftward errors, error bars indicate SEM). Results refer to the group of five subjects and the average of the group; before (grey column) and after (black column) two days of prism adaptation training.

5.4 Conclusion

In this experiment, we found that the motor-intentional aiming bias of all five neglect patients improved following two days of prism exposure. This result mirrors the result of Experiment 3 in healthy individuals, since adaptation to rightward shifting prisms primarily affected the rightward aiming bias in neglect patients, whereas adaptation to leftward shifting prisms affected the leftward aiming bias in the healthy subjects. In this forth experiment, the change in the where bias was not consistent and the five patients exhibited different patterns of modification of the perceptual-attentional component after the prism training: in 3 patients it was more rightward deviated, whereas in 2 patients it was more leftward deviated. The dissociation of the two biases after prism exposure further supports the hypothesis suggesting an important role for the motor-intentional aiming spatial systems in response to prism adaptation. This translates to the clinical possibility that neglect patients primarily disabled as a result of aiming spatial errors may benefit most from prism adaptation training, whereas those with primarily where bias may benefit less.

GENERAL DISCUSSION

The experiments described in this doctoral thesis investigated different aspects of the prism adaptation technique with a focus on its applicability to rehabilitating unilateral spatial neglect. Adaptation to prismatic goggles that laterally displace the visual scene has been studied for many years in neurologically healthy individuals (Stratton, 1896). Recently, prism adaptation (PA) has been applied in the rehabilitation of spatial neglect (Rossetti et al., 1998), revealing promising improvements in a wide range of symptoms for prolonged amounts of time. The first section of this thesis focused on the feasibility of new ecological visuo-motor activities applied during adaptation to prism. We tested the efficacy of the ecological procedure in ameliorating neglect symptoms (Experiment 1) and in generating adequate adaptation and aftereffects (Experiment 2). To better understand which symptoms, or which patients, improve optimally after prism adaptation training, in the second section of the thesis we investigated the effectiveness of prism adaptation on different aspects of spatial cognition. We tested the effect of prism exposure in perceptual-attention where and motor-intention aiming biases of a line bisection task, both in a group of neurologically healthy individuals (Experiment 3) and in a group of neglect patients (Experiment 4). In this general discussion, I will summarize, interpret, and integrate the results from the four experiments, highlighting the implications for the rehabilitation of spatial neglect.

6.1 Which adaptation task to use during the exposure phase?

The standard procedure employed in prism interventions comprises the repetition of pointing movements toward visual targets. This procedure was used for the first time for improving neglect symptoms by Rossetti et al. (1998). The same procedure has also been widely used in studies in healthy individuals (see Redding et al., 2005 and Michel, 2006 for reviews and Kornheiser, 1976 for older works). Despite its frequent employment, the pointing adaptation task may not be the optimal choice for prism adaptation paradigms. In three experiments presented in this thesis, we investigated if other adaptation tasks can - or should - be employed during prism exposure interventions.

In Experiments 1 and 2, we introduced a new adaptation procedure based on varied visuo-motor ecological activities. Indeed, the pointing adaptation task appears to be repetitive and tedious. The use of engaging and diverse visuo-motor tasks may be preferable for rehabilitation programs that require consecutive sessions for multiple weeks (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Serino et al., 2009; Ladavas et al., 2011; Shiraishi et al., 2008; Vangkilde and Habekost, 2010; Mizuno et al., 2011). A more varied procedure may provide a useful alternative if these can be shown to have similar beneficial effects.

In Experiment 3, we used a line bisection task during the exposure phase (see also Goedert et al., 2010). Subjects were requested to mark the center of lines presented in different locations. The rationale for this choice derives from the fact that during the pointing task, recording of pointing errors in the exposure condition relies on the human examiner’s visual assessment of the patient’s deviation. By contrast, when patients bisect lines on standard paper, a record of their adaptation error is created. Given the potential usefulness of recording patients’ adaptation (Serino et al, 2006) and the ease of the line bisection method, we tested the effect of the line bisection task during the adaptation phase.

6.1.1 Effectiveness of the ecological adaptation procedure in ameliorating neglect

Importantly, results from Experiment 1 showed that the ecological procedure was equally effective as the pointing procedure in ameliorating the different manifestations of the neglect syndrome in the left extra-personal and personal domain. Both treatment improvements were obtained after one week, with a further recovery after the second week, making the two-week prism adaptation treatment a reliable protocol for attenuating spatial neglect symptoms.

Similarly to our study (Experiment 1), a recent study exposed chronic neglect patients to 8 consecutive weeks of prism exposure while patients were tossing rings and performing a pegboard exercise (Shiraishi et al., 2008). The study provided evidence of improving visuo-spatial deficits, although the lack of comparison with a group of patients receiving a control treatment, and the absence of adaptation and aftereffect measures, limited definite conclusion.

In an early seminal randomized study using prism exposure to rehabilitate hemianopia and neglect (Rossi et al., 1990), 18 stroke patients who wore the prisms for four weeks showed an improvement of both deficits, assessed by psychometric testing, as compared with a control untreated group of 21 patients. However, no difference was found between the control and the experimental group in activities of daily living, assessed by the Barthel ADL mobility score (Mahoney and Barthel, 1965). This study, however, did not report information about the site of the lesion and details concerning the distinction between hemianopia and spatial neglect. Interestingly, as in the ecological procedure employed in Experiment 1, patients were engaged in everyday activities, although not specifically devised in order to enhance visuo-motor adaptation, and with no measures of adaptation and aftereffects being recorded.

Taken together, these results strongly suggest that prism adaptation training associated with varied visuomotor activities is an effective tool to ameliorate some aspects of spatial neglect.

6.1.2 The importance of aftereffects

Adaptation (i.e., error correction during the exposure condition) and aftereffects (i.e., lateral deviation in the post-exposure condition) measures provide evidence that subjects have adapted to the displacement induced by the prismatic goggle (Welch, 1978; Redding and Wallace, 1993). Three measures of aftereffects have been frequently employed in prism adaptation studies (Redding and Wallace, 2006): 1) the proprioceptive test, in which subjects are blindfolded and direct their pointing movements to the subjective straight ahead, 2) the visual-proprioceptive test, in which subjects direct their pointing movements toward visual targets in the absence of vision of their arm; 3) the visual test, in which subjects verbally estimate the position of a visual target. Previous research has shown that the visual-proprioceptive and the proprioceptive pointing movements are contralateral deviated after prism exposure (e.g., leftward deviation for rightward shifting prisms), whereas the visual perceptual judgment is oriented in the same direction as the optical displacement of the prism (e.g., rightward deviation for rightward shifting prisms; Redding and Wallace, 2010). In the experiments in this thesis, we measured adaptation and aftereffects for the three different adaptation procedures (pointing, ecological, line bisection). Below, I will argue that these measures, especially the aftereffect measures, may be important for establishing the effectiveness of adaptation procedures in neglect rehabilitation.

In Experiment 1 (mediational analysis), we found a positive correlation between the aftereffects in the visual-proprioceptive test and the performance in the cancellation tasks, with greater improvement in patients who showed greater and more prolonged leftward aftereffects. We used different mediators, such as the average 10-session aftereffects, the average 10-session duration of the aftereffects, the long-term aftereffects, and the average 10-session adaptation effect. The mediational analyses showed that the improvement in the cancellation tasks (means of letters, bells and stars), and, in part, in the FIM scores was accounted for by the aftereffects, and not by adaptation: the larger and more prolonged the aftereffects, the greater the improvement in the performance. These novel findings support the effectiveness of the prism-based treatments in neglect symptoms and overall disability, whatever the extent of any concurrent neurological recovery, either spontaneous or caused by the on-going physiotherapy. This result is in agreement with the current view that prism adaptation reduces the ipsilesional rightward bias that characterizes left spatial neglect (Rode et al., 2003). The importance of strong aftereffects has also been reported in two studies in which the magnitude and duration of the aftereffects was essential in establishing neglect recovery (Sarri et al., 2008; Farnè et al., 2002). Another study showed that patients, exhibiting no adaptation, show little improvement in the BIT and in ocular exploration, compared with patients displaying adaptation. The authors did not find differences related to the size of the aftereffects (Serino et al., 2007). However, they used different, indirect, approaches to investigate the specific roles of the adaptation and aftereffects. They split the patient sample into two groups (showing/not showing adaptation, and aftereffects, around a cut-off score based on the mean pointing error of the whole group): 75% of the 20 patients showed adaptation or aftereffects.

In a previous study by Frassinetti et al. (2002), only one out of seven right-brain-damaged patients (patient RD) did not show adaptation to prism. RD's improvement was confined to the conventional tests of the BIT (including cancellation, and copying), and to some reading tests, but did not extend to the behavioral section of the BIT. The findings of Frassinetti et al. (2002), and of Serino et al. (2007) also indicate that the patients' adaptation to prisms - which brings about leftward aftereffects - is a necessary condition for recovery from spatial neglect to take place.

Future investigation in a larger group of neglect patients are needed to assess if prism-induced leftward bias, measured by the aftereffects, accounts for the patients' improvement in neglect symptoms. If aftereffects measures are confirmed to be related to neglect improvements, the measure of the lateral deviation induced by prism may become a key indicator of rehabilitation outcome. Thus, rehabilitation specialists could use aftereffects measures to predict if PA treatment may improve neglect symptoms in their patients.

6.1.3 Adaptation and aftereffects following the pointing, ecological and line bisection adaptation procedures

In our experiments, we assessed the presence of adaptation and aftereffects generated by the pointing, the ecological and the line bisection adaptation procedures, and we compared these effects in order to establish which task induced stronger adaptation to prism.

Pointing adaptation procedure. In Experiment 1 and 4, we demonstrated that the use of the pointing adaptation task during the exposure phase generates adaptation and aftereffects in neglect patients. In Experiment 1, ten patients performed the pointing adaptation task for ten consecutive sessions. The aftereffect was assessed through the visual-proprioceptive test. In Experiment 4, five patients performed two consecutive days of the pointing adaptation task. The aftereffects were assessed through the visuo-proprioceptive and proprioceptive tests. In both experiments, we recorded error correction in each day of PA, and found that adaptation had occurred during each exposure phase. Moreover, the presence of aftereffects was demonstrated in both experiments. In Experiment 1, a significant leftward deviation was recorded in the pointing movements of the visuo-proprioceptive test in each of the 10 pointing sessions (see Figure 10). In addition, we showed that the errors recorded in the pre-exposure condition were progressively increased toward the left side over the 10 sessions (long-term aftereffect), suggesting a persistent and additive effect of the contralateral deviation induced by prism over time (for similar evidence from a single patient study, see Humphreys at al., 2006). In Experiment 4, we also recorded a significant contralateral deviation in the visuo-proprioceptive test and a trend towards significance in the proprioceptive test, in which 4 out of 5 patients exhibited a leftward deviation in the proprioceptive error.

Taking together, these results provide evidence that the pointing task is a useful tool to induce adaptation to prism in terms of error correction during the exposure phase and aftereffects, in line with previous work (e.g., Redding and Wallace, 2006).

Ecological procedure. During the ecological procedure of Experiment 1 we did not register the error induced by prism when patients executed the visuo-motor activities and we could not demonstrate the presence of adaptation and aftereffect. Therefore, in Experiment 2, we tested if the ecological tasks could generate adaptation and aftereffects in healthy individuals, as previously demonstrated in the pointing task. To measure if error correction (or adaptation effect) occurred during the exposure phase of the ecological procedure, we modified the paradigm used in Experiment 1 introducing 4 pointing movements before and after the execution of the ecological activities. We then tested the 3 measures of aftereffect: the proprioceptive, visual-proprioceptive, and visual test. In addition, we compared the amount of adaptation and aftereffects induced by the ecological task with the one induced by the pointing task. If adaptation and aftereffects following the ecological task were similar to those of the pointing task, this would increase our confidence in the effectiveness of the ecological procedure and make it a viable option for long-term neglect rehabilitation.

Results from Experiment 2 provided evidence that performing the ecological tasks during the exposure phase can induce the same amount of error correction as performing the pointing task, both in the young and elder group of subjects (see Figure 12). Interestingly, we demonstrated that the ecological procedure generated even stronger aftereffects than the pointing adaptation procedure. For both adaptation tasks we recorded a leftward deviation in the pointing movements in the proprioceptive and visual-proprioceptive tests, and a rightward deviation in the perceptual judgment of the visual test. These finding were consistent for the young and elder group of subjects. Strikingly, as compared to the pointing procedure, the ecological procedure resulted in: a) a larger leftward deviation in the proprioceptive test in both the young and aged subjects, b) a larger leftward deviation in the visual-proprioceptive test in the young group and c) a trend toward a greater rightward deviation in the visual test in both the young and aged subjects (see Figure 13).

An additional finding of Experiment 2 was that the pointing movements during the exposure phase of the second day were more accurate than the pointing movements in the first day, both for the first and for the last 4 pointing trials. It is possible that with practice subjects became more efficient in correcting the lateral deviation induced by prism. It is also possible that, as previously reported for the 10 sessions of the pointing task in Experiment 1, in the second session there was a carry-over effect of the contralateral deviation induced by prism during the first session. Several studies in healthy individuals and in primates have indeed demonstrated long-lasting aftereffects that persisted for several days and even weeks following a single day of prism exposure (Hatada et al., 2006; Lackner and Lobotovis, 1977; Klapp, 1974; Yin and Kitazawa, 2001).

Similarly, a recent study in neglect patients has shown error reduction of the exposure phase during 10 consecutive sessions of prism adaptation (Ladavas et al., 2011). Taking together, these results further suggest that the duration of the aftereffects can be increased if multiple sessions of pointing or ecological tasks during PA are performed.

Line bisection adaptation procedure. In Experiment 3, we demonstrated that the use of the line bisection adaptation task induced adaptation and aftereffects in a group of 84 healthy young individuals. During the exposure condition, participants wore either control goggles fitted with plain glass lenses or left- or right-shifting prisms inducing a 12.4 degree of lateral visual deviation. The two groups exposed to prisms showed an initial lateral deviation in the direction of the prismatic shift; this deviation was not recorded in the group who wore control goggles. Error correction occurred during the adaptation phase in both prism groups, demonstrating that the line bisection adaptation task can induce adaptation effects (see Table 9). The aftereffects were assessed through the visual-proprioceptive and the proprioceptive tests. In both measures, subjects exhibited contralateral deviation in the post exposure phase: the group exposed to right-shifting prism showed left pointing errors, whereas the group exposed to left-shifting prisms showed right pointing errors after PA (see Figure 15).

However, despite the presence of significant aftereffects, the amplitude of the deviation induced in the two tests was smaller than previously reported in studies involving a pointing adaptation task (Redding and Wallace, 2006). Indeed, the magnitude of the shift induced in the two aftereffects tests ranged from 12% to 18% of the prismatic displacement, whereas the magnitude reported after pointing adaptation task has been stated to be around 30% of the prismatic displacement. Thus, although a direct comparison of the effect of the pointing and line bisection adaptation tasks was not made in the same group of participants, our result suggests that the line bisection task may have a reduced effectiveness in inducing sensorimotor aftereffects compared to the more traditional pointing task.

Combining the results from the four experiments, it appears that the three adaptation procedures, based on pointing, ecological and line bisection tasks, can all induce error correction during the exposure phase. However, the ecological and the pointing procedure seem to create the strongest and most prolonged aftereffects, with the ecological task even better in inducing larger aftereffects than the pointing task. By contrast, the line bisection task appears to induce weaker aftereffects, suggesting that its use may not be optimal in prism paradigms. Future investigation would be needed to directly compare multiple adaptation tasks. It would also be useful to test if the ecological task induces stronger aftereffects than the pointing task in neglect patients, as we found in neurologically healthy individuals.

6.1.4 Characteristics of adaptation procedures that may enhance adaptation and aftereffects

Our studies showed that different adaptation procedures induce diverse amount of aftereffects. In this paragraph we explore possible reasons for such differences, focusing on the reasons for the increased aftereffects for the ecological procedure. If improvement of neglect after PA partly relies on the extension and duration of the aftereffects, understanding which characteristics of the adaptation procedure creates strong aftereffects becomes important and can open-up future progress for the rehabilitation of spatial neglect.

In Experiment 3, we showed a relatively small shift in the proprioceptive and visual-proprioceptive lateral deviations for the line bisection adaptation task. Different from the pointing task, in the line bisection task there is no visible target because the center of the line to bisect is estimated by the participant. A reduced adaptation was previously recorded when subjects performed the adaptation task in the absence of a visual target or in conditions in which the target was simply imagined (Finke, 1979; see also the works of Welch cited in Kornisher, 1976 for a review, page 17). Thus, performing movements to well-defined visual targets appears important for reliable aftereffects, perhaps because the errors in the movements are more evident when the target is visible.

Next, we consider four possible reasons for the greater aftereffects observed during the ecological task.

First, it is possible that the ecological task generates bigger aftereffects because of *greater and more complex visuo-motor interactions* performed during this procedure. Although in Experiment 2, the time of exposure to prism was equal in the two adaptation procedures, it is possible that during the pointing task participants performed fewer movements than during the ecological activities. The pointing task is based on timed and interrupted movements; it requires to point and return to the rest position and to wait for the experiment's signal to execute the next trial. Conversely, during the ecological task, subjects perform free movements in which they continuously manipulate several common objects. Previous studies have hypothesized that enhancing or reducing the quantity of visual and proprioceptive information available to the subjects during the exposure phase can increase or reduce the magnitude and persistence of the aftereffects. For example, Fernandez-Ruiz and Diaz (1999) have showed a greater and prolonged aftereffects in participants who performed the most numerous throwing movements during the exposure condition. On the other hand, when subjects were exposed to prism during passive movements or absence of movements, reduced or lack of aftereffects was demonstrated (Michel, Pisella, et al., 2003; Held and Hein, 1958;

Held and Bossom, 1961; Held and Freedman, 1963; Pick and Hay, 1965; Becket, 1980; see Kornisher, 1976 and Welch, 1986 for reviews).

Second, while the pointing task requires the repetition of the same out-and-back movements, the ecological tasks are based on *more varied movements* that involve different muscles and body parts. Each activity consists of visuo-motor patterns diverse in terms of range of motion, speed, orientation and, duration. Future investigation could test if the adaptation and aftereffects change as a function of the number and/or variability of the activities and movemtns performed during the exposure condition.

Third, the ecological task required *greater allocation of cognitive resources* than the pointing task, such as attentional processes, strategies of problem solving, and monitoring of the performance. It is possible that increasing the cognitive resources involved in the visuo-motor adaptation task enhances the adaptation and aftereffects, something that can be tested experimentally in future studies.

Fourth, the ecological task is based on the *execution of meaningful actions*. This suggests that participants may have been more engaged and motivated during the ecological procedure than during the pointing procedure. It is likely that an additive emotional reinforcement is linked to the result of the ecological activities and this that may have prompted quick correction of errors induced by prism. It could also be possible that adaptation and aftereffects increase as a function of the *reward* attached to the accuracy of actions performed during the exposure condition. Future investigation could test if the meaningfulness of visuo-motor actions performed during the exposure phase modulates the adaptation and aftereffects, and if adaptation and aftereffects increase as a function of reward, for example monetary reward (Wachter, Lungu, Liu, Willingham, and Ashe, 2009; Breiter, Aharon, Kahneman, Dale, and Shizgal, 2001).

Indeed, results from Experiment 1 (informal report) and Experiment 2 (Questionnaire) showed that the ecological procedure was considered *more pleasant and interesting to perform* than the pointing task. Patients and healthy neurological subjects better tolerated the ecological tasks and considered them less repetitive and more enjoyable, interesting and easy to perform. Increasing patients' compliance to the therapy may allow a higher number of brain-damaged participants to go through the whole training as result of a greater and active participation of the subjects to the training. Previous studies have indeed shown that patient's participation to the therapy can improve the rehabilitation outcome, including measures of functional independence. This can even result in shorter time of hospitalization (Lenze et al., 2004; see Maclean and Pound, 2000 for a review).

6.2 Influence of prism adaptation on perceptual and motor components

In Experiment 3 and 4, we tested how PA affects spatial cognition and whether it primarily reduces motor-intentional aiming and/or perceptual-attentional where spatial components. We investigated this hypothesis by examining decoupled perceptual-attentional where and motor-intentional aiming contributions to line bisection performance, either in a group of healthy young individuals (Experiment 3), and in a group of neglect patients (Experiment 4).

We found consistent results in the two experiments showing that, at least in the current paradigm, PA primarily affects motor-intentional aiming spatial systems. Indeed, exposure to prism decreased the aiming bias after prism exposure in both studies. In the group of healthy individuals, the initial left aiming bias was reduced after exposure to left-shifting prisms (Experiment 3). In a similar way, in the group of neglect patients the initial right aiming bias improved after exposure to right-shifting prisms (Experiment 4). In addition, in the healthy participants no changes in the aiming bias were found after exposure to right-shifting prisms and control goggles, indicating that the effect of left-shifting prisms was not due to increased familiarity with the task (Experiment 3).

Improvement in the aiming bias can also account for the amelioration recorded in neglect patients post-PA in tasks requiring visually guided motor behaviours involving eye and arm movements. Beneficial effects of PA have been reported on manual motor tasks performed under visual guidance (e.g., cancellation and drawing; for reviews see Luaute, Halligan, et al., 2006; Striemer and Danckert, 2010a), oculomotor scanning (Angeli, Benassi, and Ladavas, 2004; Serino, et al., 2004), and in tasks requiring a motor activation such as postural imbalance (Tilikete et al., 2001), and wheelchair navigation (Jacquin-Courtois et al., 2008). Similarly, a study of seven neglect patients exposed to a long-term prism adaptation training for 8 weeks found a prolonged improvement (lasting for at least six weeks) in eye movements and the alignment of the centre of pressure during a standing task on a force plate (Shiraishi et al., 2008).

For what concerns the effects of PA on the perceptual-attention where bias, we found that the change in the where spatial errors was not consistent across the five neglect patients after the prism adaptation training (Experiment 4). Three patients showed a greater rightward where bias, whereas the other two exhibited the opposite pattern with greater leftward where deviation after PA. However, it should be noted that the group of five patients we tested (Experiment 4) had on average a stronger motor-intentional aiming than perceptual-attentional where spatial bias, before the prism adaptation training (see Figure 19). Therefore, even if our studies did not show any effect of PA on perceptual-attentional where spatial errors, it is possible that prism adaptation may also improve where spatial bias in patients in whom this bias is more strongly present than in the current patients. Indeed, some improvement on perceptual tasks following prism adaptation has been reported in neglect patients (Sarri et al., 2006; Sarri et al., 2010; Saevarsson et al., 2009).

The results in healthy participants (Experiment 3) did not support a directionally-specific effect of prism adaptation on where spatial bias. Indeed, participants who adapted to both left- and right-shifting prisms showed a more rightward deviation in the where bias after prism exposure. This effect was observed only in the group of subjects who performed the computerized line bisection task as first or second test, immediately after PA. A possible (post-hoc) explanation for a non-specific effect of PA on where bias in healthy individuals (in which a similar rightward deviation in the post-exposure condition occurs after right- but also left-shifting prisms) could be that errors observed during PA triggers a correction of the initial leftward where bias through visuo-motor learning. During the exposure condition, participants learned to detect and correct the line bisection error induced by the prismatic shift. It is possible that the visuo-motor learning process acquired during the exposure condition was transferred to the computerized line bisection task, especially when the task was performed immediately after the adaptation phase. Therefore, both groups of healthy subjects could have increased their ability to correct the where bias in the post-exposure condition. Berberovic and Mattingley (2003) similarly found that both left- and right-shifting prisms induced a post-PA rightward shift on estimates of visual center for stimuli appearing in extrapersonal space. The same kind of effect was also observed by Barrett and Burkholder (2006) when both right and left monocular patching reduced leftward where spatial errors in the peripersonal space. More research is needed to understand non-directionally specific PA effects on the magnitude of perceptual-attentional where errors.

Our results may account for previous finding in studies recording eye movements in perceptual tasks such as detection of chimeric faces (Ferber et al., 2003; Ferber and Murray, 2005), and size estimation (Dijkerman et al., 2003), revealing a selective effect of prism adaptation on the oculomotor bias, without effect on perceptual-attentional errors. Results of Experiment 3 and 4 are also consistent with a recent finding in small group of neglect patients in which three neglect patients improved in a manual line bisection task (consisting of both motor-intentional and perceptual components), whereas the performance on a purely perceptual landmark test remained unchanged after rightward prism exposure (Striemer and Danckert, 2010a).

A specific neuroanatomic-behavioral mechanism for PA was recently hypothesized in a review by Striemer and Danckert (2010b). The authors suggested that adaptation to prisms may primarily influence the visuomotor circuits of the dorsal visual stream (specifically, in the superior parietal lobule and in the intraparietal sulcus) that mediate motor-related and attentional processes (Corbetta and Shulman, 2002; Milner and Goodale, 2006). On this account, PA might also influence perceptual processes indirectly through connections between dorsal and ventral stream areas, mediated by the inferior parietal lobe (IPL) and the superior temporal gyrus (STG). Since the IPL and the STG are critical sites for neglect (Karnath, Ferber, and Himmelbach, 2001; Mort et al., 2003) a failure to alter perceptual biases in neglect patients may be partly a consequence of the lesions of the connections between dorsal and ventral stream areas.

The interpretation of a primary influence of PA on the visuomotor circuits of the dorsal visual stream can also account for attentional improvements recorded after PA, since it has been demonstrated that the dorsal visual stream mediates not only motor-related but also attentional processes (Corbetta and Shulman, 2002; Milner and Goodale, 2006). Several studies in neglect patients have shown that prism adaptation can also improve covert attention tasks requiring a shift of visual attention without eye movements. For example, four right-brain damaged patients, two of them with neglect, exhibited a faster detection of targets located in the left field performing an exogenous version of the Posner task (Striemer and Danckert, 2007). Similarly, two neglect patients showed a faster detection of leftward stimuli in an endogenous version of the Posner task (Nijboer et al., 2008).

Finally, some authors have suggested that patient-based profiles should be used to categorize subtypes of spatial neglect across tasks (Buxbaum et al., 2004; Hamilton et al., 2008). Prior studies have failed to validate where/aiming subtypes of spatial neglect as rigid categories across different spatial assessment procedures, since neglect patients have shown a great deal of variation in the types of spatial errors when performing different tasks (see for example Harvey et al., 2002). However, it is also possible that robust where versus aiming biases among different tasks may also reflect relative dysfunction in distinct where versus aiming anatomical and functional brain networks. Tasks (or patients) with a primarily impairment in the motor-intentional aiming bias may benefit from this therapy, whereas tasks (or patients) with a primarily perceptual bias may not.

6.3 Which neglect manifestations are improved by PA treatment?

6.3.1 Neuropsychological and Functional Assessments

Results from the experiments performed in the groups of neglect patients of this PhD thesis (Experiment 1 and 4) showed that PA improved a wide range of symptoms. In the first experiment, we tested ten right-brain-damaged patients that were exposed to a two-week prism adaptation treatment, combining a pointing task (Frassinetti, et al., 2002), and a novel ecological task. We demonstrated amelioration of different manifestations of the neglect syndrome in the left extra-personal and personal space. Improvement was recorded both in the neuropsychological assessment and in the functional scales after one week, with a further recovery after the second week. Indeed, a better performance was observed in:

a) all the visuo-spatial paper-and-pencil tests, except the line bisection task, such as cancellation tasks (letters, bells and, stars), copy of drawings, and reading of words and sentences

b) performance in daily-live activities (CBS scale)

c) patients' independence in motor and cognitive functions (FIM scale).

Previous investigations have also demonstrated improvement in standard psychometric tests (such as the Behavioral Inattention Test, Wilson et al., 1987) after two weeks of prism adaptation training through a pointing adaptation task (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Ladavas et al., 2011; Mizuno et al., 2011). Also, a study with a shorter (four days) period of treatment showed improvement in neglect-specific tasks (such as line bisection and cancellation tests; Nys, de Haan, et al., 2008).

In Experiment 1, however, we did not show positive effects of the prism adaptation treatment on the line bisection performance. The influence of PA in line bisection tasks appears to be quite variable among studies. For example, adaptation may reduce the rightward error in line bisection (e.g., Pisella, Rode, Farnè, et al., 2002; in one out of two patients; Rossetti et al., 1998, in a group study including 16 patients). In one study, two right-brain-damaged neglect patients (#1, and #4) showed the expected leftward shift in line bisection after adaptation to rightward-displacing prisms, but one patient (#3) exhibited a paradoxical rightward deviation (Morris et al., 2004). Results from our Experiment 4, also showed a leftward deviation post PA in the line bisection task (Natural condition) in three patients (P1 – P4 – P5), whereas one patient was unaffected (P3), and one patient (P2) exhibited a paradoxical rightward deviation. In another study in five left neglect patients, adaptation improved performance in some cancellation subtests (BIT score; Wilson et al., 1987), but neither in line bisection, nor in copying (Luaute et al., 2006; see also Nys, de Haan, et al., 2008 for similar evidence). Three prism adaptation rehabilitation studies (Frassinetti et al., 2002; Serino et al., 2007; Ladavas et al., 2011; Mizuno et al., 2011) reported an overall improvement of the BIT scores, without distinguishing among the different subtests. Thus, while prism adaptation has overall positive effects on the patients' performance, as assessed by different tasks, there are differences among studies as for the specific tasks affected by the procedure. Cancellation performance, however, appears to be consistently improved. Furthermore, the lack of effects on line bisection, as well as the absence of mediational effects of aftereffects on sentence reading performance (Experiment 1), suggests some specificity of the effects of prism adaptation in a rehabilitation setting. Results from Experiment 3 and 4 also suggest a selective effect of prism adaptation on the motor-aiming spatial bias. Therefore, it is possible to speculate that the diverse responses recorded in PA studies in different tests may depend on the type of the initial spatial bias in that specific task (for further discussion, see paragraph 6.2).

6.3.2 Every-day disabilities

A relevant issue to rehabilitation medicine is whether improvement of spatial neglect, however obtained, generalizes and extends to disability in daily-life (Bowen and Lincoln, 2007). Previous studies investigating the effects of two weeks prism adaptation training through a pointing adaptation task measured an improvement of neglect symptoms on ecological tasks (room description, object reaching, cupboard search test), the behavioral part of the BIT, and self-report questionnaire of everyday functions (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2007; Serino et al., 2009; Ladavas et al., 2011; Vangkilde and Habekost, 2010). However, two other studies did not detect any quantitative improvement of activities of daily living, as measured by the Barthel Index after PA training (Rossi et al., 1990; Shiraishi et al., 2008).

In our first experiment, we provided evidence that prism adaptation contributed to the recovery of the patients' functional disability. Results showed improvement of the patients' scores in a widely used measure of independence (i.e., the FIM scale), and in a functional scale assessing patients' skills through observation of performance in everyday activities (CBS scale). This result was even confirmed by the mediational analyses in which improvement in functional disabilities (FIM) was partly accounted for by the magnitude and duration of aftereffects. The fact that the prism aftereffect could not explain improvement in neurological severity (i.e., the NIH scale) also provides evidence that the benefits of PA treatment appear to be specific to spatial neglect and may possibly generalize to whole-person activities and independence in daily life. The improvement in the FIM scale after prism adaptation is of extreme importance given the established evidence that neglect after right-hemisphere stroke is associated with a more severe overall disability, and predicts poor functional outcome (Jehkonen et al., 2006; Katz et al., 1999; Paolucci et al., 2001). Similar to the result of Experiment 4, in an initial pilot experiment in three neglect patients, who underwent a similar paradigm of computerized line bisection under natural and reversed conditions, we found a selective reduction of the motor-intention aiming component in 2 out of 3 patients (in 1 patient there was no change of the aiming component; Fortis, Kornitzer, Goedert and Barrett, 2009; poster presentation). Interestingly, we also recorded improvement of neglect deficits in everyday activities assessed by the CBS scale, and the functional improvement was recorded only in the 2 patients in whom the aiming bias improved. In addition, a recent study replicated our result of improvement in the CBS and FIM scales after PA training (Mizuno et al., 2011). The group of neglect patients that was submitted to ten sessions of PA pointing treatment improved significantly more than the control group who received the same training with neutral goggle.

Future investigation would be needed to assess if prolonged and extensive training may further increase the beneficial effect of PA on spatial neglect symptoms, including daily life activities. The ecological adaptation procedure introduced in Experiment 1 opens up new possibilities for extending rehabilitation of neglect patients for longer periods. Indeed, these visuomotor activities may be easily designed for home-based programs, customized to the domestic environment. This appears to be an especially important development, considering that it may allow for long-term rehabilitation programs that are not possible in inpatient rehabilitation facilities due to the typically short stay of the patient.

6.4 Cortical areas associated with neglect and responsiveness to PA treatment

6.4.1 Frontal and parietal brain lesions

As reported in the Introduction, several authors have hypothesized that the presence of distinct perceptual and pre-motor components in spatial neglect may reflect neuro-anatomical dissociations (Vallar and Perani, 1986). This notion was first proposed by Mesulam (1981), with posterior versus anterior anatomical brain lesions mapping onto perceptual versus premotor deficits in neglect patients.

In Experiment 1, we tested 10 neglect patients but we did not specifically separate perceptual and premotor subtypes of errors in this sample. In experiment 4, however, we explicitly dissociated pre-motor and perceptual spatial biases in a line bisection task in 5 neglect patients. All our patients exhibited a mixed pattern of both intentional and perceptual biases in the line bisection task (see Figure 19). Exploration of the brain lesion sites showed that 4 out of 5 patients had parietal and frontal lesions (see Fig. 17), consistent with an anatomical-clinical association between these regions and perceptual and premotor biases in neglect patients. However, one patient (P1) had an extensive lesion involving the parietal and temporal areas that did not extend to the frontal lobe. Contrary, to the anatomical association suggested above, the patient exhibited a large motor-intentional bias in the line bisection task. Previous studies have similarly found an association between directional bradikinesia impairments and parietal lesions in neglect patients (Mattingley et al., 1998; Husain et al., 2000).

Our result however, is limited by the small number of patients involved in the study and by the presence of mixed perceptual and attentional bias in each of them. To further extend our knowledge about a frontal versus parietal dissociation in subtypes of neglect patients, future investigations involving a large group of patients, a range of spatial cognitive tasks, and using both a priori and post-hoc radiological analytic techniques, would be useful to better explain whether perceptual versus premotor spatial bias can be seen as anatomically and functionally dissociated.

6.4.2 Brain lesions and adaptation to prism

In the Introduction of this thesis, we reviewed the current literature on the neural circuits involved in prism adaptation studies. On the basis of these data, a network of areas involving the cerebellum, the parietal, and the frontal cortex appears to be involved when adaptation to prism occurs (see Table 1 for some evidences). Several studies have investigated adaptation to prism in humans and primates with brain lesions. These studies have shown that selective cerebellar lesions impair the ability to adapt to prism during the exposure phase in patients (Gauthier et al., 1989; Thach, 1998; Martin et al., 1996a; Morton and Bastian, 2004; Pisella et al., 2005) and in monkeys (Baizer et al., 1999; Lewis and Tamago, 2001; Stein and Glickstein, 1992). Similar findings were found in patients with bilateral parietal lesions (patient JJ, Newport and Jackson, 2006, NPS; patient IG, Pisella et al. 2004; Grea et al., 2002) and in studies in monkey with selective lesions in the frontal premotor vental areas (PMv; Kurata and Hoshi, 1999).

In the experiments performed in this thesis, we tested 15 neglect patients (10 in Experiment 1, and 5 in Experiment 4). In our sample of patients we did not observe any impairment in adapting to the lateral displacement induced by prism. Indeed, each patient in our studies was able to correct the error induced by prism during the exposure phase in each session performed and showed the expected aftereffect deviation. Only one participant (P2) showed a paradoxical rightward deviation in one of the two aftereffect tests (proprioceptive test), whereas in the other (visual-proprioceptive test) he was leftward deviated after prism adaptation. Exploration of the brain lesion sites of the 10 patients (Experiment 1) showed that the areas of greatest lesion overlap were in the anterior and central white matter, and in the basal ganglia (head of the caudate nucleus, and pallidal nucleus); whereas in the other 5 patients (Experiment 4), they were in the frontal-parietal, and frontal-subcortical regions. None of the patients had a bilateral parietal brain lesion or a selective lesion in the cerebellum or the PMv areas. Our result confirms that patients with unilateral right side brain lesions in the frontal-parietal cortical and subcortical areas are still able to adapt to the lateral shift induced by prism.

A previous study provided some evidence that occipital damage may reduce prism adaptation and diminish recovery from spatial neglect (Serino et al., 2006). In this study, patients with occipital lesions were slower in correcting their pointing errors than patients without occipital lesions. After one week of PA training, they also exhibited less improvement in neglect symptoms, as measured by the BIT score and by the deviation in the eye movement. However, in another study in which neglect patients were exposed to two consecutive weeks of PA training, this association was not recorded, since one patient (RD) who did not show adaptation did not have an occipital lesion, whereas one patient (BM) exhibited adaptation and recovery from left spatial neglect, with a lesion extensively involving the right occipital lobe (Frassinetti et al., 2002).

In our sample of 15 neglect patients, only one patient (P4, Experiment 4) showed a lesion in the right occipital lobe. Our result confirmed that the patient was able to correct for the error induced by prism during the exposure phase of both days of PA and showed the expected contralateral deviation in the aftereffects measures of the visual-proprioceptive and proprioceptive tests. In addition, the same patient showed improvement in the motor-intentional aiming spatial bias of the line bisection task as the other patients without occipital lesion. Our results further suggest that adaption to prism and improvement in neglect symptoms can occur even in the presence of an occipital lesion.

Related to this issue, in another study (Serino et al., 2007), it was suggested that hemianopia is potentially problematic for adapting to prism. Hemianopia is a visual disorder that causes a loss of vision in either the whole left or the whole right half of the field of vision in both eyes. It can derive from lesions involving the contralateral visual cortex (geniculo-calcarine lesion) or from lesions that occur from the visual cortex to the optic tract. It has also been suggested that the failure to report a stimulus presented in the contralateral visual field in neglect patients may be, at least in part, related to the neglect impairment, such as visual inattention for an hemispace, rather than representing primary sensory deficit (Kooistra and Heilman, 1989;

Vallar, Sandroni, Rusconi, and Barbieri, 1991). In the series of patients tested by Serino et al. (2007), five out of the nine patients with occipital damage did not show left hemianopia, which was present in two patients with lesions sparing the occipital lobe. Results from this study found that the proportion of patients with left hemianopia was higher in the group not showing adaptation (4 out of 5 patients), than in the group exhibiting the effect (2 out of 13). However, this association also indicates that one non-hemianopic patient did not show adaptation effects, while two hemianopic patients do, thus weakening the inference of a conflict between hemianopia and adaptation.

Results from our Experiment 1 and 4 did not find an association between hemianopia and lack of adaptation. Indeed, in Experiment 1, adaptation and aftereffects were achieved in a comparable way by hemianopic and non-hemianopic patients. In Experiment 4, the small number of patients did not allow for a direct comparison of the results in the hemianopic (3 out of 5) and non-hemianopic patients (2 out of 5). However, exploration of the individual data suggests that, if anything, the opposite pattern was observed. The mean lateral deviation induced in the visual-proprioceptive test was greater in the hemianopic patients (shift = 7.50°) than in the non-hemianopic patients (shift = 4.92°). The same result was found in the proprioceptive test (hemianopic patients: shift = 8.78°; non-hemianopic: shift = 1.00°).

Our results are in line with other previous studies. Dijkerman et al. (2003) reported adaptation and aftereffects (“informally” assessed) in two right-brain-damaged patients with left neglect and hemianopia. Five right brain-damaged patients with left neglect (three with a complete left homonymous hemianopia, and two with no visual field deficits, but visual extinction) showed leftward aftereffects (Rossetti et al., 2004, two patients; Sarri et al., 2006, three patients). Similarly, Nys et al. (2008) mention preserved adaptation and aftereffects in two right-brain-damaged patients with left neglect and hemianopia.

In sum, the compatibility between left hemianopia and normal aftereffects seems to be the prevailing finding. Future investigation, comparing the effect of PA training in larger sample of neglect patients with or without hemianopia can help to clarify this issue.

6.5 How to separate spontaneous recovery from treatment improvement in studies in acute stroke patients?

Assessing the efficacy of new rehabilitation methods in stroke patients is not easy. One of the main problems is how to differentiate the effect of the experimental manipulation from spontaneous recovery. Spontaneous improvement in neglect patients, for example, has been shown to occur between two (Pizzamiglio et al., 2006) and six months (Jehkonen, Laihosalo, Koivisto, Dastidar, and Ahonen, 2007) after injury. Assessing the effect of PA training in chronic patients (> 6 moths) is therefore recommended. However, rehabilitation services have to deal with patients in a more acute phase (immediately after the stroke) and distinguish between the two types of effects becomes a problematic issue for clinicians. The best way to control the efficacy of a treatment, in patients in an early stage from stroke onset, is to use a control group of patients who do not receive any treatment over time, and compare their outcome with group of patients that are submitted to the experimental paradigm. However, there are ethical implications of leaving hospitalized patients without a specific treatment. In our Experiment 1 we compensated for the lack of a control group by using an experimental design that included a control treatment already validated. A previous study (Frassinetti et al., 2002) showed the efficacy of the pointing treatment to alleviate symptoms of left-spatial neglect in right-brain-damage patients, relative to a control group. Below, we will provide further arguments against spontaneous recovery effects in Experiment 1 and 4, and conclude with a section highlighting the usefulness of supporting studies in healthy individuals (Experiment 2 and 3).

6.5.1 Spontaneous recovery does not explain effects of PA

Neglect patients involved in our studies (Experiment 1 and 4) were still in a relatively early phase after the stroke (3.4 months in Experiment 1, and 3.2 weeks in Experiment 4). Therefore, it can be argued that the improvements recorded in our experiments could be partly due to spontaneous recovery of spatial functions. However, for both experiments we provided evidence for the specificity of our intervention.

In Experiment 1 we showed improvement in neuropsychological tests and functional scales in 10 neglect patients that underwent two weeks of PA training. Improvement was recorded in the first week and continued in the second of week of treatment. In order to show that patients' improvement was related to a specific effect of the prism exposure treatment we performed several analyses. Indeed, the improvement in each test and scale was not dependent on:

a) The baseline level, since we showed that the change in the score obtained during the treatment was not correlated with the improvement observed during the week of baseline. Any improvement observed during the baseline week was primarily related to spontaneous recovery because the patients did not receive any treatment during this time.

b) The severity of the pathology, provided by the independence between the level of the neurological impairment, assessed by the NIH scale, and the change in the score in the neuropsychological assessment and functional scales. In other words, the treatment specifically improved the visuo-spatial deficits and was not related to a general neurological improvement.

c) The duration of disease, since the benefit obtained during the treatment was not related to the time of stroke onset, and the chronic patients improved as well as the acute patients. If spontaneous recovery was the main factor involved in the improvement observed, we would expect a bigger improvement in the more acute patients, in whom the short time from the lesion favoured a spontaneous recovery.

d) Finally, results showed that the improvement in left spatial neglect and functional disabilities was related to the size of the prismatic leftward aftereffects. Indeed, the magnitude of the aftereffects and its extension over time could predict the improvement in the cancellation tasks and partly in the functional abilities as assessed by the FIM scale.

Together, these results suggest a causal effect of prism exposure on the recovery of left spatial neglect and speak against spontaneous recovery as the major factor that improved patients' symptoms.

In Experiment 4, we recorded improvement in the aiming bias of a line bisection task in five neglect patients exposed to two days of prism exposure. Based on the following considerations, it is unlikely that the effects recorded in this experiment are entirely attributable to spontaneous recovery:

a) If the motor-intentional aiming bias reduction was primarily related to a spontaneous recovery effect, we would have expected a bigger improvement in the patients with the most recent stroke (2 weeks post stroke, n=3) than in those with a less recent stroke (5 weeks post stroke, n=2). However, if anything, the opposite pattern was observed: the aiming bias reduced more in the 5 weeks post stroke group (mean pre –PA = 20.1 mm; mean post –PA = -8.9 mm; shift = 21.9 mm) than in the 2 weeks post stroke group (mean pre –PA = 18.9 mm; mean post –PA = 9.8 mm; shift = 9.1 mm). Thus, the results suggest that the improvement in the motor intentional bias was not related to the time distance from the stroke onset.

b) We observed an immediate strong improvement in each of the five patients' aiming bias after just two days of PA during the pointing adaptation task. The two days of PA training dramatically reduced the leftward motor intentional bias by 86% of its originally value. On the contrary, no consistent effects were found for the patients' where bias. The robustness and selectivity of this effect over such a short period of time speaks against spontaneous recovery as its primary cause.

c) Others have observed that the most common pattern of spontaneous change in the bias of neglect patients is either persistence or increase in motor-intentional aiming biases, with no discernable pattern in the stability of the perceptual-attentional where biases (Hamilton, et al., 2008). Consistent with what Hamilton et al. observed under natural recovery, we observed inconsistent changes in the where bias of patients. However, contrary to the increase in aiming bias Hamilton et al. observed, we found a consistent decrease in the motor-intentional aiming bias of all our patients.
d) Finally, our results are in agreement with recent work showing selective improvement of visuo-motor biases in neglect patients after a single session of PA (Striemer and Danckert, 2010a). The immediate improvement recorded in both studies is once more in support of a selective effect of PA on the aiming system and against spontaneous recovery as its primary cause.

Nonetheless, further studies fractionating where and aiming components of spatial errors in neglect patients during a more chronic phase post stroke (e.g., 6 months) may be useful to determine if the effect of PA may be different in acute versus chronic phase of the disease.

In sum, we argue that spontaneous recovery cannot fully account for the present findings of improvement in neglect symptoms after prism adaptation treatment (Experiment 1 and 4). However, we also acknowledge that group data on spontaneous recovery in neglect patients would strengthen the conclusions of our studies.

6.5.2 Studies in healthy individuals as support for effects in neglect patients

Performing studies employing healthy neurological subjects can also help in providing evidence for the effect of a treatment on cognitive function. For example, in the present thesis we performed two studies in healthy subjects that helped to support and better understand our results in neurological patients. In Experiment 2, we demonstrated that the ecological procedure induces adaptation and aftereffects that are at least as large as those of the pointing task in a group of 48 young and older healthy subjects. In Experiment 3 we provided evidence for the specific effect of PA on the motor-aiming spatial bias in a group of 84 young healthy participants.

Testing healthy neurological subjects to better understand the functioning of PA in neglect patients is facilitated by the fact that healthy individuals show biases in spatial cognition that mirror the biases in neglect patients. As reported in the Introduction, healthy individuals show a systematic leftward bias when performing a line bisection task (Bowers and Heilman, 1980; Jewell and McCourt, 2000; McCourt and Jewell, 1999; McCourt, 2001). In accordance with these findings, we also found an initial leftward bias in the line bisection task in the group of our healthy participants (line bisection task, natural condition Experiment 3). Similarly, a leftward perceptual where bias and a leftward motor-intentional aiming bias were also recorded when the two components where decoupled, replicating previous findings of leftward motor and perceptual biases in the line bisection task in healthy individuals (Garza et al., 2008). An a priori leftward bias has also been observed in numerous other spatial tasks in healthy individuals (Nicholls et al., 1999; Nicholls and Loftus, 2007; Longo and Lourenco, 2007; McGeorge et al., 2007). Thus, in contrast with neglect patients, who show a rightward spatial bias, healthy individuals appear to show a subtle but systematic leftward spatial bias.

Previous research in healthy individuals provided evidence for a lateralized effect of PA after left- but not right-shifting prisms (Berberovic and Mattingley, 2003; Michel et al., 2003; Michel et al., 2008; Colent et al., 2000; Loftus et al., 2008; Loftus et al., 2009; Nicholls and Loftus, 2007). This result mirrors the effect in neglect patients, in whom a selective lateralized effect of PA has also been demonstrated by improvement of the rightward bias after right- but not left-shifting prisms (Rossetti et al., 1998; Rossetti et al., 2004). We replicated a similar lateralized effect of PA in healthy individuals in Experiment 3. We showed a selective reduction of the leftward bias in the natural condition of the computerized line bisection task as well as of the motor-intentional aiming bias after exposure to left-shifting prisms, whereas the same two tasks were not affected by right-shifting prisms. The similarity of the results of PA paradigms in healthy individuals and neglect patients supports the idea that PA studies in healthy individuals can help to better understand the effect of PA in neglect patients.

A possible explanation for the similarity of the results in healthy subjects and neglect patients is that PA may influence cognitive functions for which the baseline performance is biased (Goedert et al., 2010; Striemer et al., 2006; Bultitude and Woods, 2010). For example, Bultitude and collaborators provided evidence that PA can reverse hierarchical perceptual processing, depending on the bias at the baseline level. Neglect patients, who typically show a local processing bias, acquired a more global processing bias after exposure to rightward shifting prisms (Bultitude, Rafal, and List, 2009). By contrast, neurologically healthy individuals, who typically show a global processing bias, acquired a more local processing bias after exposure to left-shifting prisms (Bultitude and Woods, 2010). This interpretation could also account for the result we recorded in the reversed condition of the computerized line bisection task (Experiment 3), in which the visual feedback was right-left horizontally inverted. In this task the initial bias from the veridical center of the line was deviated rightward, mirroring the initial leftward bias recorded in the natural condition. As suggested from the baseline bias interpretation, we recorded a selective lateralized effect of PA: the bias was reduced in the group of subjects who performed the task immediately after exposure to right-shifting prisms, whereas exposure to left-shifting prisms did not affect the performance.

6.6 Final conclusions

In sum, results from Experiment 1 and 2 demonstrated that the ecological procedure is an effective tool for ameliorating spatial neglect. Indeed, in Experiment 1 we found that the ecological procedure improved various neglect symptoms as well as functional disabilities, being as effective as the more established pointing task. In addition, both the patients (Experiment 1) as well as the group of neurologically healthy young individuals (Experiment 2) preferred the ecological procedure over the pointing task in terms of enjoyment in performing it, declaring it less repetitive and preferable to perform for prolonged time periods. In Experiment 2, we provided measures of adaptation and aftereffects during the new ecological procedure in the group of healthy participants, showing that the ecological visuo-motor tasks induced the same error correction as the pointing task during the exposure phase (adaptation effect). We also showed that the aftereffects were larger in magnitude than those recorded during the pointing task. Since previous studies (Sarri et al., 2008; Farnè et al., 2002) and our Experiment 1 showed positive correlations between the magnitude of the aftereffects and the improvement in neglect symptoms, this result is particular promising for rehabilitation of spatial neglect.

Results from Experiment 3 and 4 suggested that prism adaptation might act primarily on motor-intentional aiming spatial bias. A primary PA effect on aiming components of spatial errors was recorded consistently in both neurologically healthy participants (Experiment 3) and neglect patients (Experiment 4). This result may have major implications for the feasibility of PA as a therapy for stroke survivors with left neglect because it implies that neglect patients who are primarily disabled as a result of aiming spatial errors may be better candidates for PA training than those with primarily where spatial errors.

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