DOCTOR OF PHILOSOPHY

Prism adaptation in neurorehabilitation

Bultitude, Janet Helen

Award date:
2009

Awarding institution:
Bangor University

Bangor University

Prifysgol Bangor

Prism Adaptation in Neurorehabilitation

By Janet Helen Bultitude

BPsyc.(Hons.)/BSc.

A thesis submitted to the School of Psychology, Bangor University, in partial fulfilment of the requirement for the degree of Doctor of Philosophy. June 2009.

ACKNOWLEDGEMENTS

My heartfelt thanks go to my supervisor, Bob Rafal, who has been a constant source of inspiration and encouragement. Working with you is a pleasure.

I also greatly appreciate the advice of Martyn Bracewell and Alex List, technical assistance from Steve Johnston and Dave McKiernan, and Becca Henderson's invaluable help in coordinating patient research.

None of this research would have been possible without the generosity of the participants who so patiently gave their time. I am also indebted to the valuable support of hospital staff throughout the North-West Wales and Conwy Denbingshire NHS Trusts.

I am extremely grateful for financial support provided by the British Federation of Women Graduates and the North-West Wales NHS Trust.

The members of the Rafal lab, both official and unofficial, are always just as prepared to help with research as they are to have a fun time. Thanks for being such a great team: Bob, Betsy, Martijn, Jorien, Alex, and Becca.

I would never have undertaken this research without the early guidance of Anne Aimola Davies, who handed me my first paper on prism adaptation and helped me develop my earliest ideas. Thanks for getting me started.

A big thank you to those who have given me so much moral support. Susan, Jules, Pete, Deb, Luisa and Bára have provided me with encouragement at every opportunity. Karen and Danny drove me to Bangor in a van full of things they had put together to help me start my new life, and have been there for me ever since. Throughout the frustrations and triumphs of the thesis writing process, Mike has been on hand with shoulder-rubs and bottle openers as appropriate. And finally, I will always be grateful to my parents, for teaching me to pursue my interests with passion.

Janet Bultitude
June 2009

CONTENTS

ABSTRACT

Prism adaptation has been used for over a century to investigate sensory-motor plasticity and control. Recently, adaptation to rightward-shifting prisms, resulting in a leftward orienting after-effect, has demonstrated promise for producing persisting and broadly generalised improvements in hemispatial neglect ('neglect'). Also, neglect-like patterns of performance have been reported in healthy participants after adaptation to leftward-shifting prisms. This thesis explores the higher-level cognitive effects of prism adaptation in healthy participants and neurological patients. There was no change in the symptoms of twelve patients with acute neglect following single sessions of prism adaptation (Chapter 2), suggesting that neglect chronicity may influence the potential for gaining benefit from the technique. In contrast, observations in patients with chronic lesions demonstrate, for the first time, that 1) right spatial neglect is reduced by adaptation to leftward-shifting prisms (Chapter 2); and 2) adaptation to rightward-shifting prisms reverses the local processing bias in patients with lesions to the right temporo-parietal junction (Chapter 4). Experiments in healthy participants demonstrate a neglect-like withdrawal bias (Chapter 3) and a reduced global processing bias (Chapter 5) after adaptation to leftward-shifting prisms. Therefore, a major outcome of this thesis is that the higher-level spatial influence of prism adaptation in both healthy and brain-lesioned participants is not limited to lateralised spatial attention, but also extends to non-lateralised functions. Finally, Chapter 6 describes prism adaptation treatment of Complex Regional Pain Syndrome, an enigmatic disorder of neurogenically maintained pain and distorted body representation. The results of this thesis suggest that perturbation of parietal lobe function by prism adaptation modifies lateralised and non-lateralised spatial deficits including spatial attention, hierarchical processing and body schema. These novel findings have implications for the rehabilitation of neglect and other disorders of right hemisphere dysfunction.

Chapter 1

Introduction

A patient with acute hemispatial neglect ('neglect') lives in a spatially limited world. They do not turn towards a person approaching them from the contralesional side, and when this person calls their name they seem not to hear, or reply instead to someone else standing on their ipsilesional side. They may fail to dress one side of the body, and fail to eat the food on one side of the plate but then complain of hunger. The eyes, head and body are oriented to the ipsilesional side. It is as though one half of the world has ceased to exist. Although these behaviours are typical of the most extreme cases, even in less apparent forms this neuropsychological disorder is a barrier to rehabilitation and a challenge to clinicians. This thesis examines a promising treatment for neglect: prism adaptation. This chapter begins with an overview of the neglect syndrome, the neurological and cognitive mechanisms underlying the disorder, and previous attempts at its rehabilitation. This is followed by a description of prism adaptation and its effects on neglect symptoms and on higher-level spatial performance in healthy participants. Cognitive and neuroanatomical accounts for these effects are then discussed, before the chapter ends with an outline of the research contained within this thesis.

HEMISPATIAL NEGLECT: A COMPLEX, MULTIFACETED DISORDER

Neglect following unilateral brain damage is typically defined as a failure to report or orient to objects and events occurring in the contralesional side, which cannot be attributed to primary sensory or motor deficits. In many ways, however, this simple definition fails to convey the full complexity of this disorder, as neglect can manifest as a bias in many dissociable components of perception and behaviour. Although neglect has been studied most extensively in the visual modality (Figure 1.1), patients can show tactile neglect (difficulty detecting contralesional touch), or auditory neglect (problems detecting sounds coming from the contralesional side or presented to the contralesional ear; Heilman and Valenstein, 1972). Neglect in taste (Andre, Beis, Morin, & Paysant, 2000) and smell (Bellas, Novelly, Eskenazi, & Wasserstein, 1988a, 1988b) have also been reported. Neglect may also manifest as a paucity of actions, with reduced frequency of and slowness in contralesional eye movements, movements of the contralesional side of the body, or movements directed towards the contralesional side of space (Heilman, Bowers, Coslett, Whelan, & Watson, 1985). These deficits in sensory perception and movement production are commonly referred to as attentional-perceptual and motor-intentional neglect.

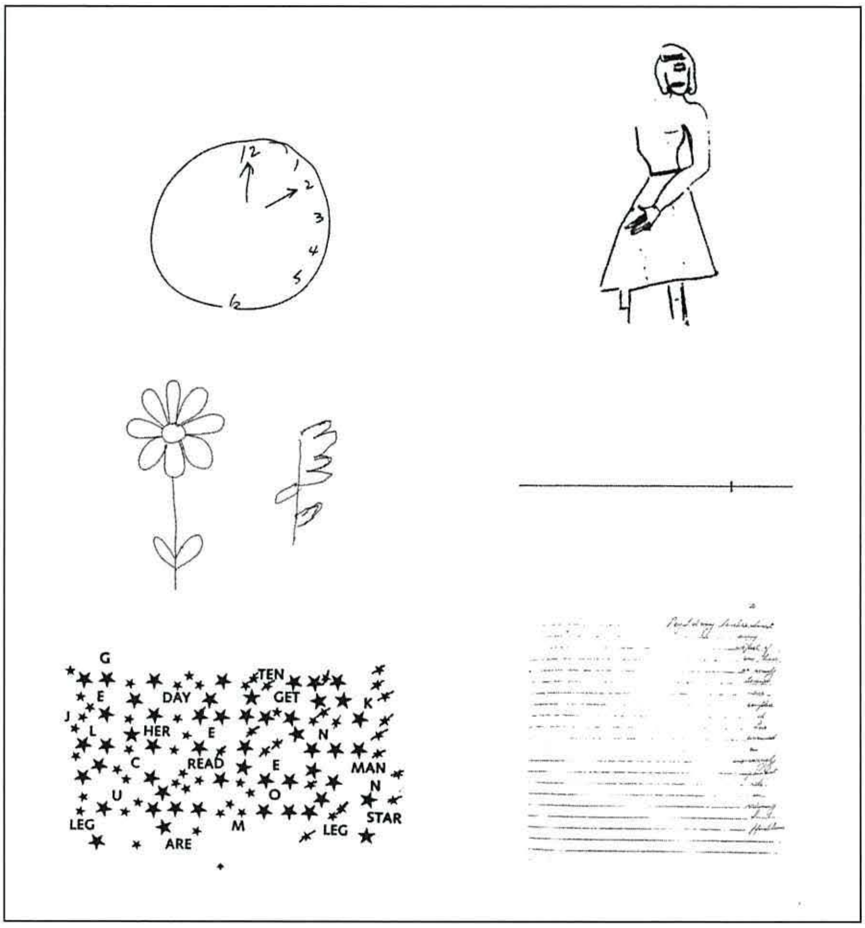

Figure 1.1. Example performance of patients completing clinical tests for neglect. In the top row the patients has drawn the numbers only on the right side of a clock face (left), and has omitted details on the left side of a self-portrait (right). The middle row shows a patient's failure to copy the left side of the provided model (left), and the typical line bisection performance in which the patient's mark is to the right of the true centre (right). In the bottom row a patient has cancelled targets (small stars) only on the right side of the page (left), and positions words only on the rightmost side of the page when writing (right; Halligan & Marshall, 1998a, 1998b).

A patient with neglect may seem to lack awareness of the left side of their body (personal neglect), the space within their reach (peripersonal neglect) and the space outside their reach (extra-personal neglect; Bisiach, Vallar, Perani, Papagno, & Berti, 1986; Guariglia & Antonucci, 1992; Halligan & Marshall, 1991; Figure 1.2). Within these distinct spatial domains neglect performance can be further dissociated by different frames of reference; for example a patient may neglect all information to the contralesional side of their own body midline (person-centred, or egocentric neglect), or the contralesional side of individual objects regardless of their spatial position (object-based neglect; Gainotti, D'Erme, Monteleone, & Silberi, 1986). When asked to close their eyes and point straight ahead they may err in the direction away from the neglected side, indicating a pathologically shifted egocentric reference frame (Heilman, Bowers, & Watson, 1983). Deficits can extend beyond the physical experience of the external environment to mental representations of the world: When describing a familiar place from memory, patients may report only objects positioned on the ipsilesional side of their imagined viewpoint (Bisiach & Luzzatti, 1978); and eye movements during REM sleep suggest that neglect even pervades the world of dreams (Doricchi, Guariglia, Paolucci, & Pizzamiglio, 1991, 1996).

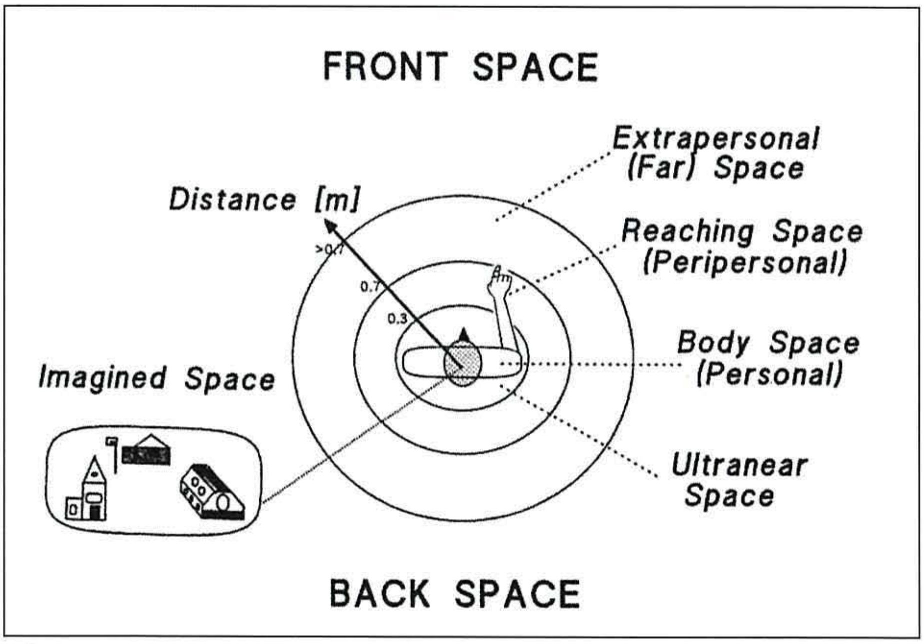

Figure 1.2. Diagram for the representation of different spatial reference frames, as demonstrated by dissociable manifestations of neglect in different spatial domains (adapted from Kerkhoff, 2001).

A multitude of dissociations have been identified between neglect in different sensory modalities and spatial domains (Cubelli, Nichelli, Bonito, De Tanti, & Inzaghi, 1991; Guariglia & Antonucci, 1992; Halligan & Marshall, 1991; Tegner & Levander, 1991; Vuilleumier, Valenza, Mayer, Reverdin, & Landis, 1998). An individual patient will most likely be affected by symptoms in more than one aspect of their behaviour; the general maxim being that no two neglect patients show the same symptom profile or test performance (Farnè et al., 2004). Importantly, the disorder does not reflect a total failure of perception or processing. There is evidence for implicit processing of information for which patients demonstrate no phenomenal experience: a kind of neglect blindsight. For example, a patient with left spatial neglect who was presented with two houses which were identical except for flames emerging from the left side of one, consistently chose the non-burning house as the one she would prefer to live in, despite declaring that there was no noticeable difference between the two (Marshall & Halligan, 1988). Doricchi and Galati (2000) extended this finding to show that implicit processing of neglected stimuli was not merely due to detection of low-level stimulus features such as symmetry. When they presented a patient with stimulus pairs in which the 'good' drawing was symmetrical and the 'bad' drawing was asymmetrical (Figure 1.3A), or vice versa (Figure 1.3B), she declared no difference between stimulus pairs in approximately half of trials, but consistently selected the semantically sensible drawing as the one she would most like to use.

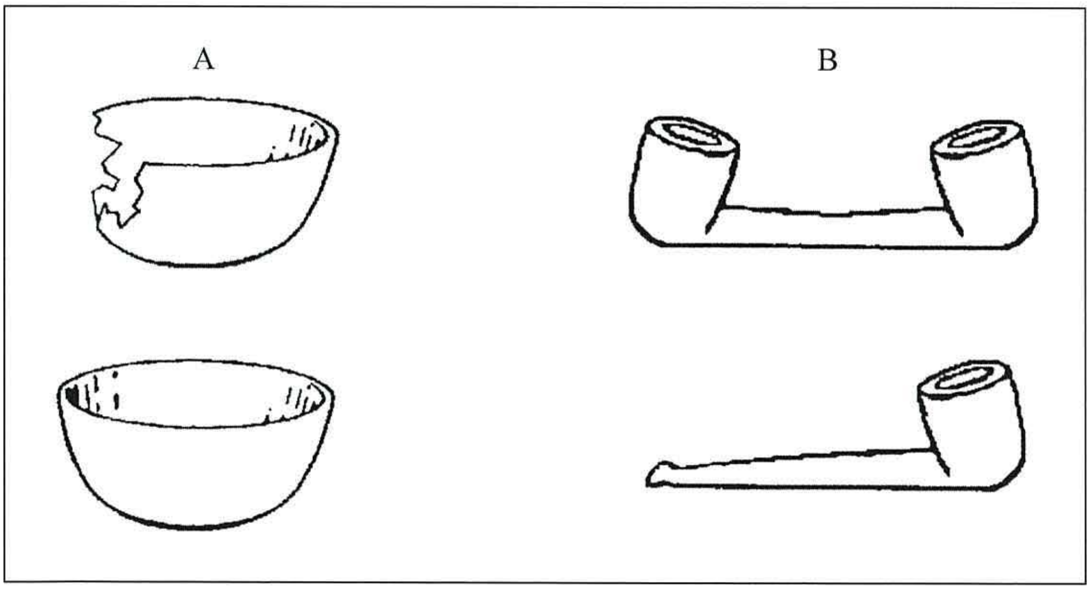

Figure 1.3. Example stimuli used by Doricchi and Galati (2000) to demonstrate implicit semantic processing of neglected stimuli in patient LP. Left-sided differences were not reported in approximately half of trials for both stimulus sets, but the patient consistently chose the semantically logical item out of each pair, regardless of whether it was symmetrical (A) or asymmetrical (B).

COGNITIVE AND NEUROLOGICAL MECHANISMS UNDERLYING NEGLECT

Cognitive Models of Neglect

The heterogeneous presentation of neglect across patients complicates the development of cognitive models to account for all recorded manifestations. Major explanations for leftward performance deficits in neglect are constructed around concepts of attention, representation, intention, and a shifted egocentric reference.

A dominant explanation for neglect is that there is reduced attentional allocation to the left side of space, resulting in impaired processing of contralesional information. According to this model, hyperattention to the ipsilesional side also contributes to the pathology of neglect, as demonstrated by patients' heightened detection of stimuli on the far right side of space compared to healthy controls (Ladavas, Petronio, & Umilta, 1990). Neglect patients are slower to respond to a left visual field target after a right visual field cue, indicating a deficit in disengaging attention from the ipsilesional side (Posner, Cohen, & Rafal, 1982). Rather than a sudden transition from poor to heightened attention as information crosses from the left to right hemispace, Kinsbourne (1993) specified that there is a gradient of attention, with the worst performance on far left, and best performance on the far right. This gradient explains not just the neglect of information positioned to the left side relative to the right side of the patient, but also, for example, neglect of the left side of objects positioned within the 'good' hemifield.

According to representational accounts of neglect, interaction with the environment is mediated by temporary mental representations of objects and task-relevant components of space, the formation of which is impaired in patients with neglect. This is best supported by neglect of imagined scenes ('representational neglect'), which was first demonstrated by Bisiach and Luzzati (1978) in neglect patients who were asked to describe the familiar Piazza Del Duomo as though standing from one end of the square and then the other. This explanation accounts well for manifestations of neglect on different spatial reference frames, but not for the heightened ipsilesional detection. In contrast, an attentional model of neglect can accommodate representational biases in the form of decreased attention to the left side of mentally represented objects and scenes.

Neither the attentional or representational accounts of neglect can explain the performance of patients in whom the primary deficit is not receptive, but productive. Observations of under-use of the contralesional limbs and slowness in eye and limb movements towards the contralesional direction led to the motor-intentional account of neglect: That patients have difficulty initiating and performing actions involving the left side of their body or space (Watson, Miller, & Heilman, 1978; for a review, see Heilman, 2004) Perceptual-attentional and motor-intentional accounts of neglect are not considered to be mutually exclusive, but instead explain the symptoms of different subsets of patients (Bisiach, Geminiani, Berti, & Rusconi, 1990; Na et al., 1998; Tegner & Levander, 1991). Motor-intentional neglect is the subject of research reported in this thesis, and will be discussed in more detail in Chapter 3.

A fourth influential explanation for neglect invokes a rightward-shifted egocentric reference frame, as indicated by the patients' rightward perception of straight ahead when their eyes are closed, with attention and behaviour centred around this pathological midpoint (See Figure 1.5; Karnath, 1994; Vallar, Bottini, Rusconi, & Sterzi, 1993). One advantage of this explanation is that it can explain both attentional-perceptual and motor-intentional deficits of neglect. However, only some patients show rightward-shifted estimations of straight ahead, and these do not correlate with neglect magnitude on standard clinical tests (Bartolomeo & Chokron, 1999; Chokron & Bartolomeo, 2000).

While the validity of these and other cognitive models has been the subject of considerable research and debate, they are mentioned here only briefly to highlight that the complex combination of symptoms in neglect has resulted in a number of considerably different accounts. More recently, revised perspectives on neglect have acknowledged that explaining all aspects of neglect performance requires not only a combination of accounts of lateralised spatial deficits such as those described above, but also consideration of dysfunction in spatial processes that are not defined along the horizontal axis, as well as non-spatial components of behaviour (Danckert & Ferber, 2006; Pisella & Mattingley, 2004; I. H. Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995).

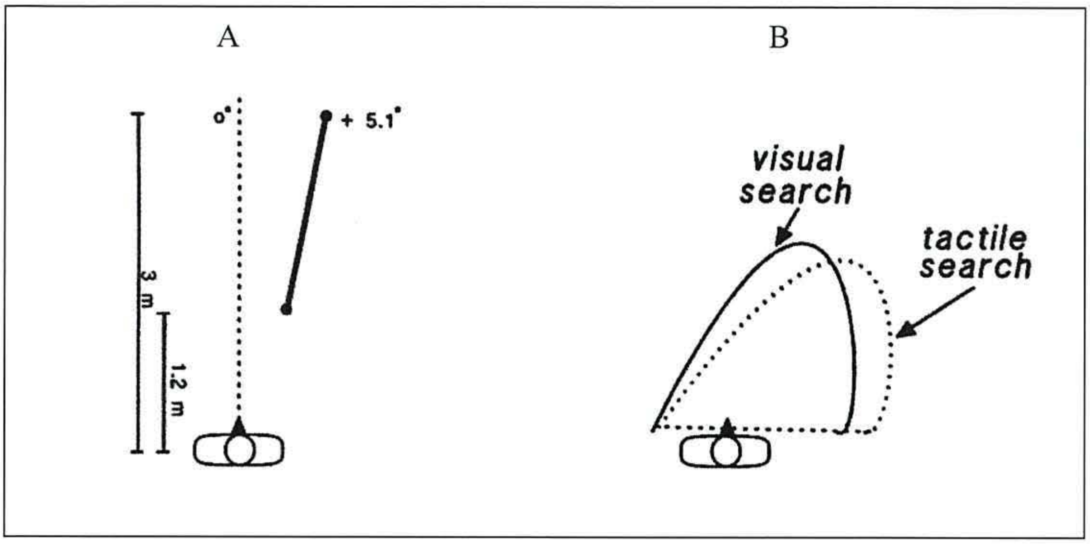

Figure 1.5. One account of neglect is that patients have a rightward-shifting egocentric reference frame (A), and their behaviour is centred around this pathological midpoint (B). Adapted from Kerkhoff (2001).

In addition to the lateralised attentional bias favouring the right side of space, patients with neglect can show a number of spatial deficits that are not more pronounced on one side than another (i.e., 'non-lateralised spatial' deficits). These include impaired spatial working memory (Husain et al., 2001), and hyperattention to local detail in preference to global scenes (Marshall and Halligan, 1995). There are also associated deficits that are not spatial in nature (i.e., 'non-spatial' deficits), such as impaired sustained attention (I. H. Robertson et al., 1997). While they are not necessarily specific to neglect, it is likely that they increase neglect severity and reduce the potential for recovery (Husain & Rorden, 2003). Like the lateralised spatial attention bias of neglect, the non-lateralised spatial and non-spatial deficits are associated with right hemisphere damage, and may be one reason why neglect is more common after right than left hemisphere damage. Non-lateralised spatial symptoms of neglect, and their modification by prism adaptation, will be a major theme of this thesis and will be discussed further in Chapters 3, 4 and 5.

NEUROLOGICAL CORRELATES OF NEGLECT

Considering the many components of perception and performance that are influenced by neglect, it is not surprising that a large number of cortical and subcortical areas have been identified that, when damaged, can lead to neglect (see Danckert & Ferber, 2006; Hillis, 2006; Vallar, 2001 for reviews). While the disorder can occur after lesions to both cerebral hemispheres, it is more frequent, severe and persisting after right hemisphere lesions (Beis et al., 2004; Kerkhoff, 2001). Therefore, for the sake of simplicity, unless otherwise indicated the remainder of this thesis will use the term 'neglect' to denote left spatial neglect following right hemisphere damage. The disorder is predominantly associated with large lesions involving the MCA territory, but can also be caused by small lesions and lesions to the ACA and PCA territories. A number of specific cortical areas have been implicated in neglect (Figure 1.4), including the inferior frontal gyrus (IFG; Husain & Kennard, 1996) middle frontal gyrus (MFG; Mort et al., 2003; Rossit, Malhotra, Muir, Reeves, Duncan, Birschel et al., 2009), parahippocampal gyrus (Bird et al., 2006) and the superior temporal gyrus (STG; Karnath, Ferber, & Himmelbach, 2001; Karnath, Fruhmann Berger, Kuker, & Rorden, 2004). Subcortically, lesions of the thalamus (Cambier, Masson, Graveleau, & Elghozi, 1982; Graveleau, Viader, & Cambier, 1986), putamen and basal ganglia (Damasio, Damasio, & Chui, 1980; Karnath et al., 2004; Karnath, Himmelbach, & Rorden, 2002) have been associated with neglect, although this connection may be due to hypoperfusion of the overlying cortical tissue (Hillis, 2006). However neglect is most strongly associated with lesion to the inferior parietal lobe including the angular and supramarginal gyri (Farnè et al., 2004; Mort et al., 2003), and especially the temporo-parietal junction (TPJ). Together these areas are thought to form a functional network for visuo-motor performance as well as sustained and spatial attention (Mesulam, 1981, 1999; Posner & Petersen, 1990). Lesions to different regions within this network has been related to many of the dissociable manifestations of neglect on different tests of the same component of behaviour (e.g. cancellation and line bisection; Rorden, Fruhmann Berger, & Karnath, 2006; Schubert & Spatt, 2001), or on the manifestation of neglect in different sensory modalities (Hillis et al., 2005).

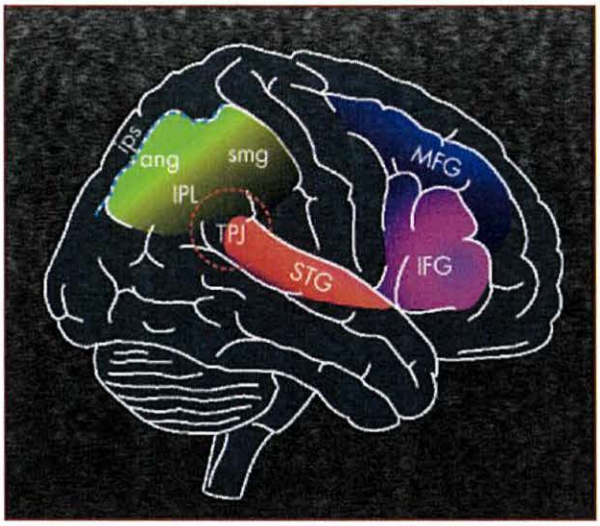

Figure 1.4. Anatomical correlates of hemispatial neglect (Parton, Malhotra, & Husain, 2004).

Neglect is therefore a multifaceted disorder that can follow lesions to a number of cortical sites, resulting in a combination of lateralised symptoms across multiple sensory modalities and spatial domains, as well as non-lateralised spatial and non-spatial deficits. The result is a syndrome that can vary considerably between individuals. Neglect has been a fruitful source for illuminating the normal mechanisms of attention and spatial reference frames. For example, the dissociable manifestations of neglect in personal, peripersonal and extrapersonal space demonstrate that information processing for these domains can occur independently. Another major focus of research with neglect patients has been aimed at developing methods to treat this problematic disorder.

REHABILITATION OF NEGLECT

For roughly one-third of patients with right-hemisphere lesions, neglect becomes a chronic disabling condition (Campbell & Oxbury, 1976), limiting motor recovery and independence in self-care (Jehkonen, Laihosalo, & Kettunen, 2006). Identifying treatments for neglect is therefore a high priority and substantial research effort has been focused on this goal (Figure 1.6).

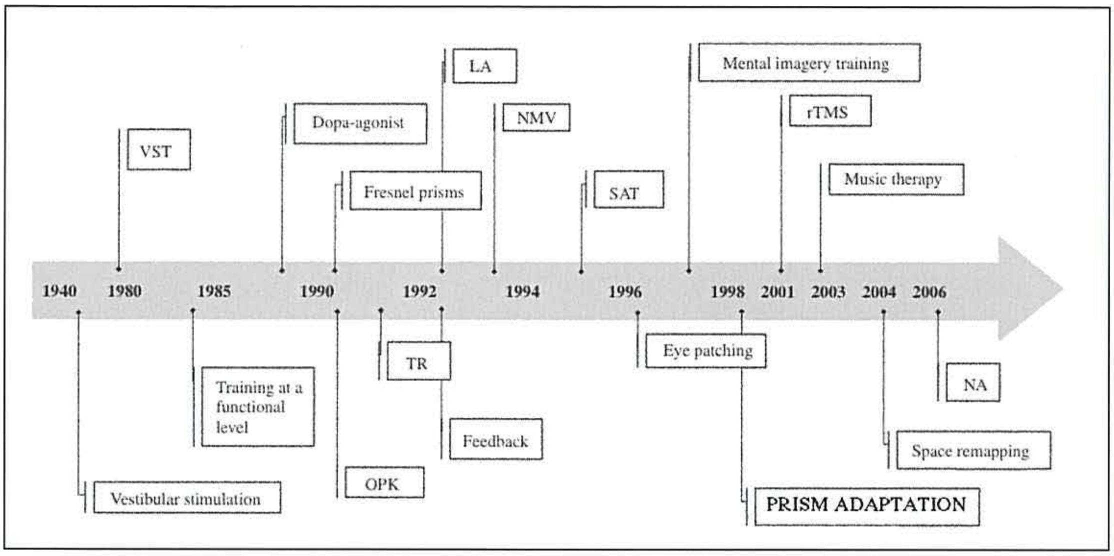

Figure 1.6. Time-line of the first publications for different methods aimed at treating neglect (Luauté et al., 2006). VST: visual scanning training; LA: limb activation; rTMS: repetitive transcranial magnetic stimulation; SAT: sustained attention training; OPK: optokinetic; NMV: neck muscle vibration; TR: trunk rotation; NA: noradrenergic agonist.

Interventions can be broadly divided into 'top-down' methods that train patients to deliberately compensate for their disorder and 'bottom-up' techniques that induce an automatic reorienting through sensory stimulation. For example, visual scanning training is a 'top-down' treatment in which patients are trained to remind themselves to direct their gaze leftward when searching a scene. Caloric stimulation is a 'bottom-up' treatment in which irrigation of the contralesional ear with ice-cold water (or the ipsilesional ear with warm water) results in a vestibular-ocular reflex inducing deviation of gaze toward the contralesional field and subsequent benefits in contralesional orienting. The effectiveness of different treatment methods has been reviewed extensively elsewhere (e.g., Luauté, Halligan, Rode, Jacquin-Courtois, & Boisson, 2006; Pizzamiglio, Guariglia, Antonucci, & Zoccolotti, 2006). However to generalise, top-down training techniques can induce some improvements in symptoms, but these tend not to extend beyond the specific task used during training, and many sessions are required to achieve any effects (Bailey, Riddoch, & Crome, 2002; Bowen, Lincoln, & Dewey, 2002a; Bowen, Lincoln, & Dewey, 2002b). In contrast, bottom-up stimulations often result in instant and dramatic improvements in many aspects of performance, but unfortunately they can be uncomfortable for the patients, and the benefits fade almost immediately upon the cessation of the stimulation (Arene & Hillis, 2007; although see Johannsen, Ackermann, & Karnath, 2003, for long-lasting improvement (>1 year) after repeated application of neck muscle vibration)

Therefore, a simple and effective treatment with long-lasting and broadly generalised benefits proved elusive for many years. Over the last decade, however, substantial interest has been generated by a promising new treatment in the form of visuo-motor adaptation to rightward-shifting prisms.

PRISM ADAPTATION

Prism adaptation has been used for over a hundred years to investigate sensory-motor plasticity and control (von Helmholz, 1925). When we wear glasses fitted with laterally refracting prismatic lenses, the light from the outside world is bent before it reaches the eye, requiring a rotation of the eye to maintain fixation on an object, and leading to the perception that the object is positioned lateral to its true location (Figure 1.7).

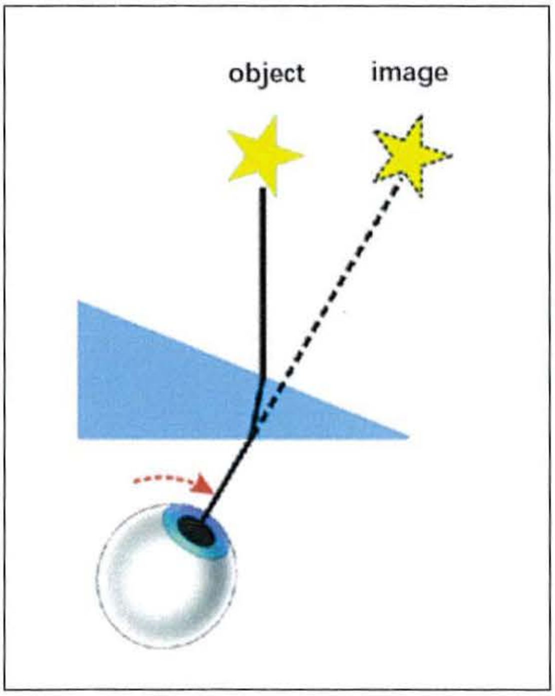

Figure 1.7. When a prismatic lens is placed in front of the eye, objects appear shifted to one side of their true location (adapted from Hanlin, 2008)

The first time we reach for an object viewed through prism lenses, we miss in the direction of the prismatic shift (Figure 1.8). This is accompanied by a peculiar sensation as the expected and actual consequences of our action differ. Reaching error quickly fades with successive attempts, and after only a few reaching trials (typically <10) we can point quickly and accurately to the object. If the prisms are then removed and we reach for the object once more, we miss again, but in the direction opposite to the prismatic shift: the adaptation after-effect.

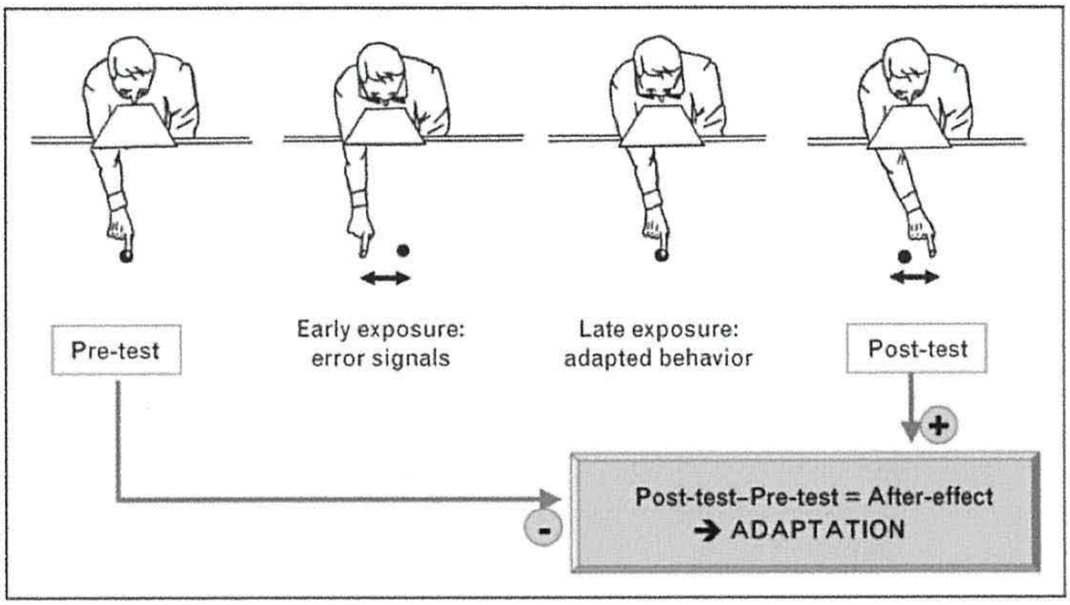

Figure 1.8. Prior to wearing prisms participants point accurately to a visual target (pre-test). When prisms are fitted, participants initially make pointing errors in the direction of the visual shift (early exposure). Errors reduce with repeated trials until pointing is once again accurate (late exposure). If the prisms are then removed, participants show a sensory-motor after-effect in the direction opposite to the visual shift (post-test; Pisella, Rode, Farne, Tilikete, & Rossetti, 2006).

At least two processes are involved in the adjustment of motor performance under prismatic distortion. During the first few trials a strategic component acts to correct movement trajectory on-line through processes of visuo-motor control, such as one might set a diagonal course when swimming across a river with a strong current in order to reach the bank immediately opposite the starting point. The strategic component is sensitive to cognitive load: Error correction was smaller when participants solved mental arithmetic problems during prism adaptation (Redding, Rader, & Lucas, 1992). Although this visual error adjustment is partially influenced by deliberate side-pointing strategies, to say that strategic control during visuomotor adaptation is completely deliberate is incorrect. Even when participants were explicitly informed of the perturbation and the action required to counter it, they were unable to sustain accurate aim (Mazzoni & Krakauer, 2006).

Through a second, slower process, shifts in visual, proprioceptive and motor references occur to reduce the sensory-motor discrepancy. This adaptive spatial realignment, or 'true' adaptation, continues to develop even once accurate pointing has been achieved, and reflects rapid plastic neural reorganisation of sensory-motor references.

The adaptation after-effect indicates the amount of adaptive realignment that occurred during prism exposure: a combination of altered perception of the perceived visual straight ahead and proprioceptive changes in the felt straight ahead according to the relationship between different effectors (e.g., the head compared to the trunk, or the trunk compared to the arm). The combined visual and proprioceptive realignment ('total shift') can be measured by asking participants to perform an open-loop pointing trial of pointing to a visual target without visual feedback of their arm position. The visual and proprioceptive components of realignment can also be measured independently by asking participants to indicate when an object that is moved across the visual field is directly in front of them ('visual shift'), and by asking them to point straight ahead of their body midline while blindfolded ('proprioceptive shift'). To an extent the strategic component and adaptive realignment of prism adaptation negate each other: The magnitude of the adaptation after-effect (i.e., the degree of adaptive realignment) is greater under conditions that minimise the possibility of strategic or online correction, such as by introducing the prismatic shift in gradually increasing increments that are below the threshold of the participant's awareness (Michel, Pisella, Prablanc, Rode, & Rossetti, 2007).

Thus far, my description of the sensory-motor changes induced by prism adaptation has been limited to the realignment of visual and proprioceptive references of human participants: the primary and most-studied influence of prism adaptation, and the one most relevant to the experiments of this thesis. However, here I will also briefly mention research demonstrating changes in sound localisation following prism adaptation, and alteration of sensory-motor correspondances in non-human primates and birds. While adult primates (especially humans) show rapid and near complete recovery of visuo-motor control during prism exposure (Harris, 1965; Held & Bossom, 1961; Yin & Kitazawa, 2001), accurate visually-guided movements are never recovered in chickens (Rossi, 1968, 1969) or barn owls (Knudsen & Knudsen, 1989b) fitted with prisms. This is the case even when the likelihood of adaptation is maximised by using prisms of moderate strength, by using very long exposure periods (60+ days), and by fitting prisms from birth. Although some short-lived visuo-motor realignment is evident in post-adaptation pecking errors of chicks (Rossi, 1968), and striking errors of owls (Knudson & Knudson, 1989), the incomplete error correction and small after-effects demonstrate that, in contrast to primates, the proprioceptive representation of space in the bird nervous system is extremely resistant to perturbation of visual information by prisms.

In contrast, prism-reared barn owls show substantial realignment of sound localisation (Knudsen & Knudsen, 1989a), which is greater when the owls hunt live prey during each day of exposure than when they are fed dead mice (Bergan, Ro, Ro, & Knudsen, 2005), and which is not shown by owls fitted with prisms at adulthood (Brainard & Knudsen, 1998). This realignment implies a dominance of vision over audition in the development and maintenance of auditory spatial representations in birds. Adaptation after-effects in sound localisation are also observed in humans, however, unlike birds, this visuo-auditory realignment occurs only partly through an adjustment of auditory representations. In humans, sound localisation after-effects can also be attributed to an adjustment of gaze direction: the perceived straight ahead eye position is shifted to compensate for the prismatic displacement – a prioprioceptive shift (Cui, Bachus, Knoth, O'Neill, & Paige, 2008). Owls are unable to adjust gaze direction in this way as their eyes are more or less fixed in their orbits. The contrasting effects of prism adaptation in birds and primates indicates that the extent and locus of realignment (visual, auditory or proprioceptive) is influenced by 1) the physical constraints of the organism, and 2) the flexibility of the nervous system, which is considerably greater in humans.

The reorganisation of spatial references that occurs during adaptive realignment was traditionally thought to be limited to low-level sensory-motor processes predominantly involving representations of the adapting limb (Harris, 1965; Kornheiser, 1976; Redding & Wallace, 1997). However, over the past decade this conclusion has been called into question by reports of improvements in hemispatial neglect following adaptation to rightward-shifting prisms.

ADAPTATION TO RIGHTWARD-SHIFTING PRISMS AMELIORATES NEGLECT

Rossetti and colleagues (1998) asked neglect patients to make 50 pointing movements to visual targets while wearing goggles fitted with neutral lenses (control group) or prisms that induced a 10° rightward shift in the visual field (treatment group). After prism adaptation the treatment group showed a leftward correction in their indications of subjective straight ahead, as well as improvements in performance on standard pen-and-paper tests (line bisection, line cancellation, copying, drawing and reading). It appeared, therefore, that in addition to inducing a leftward visuo-motor after-effect, prism adaptation also ameliorated neglect symptoms.

This finding understandably provoked considerable interest: prism adaptation is quick, inexpensive, and easy to administer. Furthermore, subsequent research has established that the improvements generalise to a broad range of symptoms (Table 1.1). Evidence amassed from single and multiple case study reports show post-adaptation improvements in multiple sensory modalities: on tests of vision (Dijkerman et al., 2003; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002; Rode, Rossetti, & Boisson, 2001), tactile detection (Maravita et al., 2003), haptic exploration (McIntosh, Rossetti, & Milner, 2002), pressure sensitivity and finger position sense (Dijkerman, Webeling, ter Wal, Groet, & van Zandvoort, 2004). Prism adaptation also improved auditory extinction in three of six patients tested (Courtois-Jacquin et al., 2002). While most of these tests were conducted in peripersonal space, reductions in personal (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Serino, Bonifazi, Pierfederici, & Làdavas, 2007) and extrapersonal neglect (Frassinetti et al., 2002) indicate that prism adaptation can influence neglect in multiple spatial domains. This influence is also not merely on sensory perception of the external environment: post-adaptation improvements in patients' abilities to form mental representations or explore mental imagery have also been found. Specifically, after prism adaptation patients named more cities on the left side of a mentally visualised map of France (Figure 1.9), and made more accurate judgments on a 'mental number bisection' task in which two numbers are presented and participants judge, without calculation, the number falling halfway between. Neglect patients usually show a consistent bias for naming larger numbers, which is taken as evidence for a rightward bias in mental representations.

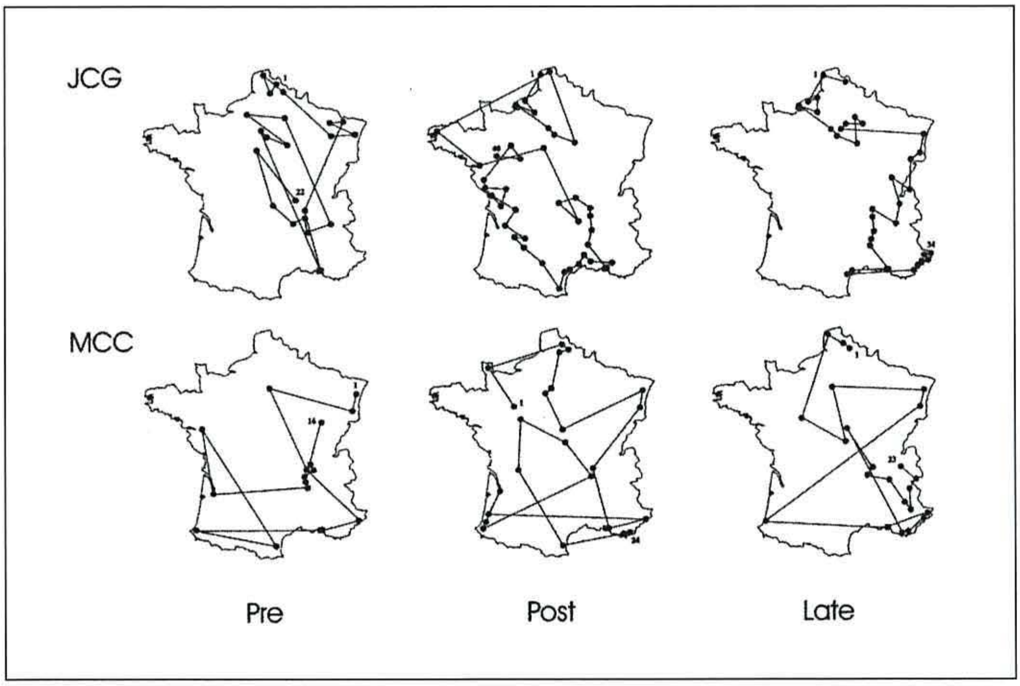

Figure 1.9. Cities named from mental evocations of the map of France by two patients, immediately before (pre-test) and after prism adaptation (post-test), and two hours after prism adaptation (late-test). City locations are indicated by the filled circles and the order of naming is indicated by lines connecting these dots (Rode et al., 2001).

Although the broad generalisation of neglect improvements following prism adaptation is well-supported, relatively few studies have examined whether the technique aids in functional recovery. Nonetheless, there is limited evidence that the improved leftward orienting transfers to functional tasks, with recovery of postural control in groups of both neglect patients (Shiraishi, Yamakawa, Itou, Muraki, & Asada, 2008) and right-hemisphere lesioned patients without neglect (Tilikete et al., 2001); as well as single case reports of improved wheelchair navigation (Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008), locomotion (Bacchini, Frassinetti, Farnè, Affanni, & Rossi, 2006; Folegatti et al., 2008; Keane, Turner, Sherrington, & Beard, 2006), and self-care (two patients; Keane et al., 2006).

The effect of prism adaptation on neglect symptoms are remarkably long-lasting. In their original study, Rossetti and colleagues (1998) observed that the improvements in the treatment group were still evident two hours after prism adaptation (and in fact, patients had shown further improvement on some measures). The two-hour duration of improvements has been replicated, (Dijkerman et al., 2003; Rossetti et al., 1998), with individual studies reporting amelioration lasting for as much as one day (Farnè, Rossetti, Toniolo, & Làdavas, 2002; Pisella et al., 2002; Rode, Rossetti, & Biosson, 2001), four days (Pisella et al., 2002), a week (McIntosh et al., 2002) and even four weeks (Dijkerman et al., 2004) after a single prism adaptation session. In comparison, traditionally the adaptation after-effect was thought to last for only minutes or hours provided no feedback of pointing errors was available (Redding and Wallace, 1997). But the full potential for the effectiveness of prism adaptation in long-term rehabilitation seems to be achieved with repeated sessions. Clinical studies examining neglect on broad batteries of tests have reported that, compared to control groups, patients who underwent two-week regimens of twice-daily adaptation sessions showed improvements that were sustained for five weeks (Frassinetti et al., 2002), three months (Serino, Angeli, Frassinetti, & Làdavas, 2005) and even six months after treatment (Serino et al., 2007). The conclusiveness of these studies is somewhat reduced by the fact that the control groups received considerably different treatment regimes, and, in one study, were even drawn from different hospitals (Frassinetti et al., 2002). Nonetheless, in a recent randomised control study two weeks of prism adaptation improved neglect symptoms, but the same treatment regimen performed using neutral glasses did not (Serino, Barbiani, Rinaldesi, & Ladavas, 2009).

Table 1.1. Summary of research examining the effects of prism adaptation on neglect symptoms

Description	Author(s)
Visuo-motor tests	
Standard pen-and-paper tests	Rossetti et al., 1998; Farné et al., 2002; Pisella et al., 2002
Visuo-verbal tests	
Reading/neglect dyslexia	Farné et al., 2002; Angeli et al., 2004; Datie et al., 2006
Describing a scene	Farné et al., 2002
Chimeric object description	Sarri et al., 2006
Non-visual tests	
Subjective straight ahead	Rossetti et al., 1998; Pisella et al., 2002;
Auditory extinction	Courtois-Jaquin et al., 2002
Tactile detection	Maravita et al., 2003; Serino et al., 2007
Haptic exploration	McIntosh et al., 2002
Pressure sensitivity, finger position sense	Dijkerman et al., 2004
Representational neglect	
Mental representations	Rode et al., 2001
Mental number bisection	Rossetti et al., 2004
Ocular exploration	Ferber et al., 2003; Dijkerman et al., 2003; Angeli et al., 2004; Datie et al., 2006; Serino et al., 2005.
Functional tasks	
Postural control	Tilikete et al., 2001; Shiraishi et al., 2008
Wheelchair navigation	Jacquin-Courtois et al., 2008
Walking	Keane et al., 2006; Bacchini et al., 2006; Folegatti et al., 2008
Computerised tasks	
Temporal order judgement	Berberovic et al., 2004
The disengage deficit	Striemer et al., 2007; Schindler et al., 2008
Endogenous orienting	Nijboer et al., 2008
Visual search (unlimited search time)	Saevarsson et al., (2009)
Multiple daily sessions (10 over 2 weeks)	
Neglect of 11 years' chronicity, 1 year follow-up	Humphreys et al., 2006
Prism treatment vs normal cognitive rehabilitation	
5 week follow-up	Frassinetti et al., 2002
3 month follow-up	Serino et al., 2005; 2007
Prism treatment vs sham treatment	
1 month follow-up	Serino et al.; 2009
Null findings	
Standard pen-and-paper tests	Rosseaux et al., 2006
Chimeric face judgements	Ferber et al., 2003
Visual Search (limited search time)	Morris et al., 2004
Exogenous orienting	Nijboer et al., 2008
Randomised clinical trial of four daily sessions of prism vs sham adaptation in acute neglect patients	Nys et al., 2007
Multiple daily sessions, 6° prisms vs sham	Turton et al., 2007

In summary, prism adaptation has been promoted as a significant development in neglect rehabilitation due to the ease with which it can be administered and the broad generalisation and longevity of the observed benefits. This notwithstanding, improved neglect performance following prism adaptation has not been universally reported. Prism adaptation failed to improve patient's perceptions of chimeric faces (Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003), relative size judgements of bilaterally presented objects (Dijkerman et al., 2003), or visual search performance (Morris et al., 2005). Using a within-subjects design, Rosseaux and colleagues (2006) also found no difference between the effects of prism adaptation and pointing with neutral lenses on the performance of neglect patients on standard pen-and-paper tests. Furthermore, the only double-blind control study of prism adaptation treatment to date found no differences in long-term outcomes for patients with acute neglect who underwent four daily sessions of prism adaptation compared to control patients who performed the same regimen using neutral lenses (Nys, de Haan, Kunneman, de Kort, & Dijkerman, 2008). These results suggest that prism adaptation may not improve all manifestations of neglect, or be effective for all patients.

Research investigating the effects of prism adaptation on neglect symptoms have been paralleled by studies reporting neglect-like patterns of performance in healthy participants following adaptation to leftward-shifting prisms.

ADAPTATION TO LEFTWARD-SHIFTING PRISMS CAN INDUCE NEGLECT-LIKE PERFORMANCE IN HEALTHY PARTICIPANTS

Healthy participants show small but consistent leftward errors when bisecting a horizontal line (Bowers & Heilman, 1980; see Jewell & McCourt, 2000, for a review). This bias, termed 'pseudoneglect' is thought to be caused by similar attentional mechanisms as those causing rightward bisection biases in hemispatial neglect (Bultitude & Aimola Davies, 2006), and can also be elicited on other tests of spatial attention such as judgements of the relative luminance of two mirror-reversed luminance gratings (the 'greyscales' task), and judging without calculating the number that is halfway between two stimulus numbers ('bisection' of the mental number line). Healthy participants who have adapted to leftward-shifting prisms show rightward shifts in their bisection errors, reducing or reversing the pseudoneglect bias (Table 2.2). This neglect-like change in bisection performance was first shown by Colent and colleagues (2000) for both manual bisection and the Landmark Test - a non-manual test of perceived midpoint in which participants are presented with lines that are pre-transected at or near veridical centre and are required to indicate whether the transector is positioned to the left or right of the midpoint. Participants who adapted to rightward shifting prisms showed no change.

Table 1.2. Summary of research examining the effects of prism adaptation on attentional and perceptual processes in healthy participants

Description	Author(s)
Visuo-motor tests	
Line bisection	Colent et al., 2000; Michel et al., 2003; Dijkerman et al., 2006
Hand-path curvature	Jackson and Newport, 2001
Visual tests (no or minimal motor response)	
Landmark test	Colent et al., 2000; Michel et al., 2003; Berberovic and Mattingley, 2003
Exogeneous and endogeneous orienting	Striemer et al., 2006
Greyscales task	Loftus et al., 2008
Non-visual tests	
Haptic exploration	Girardi et al., 2004
Representational neglect	
Mental number bisection	Loftus et al., 2008
Mental alphabet bisection	Nicholls et al., 2008
Ocular exploration	Ferber et al., 2005
Postural control	Michel et al., 2003
Goal oriented locomotion	Michel et al., 2007
Null findings	
Chimeric face judgements	Ferber et al., 2005
Temporal order judgement	Berberovic et al., 2004
Visual search (limited search time)	Morris et al., 2004
Mental number bisection	Dijkerman et al., 2006

The rightward shift in perceived midpoint following adaptation to leftward-shifting prisms has since been replicated for lines in both peripersonal and extrapersonal space (Berberovic & Mattingley, 2003); and Michel and colleagues (2003) showed that the magnitude of midpoint shift increased with more leftward line placement and longer line length, replicating the so-called 'position' and 'length' effects shown by neglect patients. As with patients, there is some evidence for a multimodal effect, with a rightward bias in the haptic exploration of healthy participants after adaptation to leftward shifting prisms (Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004). However, prism adaptation did not change the performance of healthy participants on judgements of chimeric faces (Ferber & Murray, 2005), visual search (Morris et al., 2005), or a temporal order judgement task (Berberovic, Pisella, Morris, & Mattingley, 2004).

Converging evidence therefore suggests that adaptation to leftward-shifting prisms can induce in healthy participants a spatially-lateralised bias in performance that is more than simply a visuomotor after-effect (for a review, see Michel, 2006). While significant visuomotor after-effects occur after adaptation to both leftward- and rightward-shifting prisms, these changes in higher-level spatial performance are mainly unidirectional: they usually occur only in participants who have adapted to leftward-shifting prisms. There are three exceptions to this pattern. Jackson and Newport (2001) demonstrated neglect-like increases in hand-path curvature in the visually guided reaching of six healthy subjects who had spent short periods adapting to rightward-shifting prisms. Berberovic and Mattingley (2003) observed a rightward shift in midpoint judgements of lines in extrapersonal space following adaptation to *both* leftward- *and* rightward-shifting prisms. Finally, Striemer and colleagues (2006) showed that adaptation to both leftward- and rightward-shifting prisms had significant, although differing effects on reflexive and voluntary orienting. To elaborate, they found that regardless of the shift direction, prism adaptation facilitated reflexive reorienting away from an invalid cue on the side of space opposite to the prismatic shift in a subset of participants who showed a large cueing effect before prism adaptation. In contrast, voluntary orienting on both sides of space was facilitated by adaptation to leftward-shifting prisms for participants who showed small baseline cueing effects, but was hindered by adaptation to rightward-shifting prisms for participants who showed large baseline cueing effects. Hence, although most studies report that adaptation to leftward-shifting prisms produces neglect-like performance in healthy participants, rightward-shifting prisms may also have some limited influence on performance.

Although adaptation to leftward-shifting prisms has seldom been tested with neglect patients due to the risk of accentuating their symptoms, Rossetti and colleagues

(1998) found that neglect patients did not adapt to leftward-shifting prisms at all. Tilikete and colleagues (2001) reported significant after-effects for adaptation to both leftward- and rightward-shifting prisms in two groups of five hemiparetic patients with right hemisphere lesions (three per group had previously shown neglect). However, only rightward-shifting prisms influenced postural control, with imbalance improving in the rightward-shifting prism group but not in the left prism group. Overall, the effect of prism adaptation on neglect symptoms and higher-level spatial performance in healthy participants are both asymmetrical, but are opposite to each other. A satisfactory explanation for these asymmetries has not yet arisen, but is probably associated with the same asymmetries that make neglect more frequent following right hemisphere lesions, and that results in pseudoneglect.

EXPLANATIONS FOR EFFECTS OF PRISM ADAPTATION ON HIGHER-LEVEL COGNITIVE PERFORMANCE

In recent years some efforts have been made to understanding the mechanisms of the changes in visuo-spatial performance induced by prism adaptation. These can be divided into cognitive and neuroanatomical accounts.

Cognitive Mechanisms

The simplest cognitive explanation for the improved leftward exploration of neglect patients following prism adaptation is that there is a long-lasting adaptation after-effect, partly facilitated by the patient's lack of awareness of the prismatic shift, that directly influences test performance by biasing actions of the adapted arm. Healthy participants who adapted to prismatic shifts of magnitudes that increased incrementally such that participants were unaware of the lateral visual distortion showed after-effects that lasted for more than 6 days (Hatada, Miall, & Rossetti, 2006). Adapting without awareness in this manner minimises the amount of strategic compensation and maximises the extent of true adaptive realignment. As neglect patients also report no awareness of the prismatic shift, extensive and long-lasting adaptive realignment may occur that directly influences motor behaviour. This explanation would posit that, for example, a patient's judgement of line midpoint is unchanged post-adaptation, but they make a bisection mark to the left of their intended position due to the motor bias induced by the after-effect. Alternatively, an increase in the frequency and magnitude of movements of the adapted hand into the left side of space due to the adaptation after-effect could act to draw attention leftward (c.f. spatio-motor cueing; Halligan, Manning, & Marshall, 1991). However these explanations would suggest a direct relationship between the magnitude of the after-effect and the degree of neglect improvement, and there is no correlation between these measures (Frassinetti et al., 2002). Furthermore, they cannot account for changes in performance on non-motor tasks such as reading (Datie et al., 2006; Serino et al., 2005) and describing the objects in a room (Farnè et al., 2002).

A more probable mechanism is that prism adaptation may realign the distorted egocentric reference frame of neglect by inducing a leftward proprioceptive after-effect that counters the neglect bias in subjective straight ahead. This would account for the improvements in non-motor tests, non-visual tests and representational neglect. As discussed above, however, the biased egocentric reference frame of neglect is insufficient to explain all aspects of neglect, as it is not found in all neglect patients. Furthermore, Pisella and colleagues (2002) found a double dissociation in the time course of improvements in the subjective straight ahead and line bisection errors of two patients with neglect following prism adaptation.

Improved leftward ocular exploration following prism adaptation suggests that prism adaptation induces a resetting of the ocular-motor system (Angeli, Benassi, & Làdavas, 2004; Angeli, Meneghello, Mattioli, & Làdavas, 2004; Datie et al., 2006; Serino et al., 2005). Particularly supportive of this is evidence of increased leftward ocular exploration without concurrent improvement in perceptual tasks (Ferber et al., 2003; Ferber & Murray, 2005), indicating that perceptual changes may be preceded by a normalisation of visual inspection patterns. This would explain improvements in visuoverbal tests such as reading and visual search, but not reports of post-adaptation changes in the visuospatial performance of patients and healthy participants under conditions of constant central fixation. Berberovic and colleagues

(2004) first demonstrated this in neglect patients using the temporal order judgement task: a test highly sensitive to biases in spatial attention in which patients judge which of two lateralised stimuli appeared first. Prior to prism adaptation the left visual field stimulus had to precede the right visual field stimulus by an average of 427ms for simultaneous stimulus presentation to be perceived, and after prism adaptation this had reduced to 98ms. Striemer and colleagues (2006) tested the effects of prism adaptation on a classic deficit that characterises neglect: the disengage deficit, measured as slowness in responding to a left visual field target after cuing attention to the right visual field. After prism adaptation right hemisphere lesioned patients showed both improved overall detection of left visual field stimuli as well as a reduction in the disengage deficit. A reduction of the disengage deficit after prism adaptation has since been replicated (Schindler et al., 2009) using the Egly paradigm (Egly, Driver, & Rafal, 1994), and for exogenous but not endogenous orienting (Nijboer, McIntosh, Nys, Dijkerman, & Milner, 2008).

The improved temporal order judgements and disengage deficits under conditions of fixed gaze strongly suggest that the improved performance following prism adaptation is not simply due to increased ocular exploration of the left side of space, but that there is a reduction in the rightward attentional bias that is at the very core of many aspects of hemispatial neglect. However, this improved leftward attention could be secondary to a resetting of the ocular-motor system according to the premotor theory of attention (Rizzolatti, Riggio, Dascola, & Umilta, 1987), therefore the ocular-motor and attentional accounts of the clinical effects of prism adaptation have equal validity according to current evidence.

As yet, the effects of prism adaptation on higher-level spatial performance in healthy participants have not been reported on quite as broad a set of tasks. Nonetheless, there is reason to believe that these effects are caused by similar mechanisms as those that produce improvements in neglect. Neglect-like changes have been found for a version of the landmark test with presentation times too brief to enable eye movements (Berberovic & Mattingley, 2003), and on non-visual tests (Girardi et al., 2004; Loftus, Nicholls, Mattingley, & Bradshaw, 2008; Nicholls, Kamer, & Loftus, 2008). A post-adaptation neglect-like bias was also present in healthy participants who haptically explored a circular groove while blindfolded, with a rightward shift in perceptions of circle centre (Girardi et al., 2004). Furthermore, Loftus and colleagues (2009) demonstrated that even when responses were given verbally and fixation was held constant, prism adaptation induced neglect-like changes in performance on the greyscales task: a test that is highly sensitive to biases in spatial attention in which participants make a forced-choice judgement about which is the lighter of two mirror-reversed luminance gradients. This suggests that the performance changes that follow adaptation to leftward-shifting prisms are at least partially due to alteration in attention rather than solely a direct result of the motor or ocolomotor after-effect. Although further research is required, it appears that the higher-level spatial effects of prism adaptation in healthy participants are produced by the same, but metrically opposite, mechanisms as those improving neglect symptoms.

In summary, a long-lasting motor after-effect cannot satisfactorily explain the higher-level effects of prism adaptation. Evidence instead suggests that the broadly generalised improvements are due to a decrease in the rightward attentional bias, although a realignment of the egocentric reference frame, and resetting of the ocularmotor system may also contribute. To optimise rehabilitation and identify which patients are more likely to respond to treatment, it may be more important to understand the neurological processes by which prism adaptation achieves these effects.

Neuroanatomical Mechanisms

A network of brain areas involved in spatial updating and visuo-motor control have been implicated in prism adaptation. The basal ganglia were implicated by reduced error correction during prism adaptation (Weiner, Hallet, & Funkenstein, 1983) and smaller after-effects (Fernandez-Ruiz et al., 2003) in patients with Huntington's and Parkinson's Disease. Deactivation of the premotor cortex by muscimol injection in monkeys (Kurata & Hoshi, 1999) and by TMS in humans resulted in slower adaptation rates and smaller after-effects (Lee & van Donkelaar, 2006). Error correction was impaired in patients with right temporal, parietal or occipital lesions, but not left hemisphere lesions or lesions to either frontal lobe (Weiner et al., 1983). Cerebellar lesions reduced, and in some cases entirely eliminated, both error correction and the after-effect (Morton & Bastian, 2004; Weiner et al., 1983), suggesting a key role in prism adaptation. With the discovery of the clinical effects of prism adaptation, the neurological mechanisms of prism adaptation have been examined with renewed vigour. Of particular interest is the cerebellum, due to its apparently essential role in prism adaptation, and the posterior parietal cortex (PPC), as it is implicated in both prism adaptation and neglect.

The cerebellum plays an essential role in visually-guided behaviour (see Stein & Glickstein, 1992, for a review). It receives proprioceptive information and efference copies from the limbs, as well as visual inputs, and thus has all information for the detection of sensory-motor discrepancies during pointing under prismatic distortion. Studies of prism adaptation after lesions to different regions of the cerebellum in humans and monkeys suggest that the cerebellar areas that are critically involved in prism adaptation are those that receive cortical visual input (Baizer, Kralj-Hans, & Glickstein, 1999; T. A. Martin, Keating, Goodkin, Bastian, & Thach, 1996). Interestingly, Pisella and colleagues (2005) showed that this adaptation deficit may be specific to ipsilesional prismatic shifts: a patient with a left cerebellar lesion adapted to rightward- but not leftward-shifting prisms, regardless of the hand used. A hemispheric lateralisation of detection of, or adjustment to, leftward- and rightward- prismatic shifts may be one reason for the asymmetrical effects of different shift directions on higher-level spatial performance in neglect patients and healthy participants.

In the first study of cortical activation during prism adaptation, the only area implicated was the PPC. Using Positron Emission Tomography (PET), Clower and colleagues (1996) recorded changes in the regional Cerebral Blood Flow (rCBF) of healthy participants who pointed to targets with their right arm under prismatically shifted visual feedback that switched direction every five trials. In the control condition, participants pointed to a target that changed position upon the initiation of the pointing movement, with the direction of the jump varying randomly between trials. During prism adaptation there was increased rCBF in the PPC contralateral to the adapting arm [i.e., the left PPC; specifically, area PEG on the lateral bank of the inferior parietal sulcus (IPS)].

Aside from its implication in neglect (Vallar & Perani, 1986), the PPC has been associated with sensorimotor and multi-sensory integration (Pisella et al., 2004) and online movement correction (Desmurget et al., 1999; Grea et al., 2002; Jeannerod & Rossetti, 1993). The specific role of the PPC in prism adaptation has been probed in studies of patients with bilateral parietal lobe lesions. Two patients with bilateral PPC lesions showed some evidence of reduced strategic component of adaptation: Patient IG had greater transference of the after-effect from her adapted (right) hand to her unadapted (left) hand (Pisella et al., 2004); and patient JJ showed no error correction but a normal after-effect when adapting with his right hand (Newport & Jackson, 2006, although many more pointing trials than usual were required for the development of this after-effect, c.f. Newport, Brown, Mort & Jackson, 2006). This suggests that the strategic component of adaptation involves the PPC, but adaptive realignment does not. A loss of strategic control following PPC damage is also consistent with the lack of awareness of the prismatic shift shown by neglect patients. As adaptive realignment is greater under conditions where strategic control is minimised (Redding & Wallace, 1992), patients with PPC lesions such as those that are associated with neglect may have longer-lasting and more generalised after-effects. As discussed above, a long-lasting visuomotor after-effect cannot solely explain the higher-level spatial effects of prism adaptation. However it may act as a robust bottom-up signal that serves to produce long-term modification of spatial reference frames and attention through a secondary process. It should be noted, however, that the evidence from biparietal patients only partially supports this model: when JJ adapted with his left hand there was no adaptation after-effect and some evidence of error correction: the opposite pattern to that which occurred with his right hand, and one that indicates a failure of adaptive realignment and preserved strategic compensation. This is presumably due to asymmetries in JJ's lesions, which extended more superiorly in the parietal lobe of the left hemisphere compared to the right hemisphere (Newport et al., 2006).

Two recent fMRI studies examining changes in brain activity during prism adaptation also support important roles of the cerebellum and areas within the PPC. Danckert, Ferber and Goodale (2008) compared pointing while looking through prisms (‘prism’ pointing) to pointing without prismatic distortion (‘neutral’ pointing) for alternating blocks of ten trials. To examine activity related to the strategic component of adaptation, they compared BOLD signals during the first three pointing trials of the prism blocks (when strategic compensation is high), to those during the last three trials (when pointing errors are small or non-existent and strategic compensation is reduced). To examine activity related to adaptive realignment they compared BOLD signals throughout the entire prism block to those throughout the neutral pointing blocks. Using a different design, Luaute and colleagues (2009) examined the same components of prism adaptation. Participants completed individual blocks of pointing while looking through neutral lenses before and after two consecutive blocks of pointing with prism exposure in an ABBA design, with 24 pointing trials per block. The areas implicated in adaptive realignment were determined by comparing activity during the prism blocks to the neutral pointing blocks, and the areas involved in strategic compensation were examined by comparing activity during the first prism block to the second prism block. Participants adapted using their right hand in both studies, but to opposite visual shifts: leftward-shifting (Luaute et al., 2009) or rightward-shifting (Danckert et al., 2008).

Both studies found activity in the cerebellum relating to both the strategic component and adaptive realignment of prism adaptation. Danckert and colleagues (2008) reported higher activity in the right culmen and vermis of the cerebellum during prism exposure compared to neutral pointing, and vermis activity was also higher for the first three trials than the last three trials of the prism block. They suggested that the activity in the culmen reflected a greater demand on fine motor control mechanisms during the unfamiliar experience of prism exposure. The vermis is involved in postural control, balance and movement execution, and the pattern of activation in this area suggests a role in the initial correction of movements during the strategic period of adaptation. Martin and colleagues (1996) reported that two of three patients with vermal lesions showed no after-effect when adapting with the contralesional arm. In the fMRI study of Luaute and colleagues (2009), activity was found in lobules IV and V of the right cerebellum that gradually increased over the 24 trials of the first prism adaptation block and then reduced again during the second prism block. Lobules IV and V, are involved in visually directed movements and eye-hand coordination, and the pattern of BOLD signal suggests a probable role in adaptive realignment, which is slower to develop than strategic correction but nonetheless would take place more in the first than the second block. Taken together, the cerebellar activity reported by the two fMRI indicate that cerebellar areas are involved in both strategic control (the vermis) and adaptive realignment (Lobules IV and V).

Both studies reported increased BOLD signal in the anterior cingulate and anterior IPS of the left hemisphere during the early phase of prism adaptation compared to later pointing movements. The anterior cingulate activity is likely to relate to this area's well-supported role in performance monitoring, error detection and error correction, all of which are needed in the first trials of prism adaptation where trajectory and end-point errors are most apparent. Danckert and colleagues (2008) suggested that the activity in the anterior IPS of the left hemisphere reflected a role of this area in short-term sensori-motor adjustments (i.e., strategic control). Luaute and colleagues (2009), however, also found enhanced BOLD signal for the left parietal-occipital sulcus relating to early error correction and therefore suggested a different role of the anterior IPS. By correlating BOLD signals in the POS and anterior IPS with both the raw error magnitude and the change in error from the previous trial, they found that POS activity was primarily modulated by error change, while anterior IPS activity was primarily modulated by error magnitude. Unlike Danckert and colleagues (2008), they therefore concluded that the IPS was involved in the *detection* of sensorimotor errors during prism adaptation, while the POS was involved in error correction.

Finally, Luaute and colleagues (2009) found bilateral activation of the superior temporal sulcus, extending into the STG, throughout blocks of prism adaptation compared to neutral pointing, suggesting a role of this area in adaptive realignment of visual and motor references that reflects true adaptation. Although the STG has not previously been associated with prism adaptation, it does have multimodal inputs and an association with neglect, so a role in the higher-level spatial effects of prism adaptation would not be entirely implausible.

Overall, research in patients with bilateral parietal lobe damage and brain imaging studies of healthy participants undergoing prism adaptation provide strong evidence that the PPC, specifically the anterior IPS, is important for strategic compensation, while cerebellar areas are involved in both strategic compensation and adaptive realignment. However the studies discussed thus far allow only speculation as to the cerebral mechanisms of the higher-level spatial effects of prism adaptation. Determining the neural mechanisms of the clinical effects of prism adaptation requires brain activation studies and lesion analyses in neglect patients treated with prism adaptation.

Sarri and colleagues (2007) found that neglect improvement following a single session of prism adaptation was less for patients with lesions to the right IPS and white matter underlying the right IPL and right MFG. This finding is the reverse of what would be expected if, as proposed above, the amelioration of neglect following prism adaptation occurs is facilitated by a robust and long-lasting adaptive realignment in the absence of strategic control after PPC injury. However, the authors emphasised that the conclusiveness of this finding is limited due to small patient numbers.

Luaute, Michel, Rode, Pisella Jacquin-Courtois and colleagues (2006) used PET to measure the changes in rCBF in five neglect patients following a single session of prism adaptation. Changes in blood flow were in high agreement with the functional imaging studies of healthy participants discussed above. Improved neglect performance correlated with increased activity in a region of the right cerebellum, including lobule V, as well as in temporal areas (specifically the left fusiform gyus of the temporo-occipital junction, although this activity may also be partly because the task patients performed during the PET recordings was the landmark task, which is known to produce higher temporal lobe activity than other tests for neglect such as cancellation; Rorden et al., 2006). Neglect improvement also correlated with a *decrease* in rCBF in the right posterior superior parietal lobe, an area that was partially damaged in four of the five patients tested. The authors suggested that this reduced activity may reflect increased efficiency of this area; that is, after prism adaptation there were functional improvements in residual right hemisphere areas that corresponded with neglect improvement. In contrast, seven patients who underwent an average of 4.2 prism adaptation sessions per week for eight weeks showed a significant increase in *left* parietal rCBF (Shiraishi et al., 2008), which suggests that the long-term symptom amelioration that follows repeated sessions may result from recruitment of left parietal areas for functions that are usually mediated by the damaged right parietal lobe.

Striemer and colleagues (2008) specifically hypothesised that the superior parietal lobe (SPL) may be important for the clinical effects of prism adaptation. This area is often preserved in patients suffering neglect, is involved in attention and eye and limb movements, and receives inputs from the cerebellum. In support of this theory, they showed that a patient with left spatial neglect following asymmetrical bilateral lesions involving the SPL of both hemispheres adapted to prisms but showed no neglect improvement. Although merely speculative given the bilateral SPL damage of their patient, the authors suggested that the left SPL was critical for neglect improvements following adaptation to rightward shifting prisms.

Finally, in patients who underwent two weeks of daily prism adaptation treatment, larger occipital lesions were associated with smaller error correction during prism adaptation, and less improvement on standard pen-and-paper tests and in ocular-motor exploration (Serino et al., 2007). The impaired error correction suggests that the reduced clinical effect of prism adaptation resulted from interruption to the adaptation process itself. Most of the visual input to the cerebellum comes from the dorsomedial 'where' stream - including the PPC - via the pontine nuclei (Stein and Glickstein, 1992). Large occipital lobe lesions that reduce or eliminate these signals may prevent the computation of visuo-motor misalignment in the cerebellum.

In summary, a network of regions is implicated in prism adaptation. Research to date supports a model in which visuo-motor discrepancy is detected in the cerebellum based on visual, proprioceptive and motor inputs from the cortex. This leads to the generation of a bottom-up error signal, which, in neglect patients, may be enhanced due to reduced strategic control following damage to the right anterior IPL. This signal is transferred to the left IPL, and also to the left IPS, where the error signal serves as a realignment signal, encouraging the patient to re-explore the left side of space. Either as a result of sensory input following from this re-exploration, or through direct colossal connections, reactivation and functional restoration may occur in residual right parietal areas such as the SPL.

THESIS OUTLINE

Prism adaptation is a powerful medium for inducing plastic changes in sensory-motor references. A decade of research in neglect patients and healthy participants demonstrates that the influence of prism adaptation is not limited to low-level sensory-motor function, but extends to affect higher cognitive aspects of spatial performance. The higher-level influence of prism adaptation highlights the promise of treatment for neglect, and can also be further understood through experiments in healthy participants. The experiments described in this thesis further explore the influence of prism adaptation on clinical neglect symptoms and higher-level spatial performance in healthy and brain-lesioned participants.

There is now sufficient evidence to support that prism adaptation treatment can begin to be incorporated into neglect rehabilitation programs. However, the number of studies reporting null results indicate that ongoing monitoring of its basic clinical effects is still pertinent. With this in mind, Chapter 2 describes the effectiveness of prism adaptation in the rehabilitation of patients with hemispatial neglect who were referred for prism treatment over a three-year period.

Changes in the perceptual-attentional performance of healthy participants and neglect patients following prism adaptation is now well-established. Few efforts, however, have been made to examine the effects of prism adaptation on motor-intentional aspects of behaviour. In Chapter 3, three experiments examine the effects of prism adaptation on motor-intentional performance in healthy participants. Furthermore, despite evidence that non-spatially lateralised deficits can accompany and aggravate the rightward attentional bias of neglect, whether these can be reduced by prism adaptation has hitherto been unexplored. The experiments in Chapter 3 examine whether adaptation to leftward-shifting prisms result in two motor-intentional biases that are associated with neglect: one lateralised spatial deficit (directional hypokinesia) and one non-lateralised spatial deficit (the withdrawal bias).

In Chapters 4 and 5 the effects of prism adaptation on non-spatially lateralised performance is further examined. Divided and directed tests of hierarchical processing are used to examine whether prism adaptation can reduce the local processing bias of five patients with lesions to the right temporo-parietal junction (Chapter 4). Such a reduction would suggest that the improved performance of patients with neglect who have adapted to rightward-shifting prisms may be partially due to reduction in this bias. Similarly, Chapter 5 examines whether the global processing bias demonstrated by healthy participants is reduced by prism adaptation, suggesting an induction of a neglect-like pattern of performance on this aspect of non-lateralised spatial attention.

Chapter 6 describes a new application of prism adaptation in the treatment of Complex Regional Pain Syndrome (CRPS), a disorder affecting one or more limbs that is characterised by sympathetically maintained pain, motor disability, and autonomic dysfunction. Recent developments demonstrate that CRPS is not limited to the peripheral and autonomic nervous system, but that there is also a reorganisation of cortical function, resulting in a distorted body image and symptoms that resemble some aspects of neglect. A recent study reported reduced pain and autonomic symptoms in five patients who underwent two weeks of daily adaptation to 20° prismatic shifts that induced an after-effect towards the affected limb (Sumitani et al., 2007). I report observations on the benefits of prism adaptation in a woman with CRPS over fifteen weeks in which she underwent periods of daily prism adaptation, and adaptation-free periods.

Chapter 2

The effects of prism adaptation on hemispatial neglect

ABSTRACT

Prism adaptation is a promising treatment for hemispatial neglect, with enough amounted evidence to support integrating the treatment into standard rehabilitation programs. This chapter provides an overview of the effectiveness of prism adaptation in the rehabilitation of fourteen patients. The effects of a single session of prism adaptation on neglect symptoms are reported for a group of twelve hospitalised patients with acute neglect (Part 2.1). Four longitudinal case studies were also conducted (Part 2.2), examining in individual patients the effects of single and multiple treatment sessions on specific neglect symptoms: vertical and radial neglect, anosognosia, spatial navigation, and right spatial neglect following left hemisphere damage. Overall, the results provide little evidence that prism adaptation improved symptoms in patients with left spatial neglect, possibly because any benefits of prism adaptation may be negligible compared to the amount of spontaneous recovery that occurs during the acute stage. In contrast, a patient with mild right spatial neglect of three months' chronicity showed improved line bisection performance after a single session of adaptation to leftward-shifting prisms. An important avenue for future research is to examine whether neglect patients in the acute stages of recovery have improved outcomes following two-week treatment regimens similar to those that give rise to long-lasting improvements in chronic neglect patients.

Since Rossetti and colleagues (1998) first reported that visuo-motor adaptation to rightward-shifting prisms improved symptoms of hemispatial neglect, over thirty studies have demonstrated improvements in more than 150 patients on an exhaustive array of standard pen-and-paper tests, clinical measures and experimental tasks. Prism adaptation is therefore a promising treatment for hemispatial neglect, with enough amounted evidence to support integrating the treatment into standard rehabilitation programs. However, there are also sufficient studies reporting no benefit of prism adaptation to indicate that the technique cannot yet be considered a verified treatement. This chapter gives an overview of the effectiveness of prism adaptation in the rehabilitation of patients with hemispatial neglect who were referred for treatment over a three-year period. In Part 2.1 the effects of a single session of prism adaptation on symptoms of twelve patients with acute left spatial neglect are reported. In Part 2.2 the details of four longitudinal case-studies are reported.

PART 2.1: THE EFFECTS OF A SINGLE SESSION OF PRISM ADAPTATION ON ACUTE HEMISPATIAL NEGLECT

Method

Patients

Patients were recruited from the North West Wales and Conwy-Denbighshire NHS Trusts. Hemispatial neglect was diagnosed by a Consultant Neurologist or referred by an occupational therapist. The diagnosis of hemispatial neglect was made on the basis of a standard neurological examination and neuropsychological testing [drawing a clock from memory, copying a simple scene (Ogden, 1985; or Gainotti, 1972), line bisection (Schenkenberg, Bradford & Ajax, 1980; or Wilson, Cockburn, & Halligan, 1987) cancellation (Edgeworth, Robertson, & McMillan, 1998; Gauthier, Dehaut, & Joanette, 1989; and/or Wilson, Cockburn, & Halligan, 1987), and picture description (Wells & Reusch, 1945), see Table 2.1]. The patients received prism adaptation treatment as part of their rehabilitation program. In addition, patients who were identified as suitable research candidates were asked if they were willing to complete additional assessments further to prism treatment. Participation in the research did not impact on whether the patient received prism treatment; however prism treatment was administered to the research participants by the experimenter, an Honorary Research Assistant Psychologist working under the supervision of a Consultant, rather than hospital staff to ensure treatment conditions were controlled across sessions and subjects.

Forty patients were referred and the presence of hemispatial neglect was confirmed in 36. Four patients did not receive prism treatment as their symptoms resolved within a few days of assessment. Of the remaining 32 patients, seven were excluded due to: 1) Impaired cognitive function indicated by scores of less than 23 on the Mini Mental State Examination (N=2); 2) Impaired ability to complete the neglect testing due to aphasia following left hemisphere damage (N=2) or poor recovery of motor function and sustained attention (N=4); and 3) Transferral to another part of the county (N=1). Of the remaining eighteen patients thirteen took part in research testing, one of whom had right spatial neglect following left hemisphere lesions. Clinical details of the twelve patients with right hemispatial neglect who participated in the study are provided in Table 2.2, and lesion information is provided in Table 2.3.

Table 2.1. A summary of all tests used for initial patient assessments and the evaluation of symptoms before and after prism adaptation.

Test	*Authors*	*Description*	*Scoring / cut-off*
Drawing from Memory			
Clock Drawing	Wilson et al., 1987	Patient is asked to draw a clockface from memory, complete with numbers and hands.	Visual inspection for completeness and number placement
Figure Copying			
Ogden Copying Task	Ogden et al., 1985	Patient is asked to copy a simple scene depicting a house with two trees and a fence.	Visual inspection for object- and space-based neglect
Gainotti Copying Task	Gainotti et al. 1972	Patient is asked to copy a simple scene depicting a house with four trees.	As above
Line Bisection			
Single Line Bisection		Patients are asked to place a mark in the middle of a 100mm horizontal line positioned in the centre of an A4 sheet	Average deviation of bisection marks from veridical centre, as a percentage of line length
Line Bisection Subtest of the BIT	Wilson et al., 1987	Patients bisect 3 200mm horizontal lines positioned to the right, left and centre of an A4 sheet.	As above
Schenkenberg Line Bisection Test	Schenkenberg, et al., 1980	Patients bisect 20 horizontal lines of three different lengths positioned on the left, middle and right of an A4 page.	As above
Cancellation Tasks			
Star Cancellation Subtest of the BIT	Wilson et al., 1987	Patients search for small stars (N=54) amongst distracters (large stars, letters)	Fewer than 44 targets cancelled, or a laterality index less than 0.46, indicates neglect.
Letters Cancellation Subtest of the BIT		Patients search for two upper case letters (N=68) amongst 102 distracter letters	More than 8 omissions
Balloons Cancellation task, Subtest A	Edgmorth et al., 1998	A parallel ('pop-out') search task in which 22 target balloons are hidden amongst 180 distracters circles.	Worse performance on subtest B than A excludes the possibility that poor performance is due to a visual field deficit. Less than 17 targets cancelled and a laterality index less than .45 on subtest B indicates neglect.
Balloons Cancellation task, Subtest B		A test of serial search in which the targets are 22 circles hidden amongst 180 distracter balloons	
Bells Cancellation test	Gauthier et al., 1989	Patients search for target bells (N=35) from amongst 280 distractor objects.	Omission of six or more targets, with two more omissions on the left than the right side
Picture description	Wells and Reusch, 1945	The patient is asked to describe the 'broken window' picture (Figure 2.1), and is asked 'who broke the window?' and 'who is getting the blame?'	A patient who fails to notice the 'guilty' boy is classified as showing neglect.

Figure 2.1. The 'broken window' picture used for the picture description task (a mirror-reversed version was used to screen for right spatial neglect). Patients with neglect initially may not describe the 'guilty boy' or possibly even the 'angry man'. The test was also used for rudimentary screening for aphasia and dementia (unlike many patient with dementia, neglect patients will correctly interpret the scene once they are aware of all the characters). (Wells and Reusch, 1945).

Design and Procedure

The research protocol was approved by NHS and Bangor University ethics committees. Participants gave informed written consent for their participation in accordance with the Declaration of Helsinki. Research was conducted at the patient's bedside or in a quiet room at the hospital. Neglect symptoms before and after prism adaptation were assessed using standard pen-and-paper tests. A multiple case-studies design was used in which the number of testing sessions and the exact tests used varied for each patient depending on the time available and the patient's capabilities (see Table 2.4 for a summary). However, all patients completed at least one of the following types of tests: figure copying, line bisection or cancellation. For nine patients the effects of sham adaptation were also examined, with sham treatment preceding prism treatment by 1-3 days. Prism adaptation and the majority of neglect testing sessions were performed in the morning when patients were most rested and ward activity was at its lowest. Six patients also completed two-hour post-adaptation testing sessions (late-tests) in the early afternoon.

Table 2.2. Demographic and lesion information for the twelve patients.

	NB	JH	TJ	AM	ER	VW	BP	RR	VP	AC	EW	MW
Age	27	81	75	55	72	73	79	71	57	71	74	61
Sex	F	M	M	M	M	F	M	M	F	M	M	F
Handedness	R	R	R	R	R	R		R	R	R	R	R
# Days since CVA*	31	21	11	46	9	70	22	7	98	14	23	20
Type of stroke†	Sub Arr Haem, Isch, secondary to PostCA aneurysm	Isch	Isch	Isch, haem.	Isch	Isch	Isch	Isch	Sub Arr Haem secondary to AntCA aneurysm	Isch	Isch	Isch
Vascular territory	ACA, MCA, watershed	MCA	MCA	ACA, MCA	ACA, MCA	MCA	MCA	ACA, MCA		MCA	MCA	MCA
Summary of lesion §	F,P, Thal	IntC, BG	T, P, BG, Ins, ExtC, IntC			ExtC, BG	F, P, O, Hipp.	F, P, T		F, P, T, Ins	F, P, Ins	F, P

*at the time of the initial assessment.

†Sub Arr Haem = subarrachnoid haemorrhage; Isch = ischemia; AntCA = Anterior Communicating Artery; PostCA = Posterior Communicating Artery

§ F = frontal lobe; P = parietal lobe; T = temporal lobe; O = occipital lobe; Thal = thalamus; BG = basal ganglia; Ins = Insula; IntC = internal capsule; ExtC = external capsule

Table 2.3. Assessment outcomes for the twelve patients.

	NB	JH	TJ	AM	ER	VW	BP	RR	VP	AC	EW	MW
Patient Details												
Age	27	81	75	55	72	73	79	71	57	71	74	61
Sex	F	M	M	M	M	F	M	M	F	M	M	F
Handedness	R	R	R	R	R	R		R	R	R	R	R
# Days since CVA	31	21	11	46	9	70	22	7	98	14	23	20
Neurological examination												
Hemiparesis	+	+	+	+	+	+	+	+		+	+	
Hemianopia	-					-	+	+				
Visual extinction	+	+			-	+	+			+		
Tactile extinction										+		
Anosognosia							+			+	+	
Somatoparaphrenia			+							-	+	
Neuropsychological Testing												
Drawing from memory	-	-		-	-	+	+	+	-	-	+	
Copying	+	+	+	-	+	+	+	+	+	+	+	+
Line Bisection (% deviation)*												
Single line									+9.7			
BIT	+42.7				+33						+8.5	
Schenkenberg	+26.2	+2.3		+3.2		+12.8	+44	+17.4	+13	p		p
Cancellation (# cancelled)												
Balloons A (/20)		9	6	19	3	18	4	5	15	5	9	
Balloons B (/20)					1		1	5	4	1	p	
Bells (/35)	4	3	13	19	4	21	3	5	15	3	12	19
Broken window picture	+			+	+	+	+	+		+		+
Notes			Constructional apraxia	P; diff. following simple instructions			Leaning to right					

'-' indicates symptom absent / normal performance; '+' indicates symptom present / neglect; 'p' indicates perseveration
*positive numbers indicate rightward errors

Table 2.4. Testing schedule for each participant.

	NB	JH	TJ	AM	ER	VW	BP	RR	VP	AC	EW	MW
Test Schedule												
Days since stroke	32*	26	34	72	72	86	20	20	106	14	23	20
Sham adaptation	+	+	+	+	+	+						
Pre-test	+	+	+	+	+	+	+	+	+	+	+	+
Post-test	+		+	+	+	+	+	+	+	+	+	+
Late-test	+	+		+		+	+	+				
Test Battery												
Straight-ahead pointing							+	+				
Copying	Ogden	Ogden	Ogden	Gainnotti		Ogden			Ogden			
Line Bisection	Schenk.	Schenk.	Schenk.	Schenk.	10 lines	Schenk.	Schenk.	4 x BIT	1 x BIT	1 x BIT		
Cancellation	Balloons A	Balloons A	Balloons A	Bells		Balloons A	Bells	Bells	Bells	Bells	Bells	Bells

*NB had undergone adaptation to 10° shifting prisms on day 30 post-stroke. However as there was no motor-after effect after this session, and to maintain consistent treatment conditions between patients, only the results of treatment with 15° prisms on day 32 are considered here.

Prism adaptation

Prism glasses were constructed by inserting two adjustable Risley biprisms into trial frames which were fitted for each patient so that the prisms were centred in front of each eye. To ensure patient comfort by relieving the pressure of the glasses on the face, a head-mount was used that consisted of a broad band that encircled the head that was tightened to provide a snug but comfortable fit. The glasses then connected to the head-mount. The prisms were set to induce no shift ('sham' treatment), or a rightward 15° visual shift direction ('prism' treatment). During exposure patients made 50-90 pointing movements with their ipsilesional hand, alternating between two targets positioned at eye level and arm's length 10° to the left and right of straight ahead. The glasses restricted the visual field such that patients received visual feedback of the second half of their pointing movement only ('concurrent' feedback). After touching each target, they returned their hand to their torso.

Adaptation was confirmed by measuring an after-effect: A 59-cm diameter semi-circular panel was positioned under the patient's chin upon which three lines were drawn radiating from the patient's midline at angles of 10° left, 0° and 10° right from the mid-sagittal plane. These lines served as targets for an open-loop pointing task. Patients pointed with their ipsilesional arm under one of the lines according to the experimenter's instruction. Pointing error was measured in degrees with the aid of markings on the underside of the panel, with negative numbers indicating leftward deviation. Patients returned their arm to their torso in between each pointing movement. Twelve pointing measurements were taken before and after each adaptation session.

Results

Prism Adaptation

Patients experienced no ill-effects, with the exception of JH who felt nauseated after prism treatment. Patients also showed no awareness of the visual shift.

Individual pointing errors before and after prism adaptation are presented in Table 2.5. For the six patients who underwent sham adaptation the mean shift in pointing error of -0.68° was not significant (*SEM*=1.68, *t*(5)=0.51, *p*=0.63). In contrast, prism treatment resulted in a significant average leftward shift of 3.19° (*SEM*=0.77, *t*(11)=4.14, *p*<0.005). As there was considerable inter-individual variability in the magnitude of the changes in pointing error between sessions, these were compared for each patient to a 95% confidence interval constructed around the mean shift magnitude reported in a recent meta-analysis of visual open-loop after-effects in neglect patients (CI0.95=[7.09°, 1.21°]; Sarri et al., 2008). Of the six patients who underwent sham treatment, only AM showed a leftward shift in pointing error that was larger than the upper bound of the 95% confidence interval. However, after prism treatment all but two of the twelve patients showed shifts in pointing error that fell within the 95% confidence interval, indicating an after-effect within the range of those shown by patients in previous studies.

Neglect Measures

The results of the copying, bisection and cancellations tests were evaluated for individual and group changes following prism adaptation.

Copying tasks

Six patients completed copying tasks as part of their neglect testing. Of those, two patients (BW and AM) made complete copies in every session. The pictures of the remaining four patients were evaluated for the presence of spatial and object-based neglect. Spatial neglect was defined as omission of entire objects to the left of the picture, and object-based neglect was defined as omission of left-sided details of copied objects.

NB made both space-based and object based omissions in all of the three copies made on the day of sham adaptation (Figure 2.2). Compared to these, all three copies made on the day of prism adaptation were improved. Comparison of copies made on the same day show that there was no improvement across the three sessions on the day of sham adaptation. Likewise, no marked improvement was observed immediately after prism treatment, although NB made a perfect copy of the figure in the late-prism session.

Table 2.5. Individual open-loop target pointing errors before and after sham and prism treatment. Shift magnitudes that fall within the confidence interval provided by the meta-analysis of Sarri and colleagues are underlined.

	Sham			Prism		
	Pre	**Post**	**Shift**	**Pre**	**Post**	**Shift**
NB	3.25	5.92	2.67	1.83	-2.75	-4.58
JH	-0.17	0.92	1.08	-0.67	-0.83	-0.17
TJ	0.33	-0.58	-0.92	-3.08	-10.00	-6.92
AM	-1.92	-8.75	-6.83	-4.25	-13.17	-8.92
ER	1.71	1.04	-0.67	-0.17	-2.33	-2.17
VW	-0.83	-0.25	0.58	2.42	-0.25	-2.67
BP				-6.67	-5.92	0.75
RR				-2.67	-4.67	-2.00
VP*				0.00	-3.00	-3.00
AC*				1.00	-1.00	-2.00
EW*				-2.00	-6.00	-4.00
MW				-0.13	-2.75	-2.63
Average	0.40	-0.28	-0.68	-1.20	-4.39	-3.19
SEM	0.75	1.94	1.34	0.76	1.12	0.77

*Open-loop pointing error measured with only three trials per session due to patient fatigue.

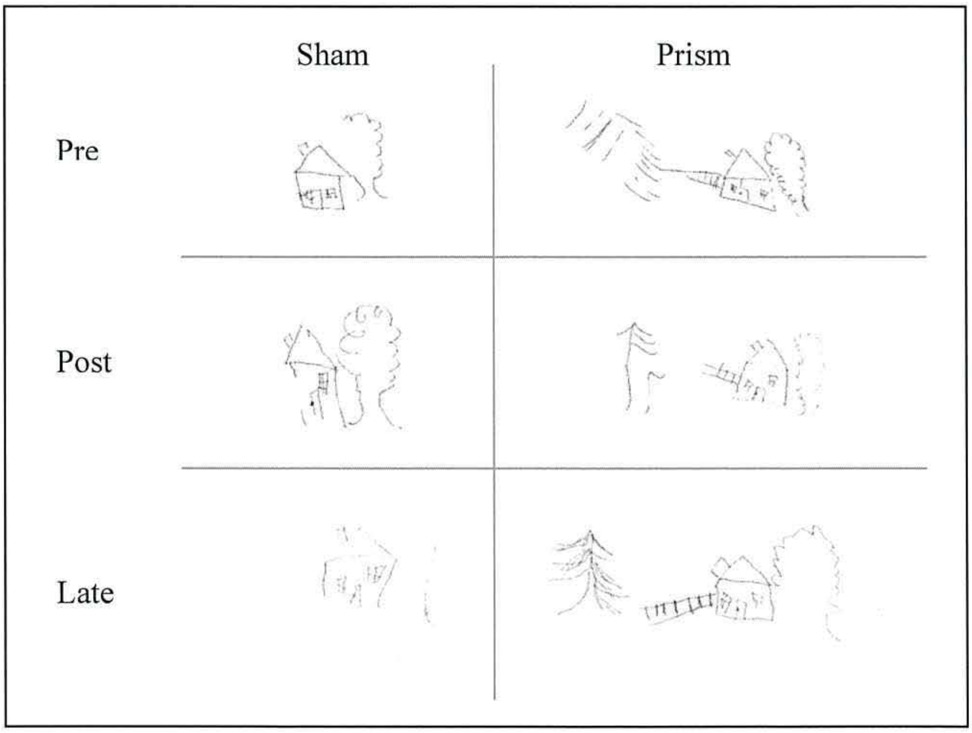

Figure 2.2. Copies of the Ogden figure made by NB immediately before, immediately after and two hours after sham and prism treatment.

JH showed minor improvement in copying between the pre-sham and late-sham tests (Figure 2.3). He made a near-perfect copy before prism treatment, but showed both spatial and object-based neglect in his post-prism copy.

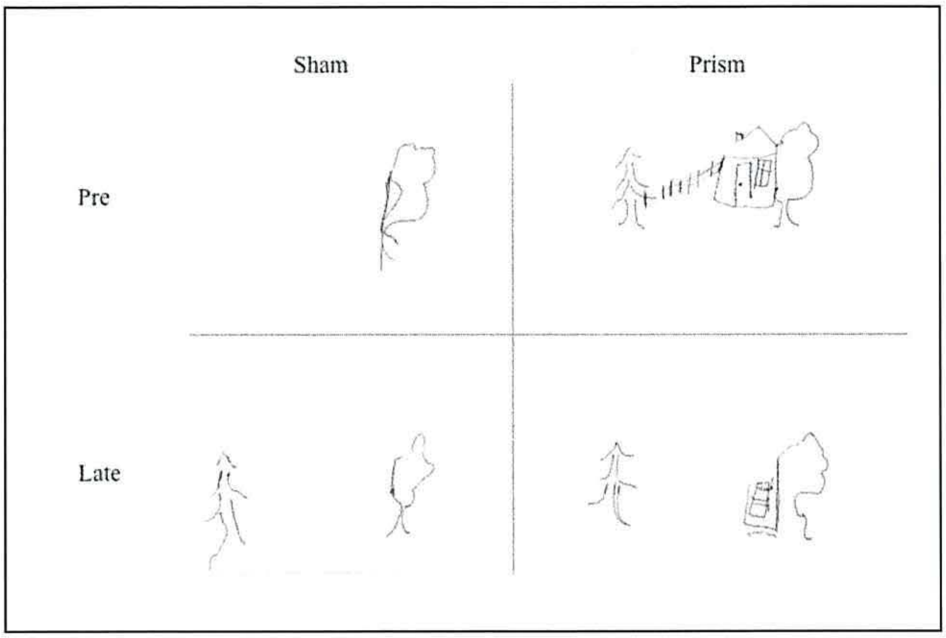

Figure 2.3. Copies of the Ogden figure made by JH immediately before and two hours after sham and prism treatment.

Constructional errors were present in TJ's copies of the Ogden scene (Figure 2.4). Copies made on the day of prism treatment were more complete than those made on the day of sham treatment, but there did not appear to be any difference across the pre-, post- and late-prism testing sessions on each day.

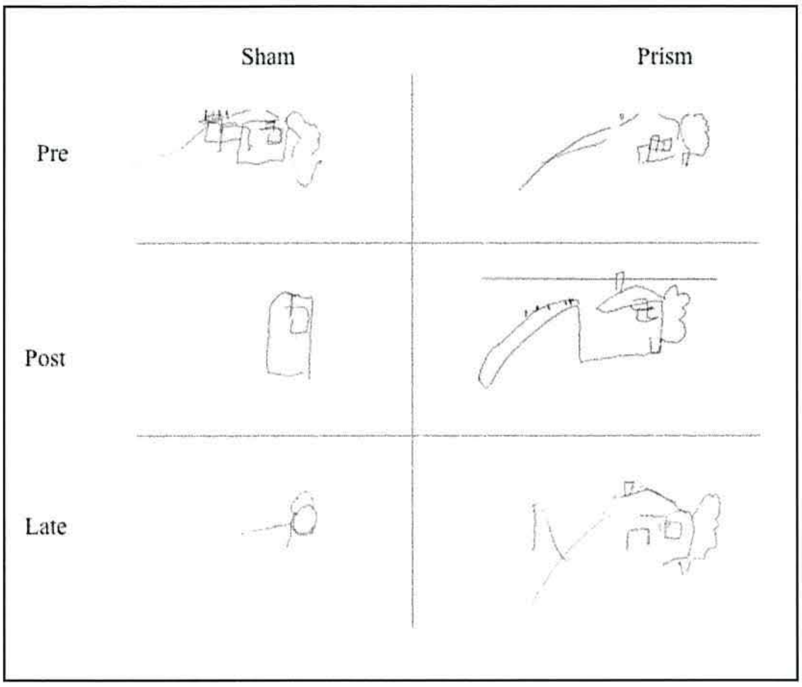

Figure 2.4. Copies of the Ogden scene made by TJ immediately before, immediately after and two hours after sham and prism treatment.

There was no change between sessions in the degree of spatial neglect exhibited in VP's copies of the Ogden scene, but object-based neglect decreased (Figure 2.4).

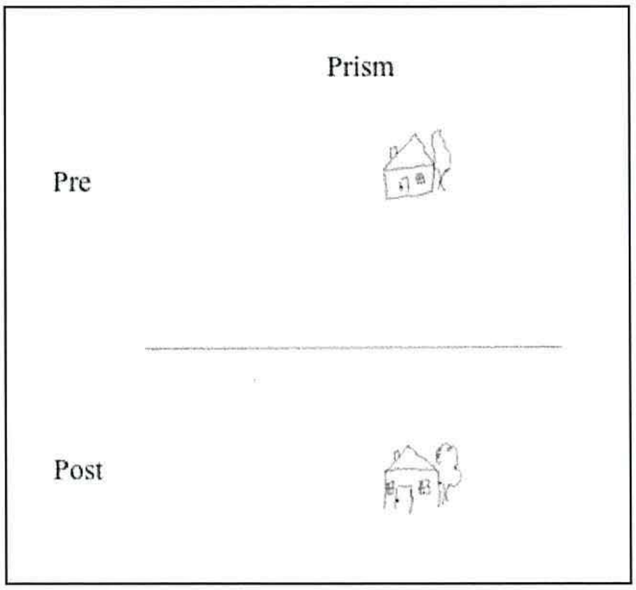

Figure 2.4. Copies of the Ogden scene made by VP immediately before and after prism treatment.

Line Bisection

For each of the ten patients who completed line bisection tests, bisection error proportional to line length were calculated according to the following formula (based on Schenkenberg et al., 1980):

$$\text{Error} = (\text{line length to left of bisection mark} - \text{true half-length}) * 100 / \text{true half length}$$

Using this formula, leftward errors are indicated by negative numbers. The average bisection errors for each patient are shown in Table 2.6. Paired-samples t-tests were performed to compare group pointing errors for the immediate and late post-tests to baseline for both the sham and prism sessions. No comparisons were significant for either treatment condition. ANOVAs on individual raw bisection errors for eight of the patients also revealed no error reduction following prism adaptation for any patient, with a main effect of session indicating a significant *increase* in pointing error across session for RR ($F(2,33)=5.1$, $p<0.05$).

Table 2.6. Bisection errors of ten patients.

		Sham			**Prism**		**Individual**
	Pre	**Post**	**Late**	**Pre**	**Post**	**Late**	**Analysis**
NB	36	31	50	33	27	22	n.s.
JH	0		-8	4		-2	n.s.
TPJ	36	60		22	36	46	n.s.
AM	11	5	3	-2	-1	1	n.s.
ER	2	1		10	6		n.s.
VW	3	6	10	11	15	4	n.s.
BP				47	48	50	n.s.
RR				10	17	25	Sig. *increase*
VP*				6	14		
AC*				19	18		
Average	15	21	14	16	20	21	

* Line bisection was measured with only three trials per session due to patient fatigue.

Cancellation tests

Eleven patients completed cancellation tests (Table 2.7). Chi-squares tests were performed on the total number of hits versus misses in each session summed across patients. The six patients who underwent sham treatment showed a significant increase in the number of targets cancelled between the pre-sham (31%) and post-sham (46%) sessions ($\chi^2(1)=8.4$, $p<0.005$). There was also a trend for a significantly greater proportion of targets cancelled in the late-sham (45%) testing session compared to baseline ($\chi^2(1)=3.2$, $p<0.01$). There was no difference in the proportion of targets cancelled immediately before (42%) and after (42%) prism treatment ($\chi^2(1)=0.5$, $p=0.48$). However, a greater proportion of targets were cancelled in the late-prism session (57%) than in both the pre-prism, ($\chi^2(1)=6.8$, $p<0.01$) and post-prism ($\chi^2(1)=4.0$, $p<0.05$) sessions.

Table 2.7. Percentage of targets cancelled in each session for eleven patients.

	Sham			**Prism**			**Individual Analyses**
	Pre	**Post**	**Late**	**Pre**	**Post**	**Late**	
NB	25	20		40	35	40	n.s.
JH	45		40	30		55	n.s.
TJ	10	15		15	30		n.s.
AM	43	77	40	74	80	86	Sig. increase between pre- and post-sham.
BP	9	17	11	17	11	17	n.s.
VW	50	100	90	90	90	100	Sig. increase between pre- and post-sham, then at ceiling for remaining sessions.
RR				43	51	43	n.s.
VP				57	54		n.s.
EW				34	29		
MW				54	69		
AC				11	9		
Average	**30**	**46**	**45**	**42**	**42**	**57**	

Chi-squares analyses on individual cancellation performance for each patient revealed that two patients, AM and VP, had significantly improved cancellation immediately after sham treatment. There were no further differences in the performance of individual patients across sessions (*ps*>0.05). Overall, the analyses suggest improved cancellation performance over time, independent of treatment condition.

Summary of performance changes. The group changes in open-loop pointing errors and neglect measures are summarised in Table 2.8. As there was considerable between-patient variability in the magnitude of the leftward adaptation after-effect (range=0.17° to 8.92°), Pearson's product-moment correlation coefficients were computed assessing the relationship between after-effect magnitude and pre- versus post-adaptation changes in line bisection and cancellation. There was no correlation between after-effect magnitude and change in bisection error (r=0.33, n=10, p=0.35), or between the after-effect and the change in targets cancelled (r=-0.12, n=11, p=0.72).

Table 2.8. Summary of group changes in open-loop pointing and neglect measures after sham and prism treatment.

	N	**Sham**		**Prism**	
		Pre vs Post	**Pre vs Late**	**Pre vs Post**	**Pre vs Late**
Open-loop pointing	12	No change	-	Sig. leftward shift	-
Copying	4	No patients improved (N=2)	JH improved (N=3)	VP improved (N=3)	NB improved, JH deteriorated (N=3)
Line Bisection	10	No change	No change	No change	No change
Cancellation	11	Sig. improvement	Trend for improvement	No change	Sig improvement

Discussion

A single session of prism adaptation induced a leftward after-effect of 3.19° in twelve patients. However there was no evidence of reduced symptoms as measured by three standard tests of neglect. The results contrast with a number of studies reporting improvements in standard clinical measures of neglect following single sessions of prism adaptation (Farnè et al., 2002; Humphreys, Watelet, & Riddoch, 2006; Pisella et al., 2002; Rode, Rossetti, & Boisson, 2001; Rossetti et al., 1998).

PART 2.2: LONGITUDINAL STUDIES OF THE USE OF PRISM ADAPTATION IN THE REHABILITATION OF FOUR PATIENTS WITH HEMISPATIAL NEGLECT

The following section outlines four case studies of patients with hemispatial neglect who underwent prism treatment. The effects of single adaptation sessions spaced several days apart (Case 1, Case 2) as well as sessions repeated over three (Case 1) or five (Case 3) days were examined. These include measures of the effects of prism adaptation on patients presenting with left spatial neglect with anosognosia (Case 2) and homonymous hemianopia (Case 3) as well as a patient with mild *right* spatial neglect following left hemisphere stroke (Case 4). In addition to standard neglect measures, the effects of prism adaptation on vertical and radial neglect (Case 1) and on spatial navigation (Case 3) were examined.

Unless otherwise indicated, procedures for adaptation and after-effect measurement were identical to those described in Part 2.1 above.

Case 1: A young woman with hemispatial neglect following subarrachnoid haemorrhage.

NB, a 27-year old, right-handed woman, reported to hospital suffering from a severe headache with a sudden onset. There was no neurological deficit. A CT scan revealed blood in the basal cisterns and lateral and interhemispheric fissue. Lumbar puncture revealed bloody spinal fluid confirming the diagnosis of subarrachnoid haemorrhage. MR angiography the following day demonstrated a posterior communicating artery aneurysm. Endovascular coiling was performed three days after admission, during which the aneurysm re-bled. Vasospasm resulted in hypo-perfusion of most of the right hemisphere, revealed by perfusion MRI, with multifocal stroke in temporo-parietal cortex, the right anterior thalamus, anterior cerebral artery territory and watershed territories of the right hemisphere including intraparietal cortex and dorsolateral prefrontal cortex.

Neurological examination of NB one month after admission revealed left hemiplegia (with some movement in the left hip and knee), memory impairment, left visual neglect and left tactile neglect. There was no hemianopia. Formal neuropsychological testing confirmed that NB suffered from hemispatial neglect and was an appropriate candidate for prism adaptation (Table 2.2).

General Design

Neglect was measured in 56 testing sessions spanning seven weeks. During this time NB underwent prism adaptation nine times and sham adaptation four times, with ninety pointing movements in each session. In each testing session neglect was assessed using at least two of the following classic measures of neglect: figure copying, line bisection and cancellation.

Testing sessions included pre-, post- and late-testing sessions on adaptation days as well as individual testing sessions on days where no adaptation was administered. The effect of prism adaptation compared to sham adaptation on neglect symptoms was examined by comparing the pooled results of tests administered on sham and prism treatment days across the entire rehabilitation period. In addition, two separate longitudinal studies were conducted to test specific hypotheses about the affects of prism adaptation on neglect symptoms. In week one of the rehabilitation program a multiple baselines study commenced with sixteen testing sessions spanning ten days to examine the affects of prism adaptation on horizontal, vertical and radial components of neglect. At the beginning of week three a second study commenced with fourteen testing sessions spanning ten days to examine changes in neglect symptoms with repeated prism adaptation sessions.

As bisection tests are usually normalised to older control groups, the bisection tests were also administered to a group of ten age-matched controls to provide an appropriate comparison group for NB. However established neglect cut-offs were used for the cancellation tests as healthy controls perform at ceiling in these tasks.

1. Comparison of the effects of sham adaptation and prism adaptation, pooled across days.

Comparisons were made between the results of copying, line bisection and cancellation tests in sessions before and after sham treatment (Days 3, 12, 21 and 48) and adaptation to 10° or 15° rightward prismatic shifts (Days 4, 6, 13, 22, 34 and 49; Table 2.9). Since the effects of prism adaptation on neglect has frequently been shown to last as much as twenty-four hours after treatment, only days for which prism adaptation had not been administered on the previous day were included. Pointing error, bisection error and the number of targets cancelled were pooled across days for pre-, post- and late-testing sessions for sham and prism adaptation.

Table 2.9. Treatment and testing details for NB.

Day	Condition	Late-test?	Copying	Line Bisection	Cancellation
3	Sham	Y	Ogden	Schenkenberg	BalloonsA BalloonsB Bells
4	10° Prism	Y	Ogden	Schenkenberg	BalloonsA BalloonsB Bells
6	15° Prism	Y	Ogden	Schenkenberg	BalloonsA
12	Sham	Y	Gainotti	Schenkenberg	Bells BalloonsB
13	15° Prism	Y	Gainotti	Schenkenberg	BalloonsB
21	Sham	N	-	4 x BIT	Stars
22	10° Prism	N	-	4 x BIT	Stars
34	15° Prism	N	Ogden	Schenkenberg	-
48	Sham	N	-	Schenkenberg	BalloonsA BalloonsB
49	15° Prism	N	-	Schenkenberg	BalloonsA BalloonsB

Results

Prism adaptation. A Treatment (sham, prism) x Session (pre, post) repeated-measures ANOVA revealed a significant two-way interaction. Pointing error was unchanged following sham treatment but shifted leftward by 5.44° following prism treatment ($F(1,236)=12.3, p<0.005$).

Copying. NB's figure copying for the first sham and prism treatment sessions were discussed in the group analysis (Figure 2.2). Copying performance in subsequent sessions was at ceiling.

Line Bisection. A Treatment (sham, prism) x Session (pre, post, late) repeated-measures ANOVA revealed significantly larger overall bisection errors for the sham testing sessions (*M*=18.80, *SEM*=2.22) than the prism testing sessions (*M*=13.08, *SEM*=1.80); $F(1,388)=124.50$, $p<0.05$. There was also a main effect of Session ($F(2,388)=3436.53$, $p<0.01$), reflecting larger bisection errors for late-testing sessions (*M*=21.82, *SEM*=3.02) compared to pre-treatment (*M*=14.00, *SEM*=1.99; $t(232)=2.17$, $p<0.05$) and post-treatment (*M*=10.20, *SEM*=2.09; $t(230)=2.12$, $p<0.005$). Bisection errors in the pre- and post-treatment sessions were not significantly different ($t(320)=1.32$, $p=0.19$). There was no significant Treatment x Session interaction, indicating no differential effects of sham and prism treatment on bisection errors.

Cancellation. Chi-squares analyses on the number of hits compared to misses across all cancellation tests revealed that there was no difference in the number of targets cancelled immediately before (84/180) and after sham adaptation (79/180), $\chi^2(1)=0.15$, $p=0.70$. In contrast, the proportion of targets cancelled immediately after prism treatment (103/215) was significantly greater than before prism treatment (85/215), $\chi^2(1)=25.16$, $p<0.001$. For both sham treatment and prism treatment a smaller proportion of targets were cancelled in the late-test (20/90 and 41/150 respectively) compared to the pre-treatment sessions ($\chi^2(1) = 21.0$ and 5.51 respectively, $p<0.05$).

Discussion

Open-loop pointing errors were shifted significantly leftward by prism adaptation. NB's cancellation performance was significantly better immediately following prism treatment but not sham treatment, while bisection errors were unchanged in immediate post-tests following either treatment types. Cancellation and bisection performance were significantly worse in the late-tests compared to baseline for both sham and prism treatment. This observation is in contrast with previous studies that have reported improvements that were still evident, and were even larger, two-hours following prism adaptation. In the case of NB all late-test measures took place in the first 13 days of rehabilitation. The deterioration in her neglect symptoms in the late-test sessions may have been due to fatigue due to either the early stage of her recovery or as a direct result of the exertions of the morning testing and treatment sessions. Overall, the results suggest that prism adaptation stimulated only modest, short-lived improvements in NB's neglect symptoms.

2. The effects of single sessions of prism adaptation on horizontal, vertical and radial components of neglect.

Although the defining feature of neglect is the horizontal spatial bias, patients can also show systematic deficits in the vertical and radial dimensions. Neglect of inferior space has been demonstrated by patients in several studies as upward errors in vertical line bisection (Ergun-Marterer, Ergun, Mentes, & Oder, 2001; Kori & Geldmacher, 1999), a greater number of omissions in the lower left quadrant of cancellation tasks (Halligan & Marshall, 1989; Pitzalis, Spinelli, & Zoccolotti, 1997), and higher latencies for covert orienting to lower visual field targets (Ladavas, Carletti, & Gori, 1994). Cappilletti, Freeman and Cipolotti (2007) asked five patients with neglect to guess, without calculating, the floor falling halfway between two numerically indicated floors of a building (for example, floors 3 and 7). Three of the patients consistently erred higher than the true middle number, suggesting vertical representational neglect. Patients with left spatial neglect also bisect radial lines distal to their midpoint, indicating neglect of proximal space (Halligan & Marshall, 1993; Kori & Geldmacher, 1999; Marshall & Halligan, 1990)

While the benefits of prism adaptation generalise to a wide variety of tests, including some in non-visual modalities, improvements have only been demonstrated on the horizontal plane: that is, on the same dimension as that of the visuo-motor realignment induced by prism adaptation. To examine whether prism adaptation can improve spatial neglect on dimensions that are orthogonal to the plane of the adaptation after-effect, a multiple baselines study was conducted with NB to examine whether prism treatment can reduce vertical and radial components of neglect in addition to reducing the leftward horizontal bias.

Procedure

Neglect was measured in sixteen testing sessions spanning ten days using the Ogden copying task, subtest A of the Balloons Test, and three versions of the Schenkenberg line bisection test that were aligned horizontally, vertically and radially with respect to the patient. Effects of neutral prisms (sham, Day 4), 10° rightward-shifting prisms (10°R, Day 5) and 15° rightward-shifting prisms (15°R, Day 7) were examined, with 90 pointing movements in each exposure period.

Results

Prism adaptation. A repeated-measures ANOVA of pointing error with two factors, treatment (sham, 10°R and 15°R) x session (pre and post) revealed a significant two-way interaction ($F(2,66)=22.06, p<0.001$). Pointing error shifted 2.7° *rightward* following sham adaptation ($t(11)=4.3$ $p<0.005$), was unchanged by adaptation to 10° prisms ($t(11)=0.08, p=0.94$), and shifted 4.4° leftward following adaptation to 15° prisms ($t(11)=6.03, p<0.001$).

Ogden copying task. Although NB completed the Ogden copying task in each testing session, for the sake of brevity only those that she completed on the three days that she underwent adaptation (sham, 10°R and 15°R) are considered here. Figure 2.6 shows the copies of the Ogden scene that were made by NB immediately before adaptation (pre), immediately after adaptation (post) and 2 hours after adaptation (late) on these days.

NB showed aspects of both space- and object-based neglect in each of the copies made on the day of sham adaptation, neglecting entire objects on the left side of the scene as well as left-sided details of copied objects. Before adaptation to 10°R prisms she showed space- and object-based neglect to a similar extent as in the copies made on the day of sham treatment. In the immediate post-test, however, space-based neglect had decreased and there was no object-based neglect. This improvement was no longer apparent in the 10°R late-test. The pre-prism2 copying performance showed an improvement in space-based and object-based neglect compared to the previous days, with some constructional apraxia. There was no improvement in the immediate post-test, but in the late-test NB drew a complete copy of the figure with no constructional errors. Copying performance in sessions from this point onwards was at ceiling.

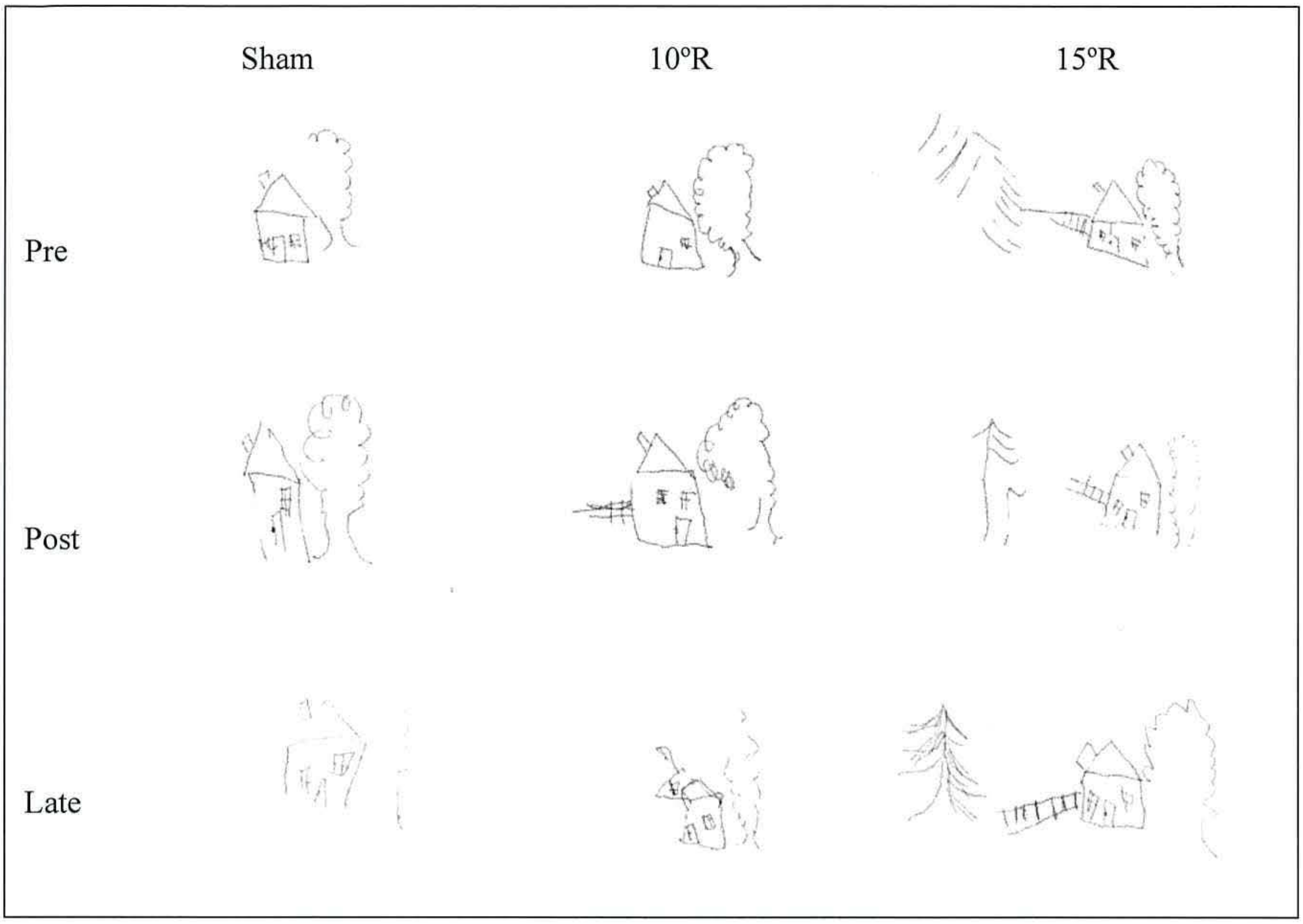

Figure 2.6. Copies made by NB in the three different testing sessions on each of the treatment days.

Balloons Test (Subtest A). Figure 2.7 shows NB's cancellation performance for Subtest A of the Balloons Test across sessions. Unfortunately the Balloons test was not completed in some early sessions due to patient fatigue. This precluded analysis of baseline performance compared to post-sham performance. The number of hits and misses were summed across three stages: pre-prism (sham pre, sham post, and 10° pre), post-prism1 (10°R post, 10°R late, Day 6, 15°R pre) and post-prism2 (15°R post, 15°R late, day 8, day9, day10 and day11). There was no change in cancellation performance after adaptation to 10°R prism (Pre-prism=14/60 vs post-prism1=26/80, $\chi^2(1)=1.41$, $p=0.235$). However, the proportion of targets cancelled was significantly greater following adaptation to 15°R prisms (60/120; $\chi^2(1)=6.00$, $p<0.05$).

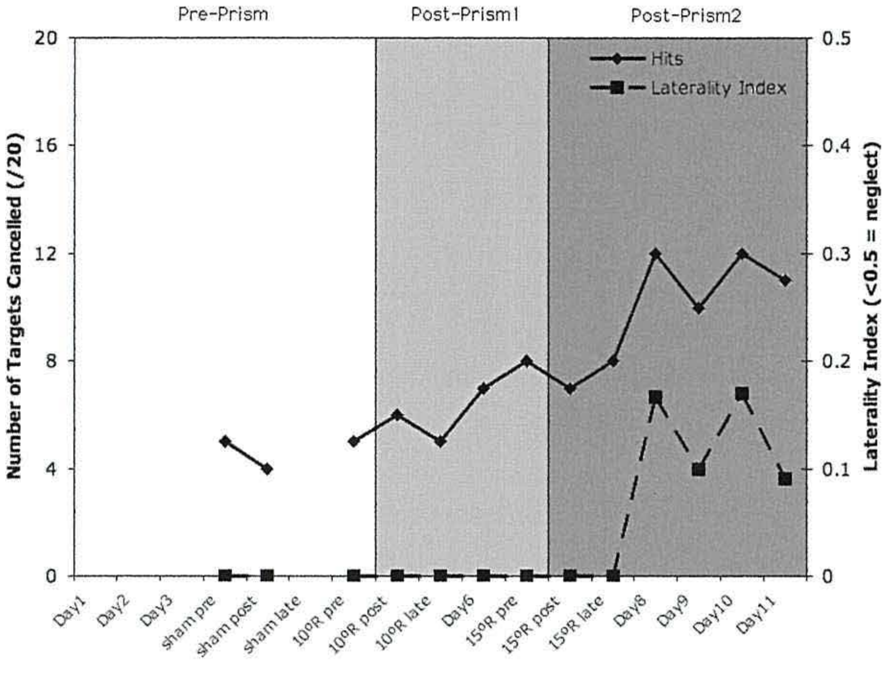

Figure 2.7. Number of targets cancelled and laterality index (i.e., number of left-sided targets cancelled as a percentage of all targets cancelled) for NB's performance on subtest A of the Balloons Cancellation task across sessions.

Line Bisection. Bisection error proportional to line length was calculated for each line, with negative numbers indicating leftward, downward and proximal errors. For each test these errors were also expressed proportional to the percentage of lines that were bisected versus missed. Figure 2.8 shows both proportional bisection errors and error-by-accuracy across sessions for each line orientation, along with the upper and lower bounds of the 95% confidence interval around the bisection errors for the control group. Analyses of both the proportional bisection errors and error-by-accuracy gave identical outcomes, therefore only the proportional bisection errors are discussed here.

Sessions were grouped into four stages: baseline, post-sham, post-prism1 and post-prism2. One-way ANOVAs revealed significant main effects of stage for horizontal line bisection ($F(1,3)=157.68, p<0.05$), and radial line bisection ($F(1,3)=14.1$, $p<0.05$) and a trend for a main effect of stage for vertical line bisection ($F(1,3)=27.43, p=0.081$). These reflected a significant *increase* in magnitude of horizontal bisection errors from 19.5 to 39.7 between the baseline and post-sham sessions $t(97)=2.98, p<0.01$), and no change in vertical and radial bisection errors between the same sessions ($ps>0.05$).

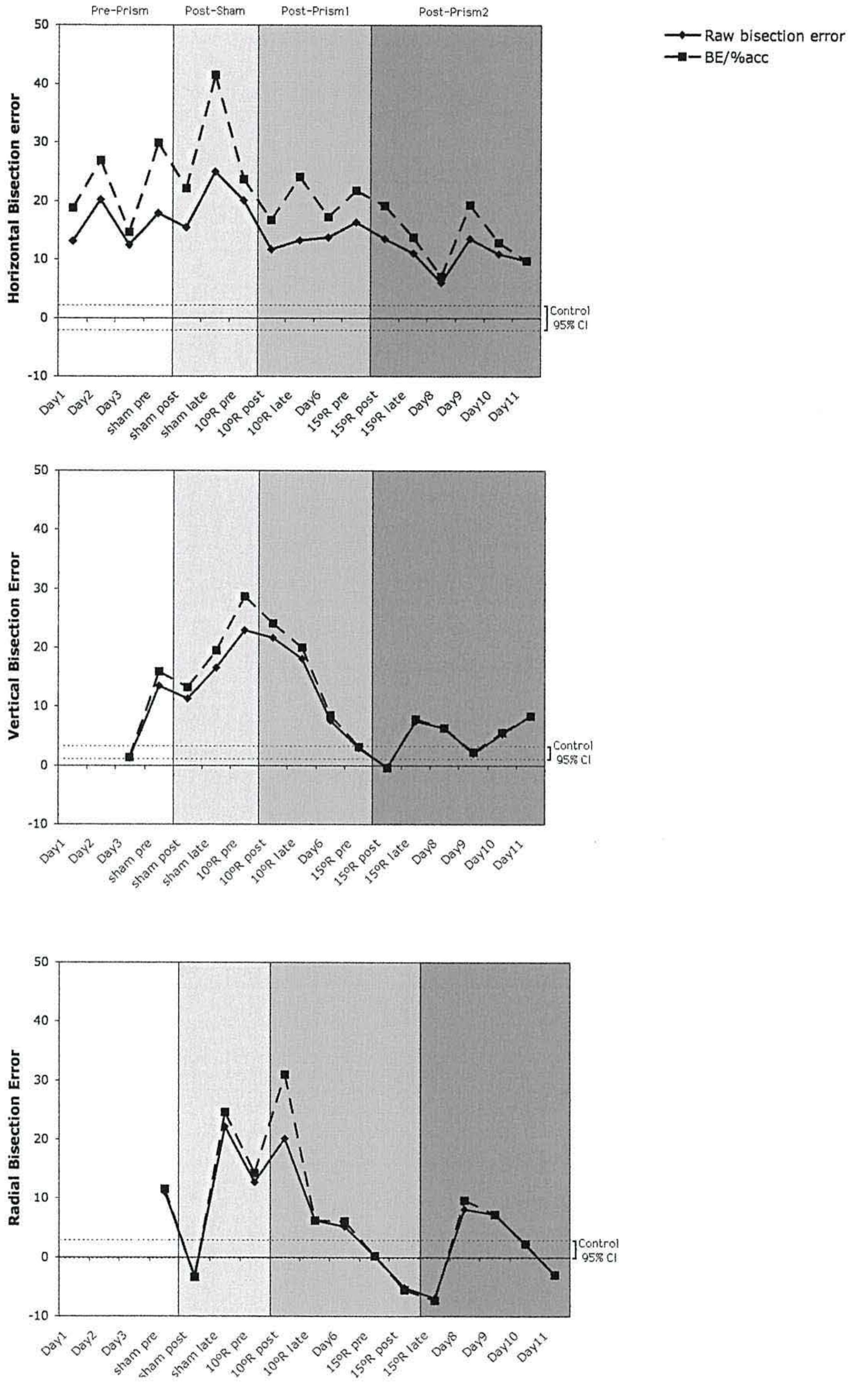

Figure 2.8. Proportional bisection errors (solid line) and errors-by-accuracy (dashed line) for horizontal (top), vertical (middle) and radial (bottom) lines compared to control participants.

For all three line orientations there was no difference between bisection errors in the post-sham and post-prism1 sessions. Comparison of the post-prism1 and post-prism2 stages showed that following adaptation to 15°R prisms there was no improvement in horizontal bisection errors (*ps*>0.05) but there was a significant reduction in vertical bisection errors ($t(184)=8.74$, $p<0.05$) and a trend for a reduction in radial bisection errors ($t(181)=6.8$, $p=0.073$). In the post-prism2 testing stage both vertical and radial bisection errors overlapped the 95% confidence intervals around bisection errors for the control group.

To re-examine the effect of prism adaptation on horizontal line bisection, NB completed daily horizontal line bisection tasks over a further week (Days 12-18), during which she underwent another session of adaptation to neutral prisms (Day 12) and to 15° rightward shifting prisms (Day 13). Once again, t-tests revealed no change in horizontal bisection errors following sham or prism treatment (*ps*>0.05).

No improvements in performance were observed following sham adaptation. Exposure to 10° rightward-shifting prisms resulted in no change in NB's visual open-loop pointing errors, suggesting she did not adapt to the prismatic shift. Consistent with this, there was also no difference in line bisection and cancellation performance in the post-sham and post-prism1 conditions, although there was a small improvement in copying performance that was not sustained to the late-test. In contrast, the significant leftward pointing after-effect that followed exposure to 15° rightward-shifting prisms was accompanied by reduced vertical and radial bisection errors, and an increase in targets cancelled.

Discussion

As the present study was conducted within the first two weeks of rehabilitation, spontaneous recovery cannot be completely excluded as a cause of the observed improvements. However the correspondence between improved test performance and significant adaptive realignment to 15° prisms somewhat counterbalances this argument.

Previous research has demonstrated that adaptation to leftward-shifting prisms improved left spatial neglect in peripersonal and extrapersonal space, as well as personal neglect (Frassinetti et al, 2002). The significant reduction in NB's vertical errors, and the trend for reduced radial errors, that followed treatment with 15° prisms may provide further evidence that prism adaptation improves neglect symptoms at a level accessing multiple reference frames, including those orthogonal to the dimension of the adaptation after-effect. Curiously, however, NB's horizontal bisection errors did not improve following prism adaptation, and in fact increased between baseline and sham treatment. Also, it is unclear that NBs vertical and radial bisection errors were significantly different to controls' at baseline: for each of these line orientations her errors in one baseline session were within the 95% confidence interval around the mean bisection error of the control participants. The clinical importance of her improvements in these dimensions are therefore unclear.

3. Cumulative effects of daily adaptation sessions

While the benefits of a single session of prism adaptation can be maintained for 24 hours, and even as much as one-week, patients with chronic neglect who received two weeks of twice-daily adaptation sessions showed improvements compared to controls that were still apparent one, six and twelve months after the end of treatment (Frassinetti et al., 2002; Serino et al., 2005; Serino et al., 2009; Serino et al., 2007). Nys and colleagues suggested that an intermediate treatment period of four daily sessions may be more manageable for neglect patients in the acute stages of recovery. In line with this, the effects of three consecutive days of prism treatment on NB's neglect symptoms were examined, with neglect measures administered before and after each treatment to examine for any cumulative benefits.

Procedure

In fourteen sessions spanning twelve days (Days 19-30) neglect was assessed using straight ahead pointing, the stars cancellation subtest of the BIT, and a modified version of the line bisection subtest of the BIT in which the patient bisected four copies of the test, or a total of 12 lines per session. NB underwent one session of sham adaptation (Day 20) followed by three consecutive days of adaptation to 10° rightward shifting prisms (Days 21-22).

Results

Prism adaptation. NB's open-loop and straight ahead pointing errors are shown in Figure 2.9. A repeated-measures ANOVA of open-loop pointing error with two factors, Treatment (sham, prism1, prism2, and prism3) and Session (pre, post) revealed significant Treatment x Session interaction ($F(3,33)=22.4, p<0.001$). T-tests revealed that pointing error shifted significantly leftward from 8.8° to 2.2° following *sham* adaptation ($t(11)=9.5, p<0.001$). The first day of prism treatment resulted in no significant change in pointing error (4.3° compared to 3.3°; $p=0.146$). However significant leftward shifts in pointing error were found for the second and third prism treatment days (from 6.5° to 5.1°, $t(11)=1.93, p<0.05$; and from 6.8° to 3.3°, $t(11)=7.5, p<0.001$ respectively).

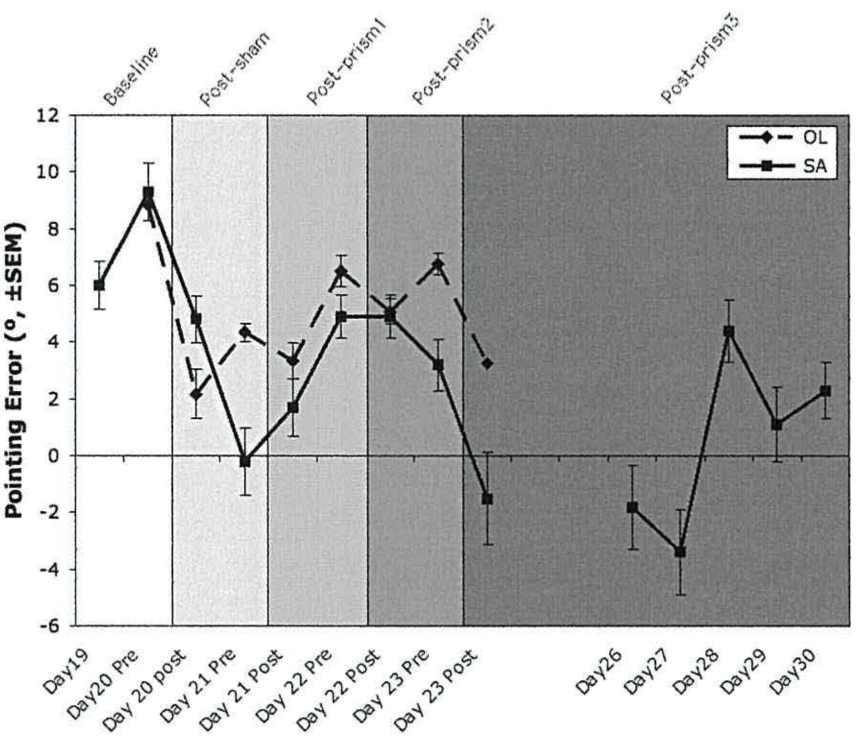

Figure 2.9. NB's open-loop and straight ahead pointing errors across sessions.

Straight-ahead pointing. Changes in straight ahead pointing were similar to those shown for visual target pointing. That is, there were significant leftward shifts in pointing error between the baseline and post-sham stages (from 7.7° to 2.3°; $t(38)=4.57, p<0.001$), and between post-prism2 and post-prism3 (from 2.6° to -2.2°; $t(178)=3.36, p<0.005$), but no change between the post-sham and post-prism1 stages (2.3° compared to 3.3°, $t(38)=0.87, p=0.39$). Straight ahead pointing shifted *rightward*, in the opposite direction to visual target pointing, following the third prism treatment (from -2.3° to 2.6°, $t(58)=4.38$ $p<0.001$).

A regression analysis comparing visual target pointing and straight ahead pointing in the pre- and post-adaptation sessions on the four treatment days showed a significant correlation ($r=0.65$, $n=8$, $p<0.05$), with larger errors for visual target pointing ($M=5.0^\circ$, $SEM=0.30$) than straight ahead pointing ($M=3.4^\circ$, $SEM=0.5$), $t(174)=1.64$, $p<0.005$.

Line bisection. In all sessions mean bisection errors were outside the 95% confidence interval around the mean for the control group (Figure 2.10). A one-way ANOVA revealed no main effect of Stage ($ps>0.05$), therefore bisection error did not significantly reduce with prism treatment. There was also no correlation between bisection error and visual target pointing ($r=0.30$, $n=8$, $p=0.47$).

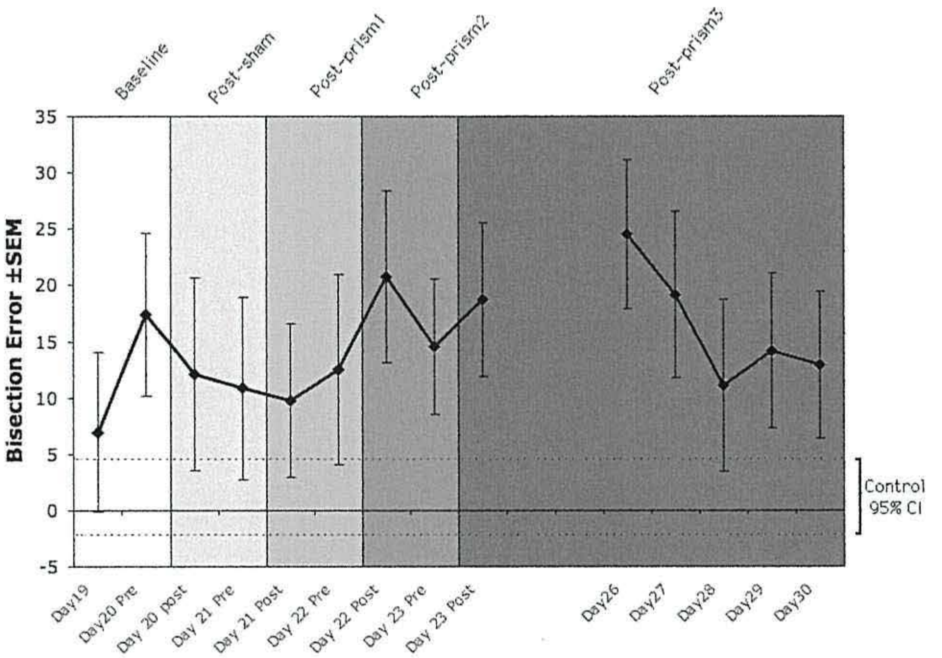

Figure 2.10. NB's line bisection errors across sessions.

Stars Cancellation Test. Figure 2.11 shows the number of hits and the laterality indices for NB's stars cancellation performance across sessions. Chi-squares tests on the proportion of hits in each of the five stages revealed that there was no significant change in the number of bells cancelled between baseline (78/108) and sham adaptation (80/108), $ps>0.05$. However, significantly more bells were cancelled (101/108) following the first prism adaptation session ($\chi^2(1)=15.04$, $p<0.001$), with performance reaching ceiling levels both the number of targets cancelled and the laterality indices were above the neglect cut-offs for the remainder of the testing period. The number of targets cancelled did not correlate with visual target pointing errors (*r*=0.46, *n*=8, *p*=0.47).

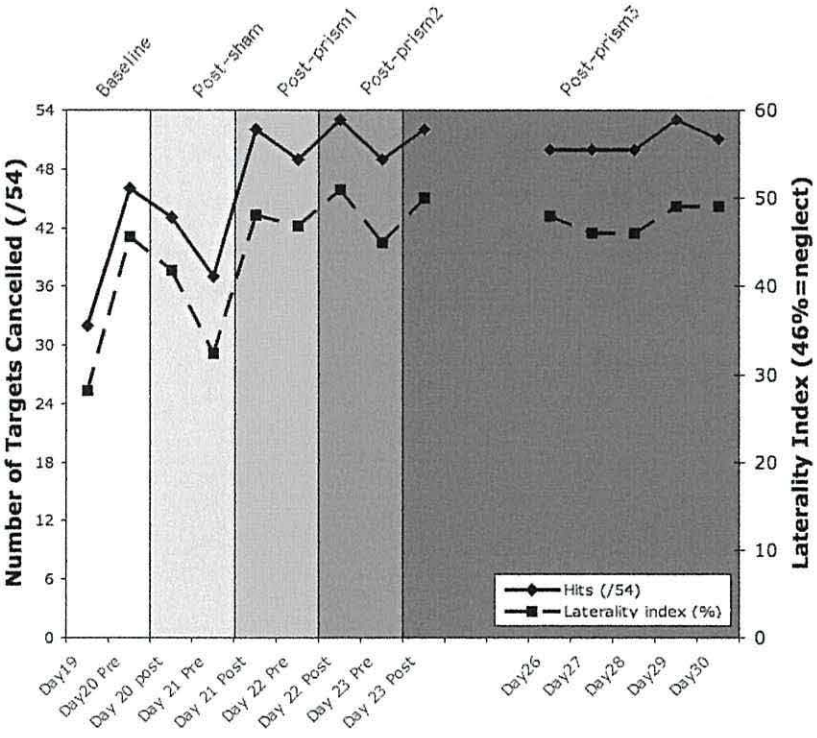

Figure 2.11. The number of targets cancelled by NB (hits) and laterality indices (i.e., number of left-sided targets cancelled as a percentage of all targets cancelled) across sessions for the star cancellation test.

Discussion

The results do not support an improvement in neglect following three daily sessions of adaptation to 10° prisms, but instead show fluctuations in performance across sessions. There was no significant change in open-loop pointing error after the first prism treatment session, suggesting that adaptive realignment did not occur on this day. Unusually, sham treatment resulted in a significant leftward shift in open-loop pointing error. The cause of this is unclear, and the change may throw doubt on whether the leftward pointing after-effects observed after the second and third treatment sessions reflected a true visuo-motor realignment or resulted from the same unknown mechanism that caused the shift in pointing errors on the day of sham treatment. However, of the four sham treatment sessions undergone by NB during her rehabilitation period (see part 1 of this case report), this was the only one for which she showed a significant leftward shift in pointing.

Prism adaptation usually induces larger shifts in the subjective straight ahead than the visual open-loop pointing errors of patients with neglect (Sarri and colleagues, 2008). This is because while both can be changed due to the visuo-motor after-effect, shifts in straight ahead pointing can also occur due to improvements in the distorted egocentric reference frame that is exhibited by many neglect patients. NB's pointing errors for subjective straight ahead pointing correlated with visual open-loop pointing, however visual open-loop errors were the larger of the two. One possible explanation for this would be that NB had a normal perception of proprioceptive straight ahead before prism adaptation. However, straight ahead pointing errors were significantly right of midline (Figure 2.9), suggesting that, rather, NB made pathologically biased pointing errors on *both* visual open-loop pointing and subjective straight ahead pointing. This conflicts with evidence that patients with neglect generally show a relatively preserved ability to point to visual targets, even when their pointing arm is hidden from view (Jackson, Newport, Husain, Harvey, & Hindle, 2000; Rossit, Malhotra, Muir, Reeves, Duncan, Livingstone et al., 2009). The correlation between the two measures, and their relative magnitudes, also suggests that the change in straight ahead pointing over time was predominantly due to visuo-motor after effect rather than changes in biased egocentric reference.

NB's bisection errors did not change significantly across sessions. She did, however, show improved performance on the stars cancellation task coinciding with the first prism treatment, with no change after sham treatment. As NB showed no significant after-effect for this session, and her task performance was near ceiling at baseline, it is unclear whether the change in performance represents an improvement due to prism adaptation. In summary, there was no evidence of a cumulative beneficial effect of three daily sessions of prism adaptation on NB's neglect symptoms.

Overview and Patient Outcome

An assessment 68 days after the beginning of the rehabilitation period showed that NB's neglect symptoms had largely recovered. She drew a complete clock and the full copy of the Ogden figure. Her bisection bias on the Schenkenberg task was within normal limits (2.4% rightward error), as was her performance on the Bells cancellation task (31/35 targets cancelled, lateralisation score=50%). The results of testing throughout NB's rehabilitation program provide some evidence that prism adaptation improved her cancellation performance and reduced bisection errors in the vertical and radial dimensions. Only modest benefits were observed, however, and it is possible that these were due to spontaneous recovery independent of prism adaptation. It is therefore unclear whether prism adaptation contributed NB's recovery.

Case 2: An artist suffering hemispatial neglect and anosognosia following stroke of the MCA territory.

In as many as 56% of patients with neglect, rehabilitation is further hindered by a lack of awareness of motor or sensory deficits: anosognosia (Berti et al., 2005). One advantage of bottom-up neglect treatments such as prism adaptation compared to top-down methods such as visual scanning training is that they do not require the patient to be aware of their disability. Prism adaptation may therefore be especially important for treating patients in whom physical and cognitive rehabilitation is challenged by anosognosia. In fact, there is anecdotal evidence for sudden recovery of awareness of left sided hemiparesis following prism treatment (Pisella et al., 2002). A longitudinal study was performed to examine the affect of prism adaptation on neglect symptoms in a patient with anosognosia.

Methods

Patient

AC, a 71 year-old right-handed artist, was admitted to hospital after collapsing while walking in the mountains. He presented with left sided weakness, dense sensory loss, confusion and slurred speech. A CT scan showed a hypodense lesion in the right insula extending into the parietal and temporal lobes, consistent with a stroke of the right MCA territory. Neurological examination two days after admission revealed dense weakness and sensory loss in the left upper limb, and weakness in the left lower limb. While he recognised his left hand as being his, he showed no insight into his disability (3/3 on the Bisiach scale) and a diagnosis of anosognosia was made. He also demonstrated pusher syndrome: the tendency to actively push away from the ipsilesional side of the body, leading to postural imbalance. A neuropsychological assessment performed fourteen days after admission confirmed that AC suffered from hemispatial neglect and was an appropriate candidate for prism adaptation (Table 2.2).

Design and Procedure

AC underwent adaptation to 15° rightward-shifting prisms eleven times over three months following his initial assessment. No sham adaptation was performed. Neglect symptoms were measured immediately before and after adaptation with at least two of the following tests: copying (Ogden or Gainotti), the line bisection subtest of the BIT (3 lines per session) and cancellation (Balloons Subtest B or Bells test). Anosognosia was also monitored using structured interview questions (Table 2.10).

Table 2.10. Structured interview (Anderson & Tranel, 1989)

Description	**Examples**
General questions about reason for being in hospital	'Why are you in hospital?' 'Can you tell me what happened to you?'
General questions about patient's health	'How are you?' 'Are you having any problems with anything?'
General question about patient's deficit	'Is there anything wrong with your arms or legs?' 'Can you walk?'
Specific questions about patient's deficit	'Are you having any difficulty moving your arm or leg on this side?'
Patient is asked to move their arm or leg	

Results

Prism adaptation

Pre- and post-adaptation pointing errors for each treatment session are shown in Table 2.11. A paired-samples t-test of pointing errors pooled across day confirmed a significant average shift 2.0° leftward after prism adaptation ($t(7)=5.2$, $p<0.005$). On all but three days visual target pointing was measured with only three trials, therefore analyses of pointing errors on each individual day were not performed.

Table 2.11. AC's pointing errors before and after each session of prism adaptation.

Day	**Pre**	**Post**	**Shift**
1	2.7	-1	-4
3	Not measured	Not measured	
11	1	-1	-2
44	0.3	-2.7	-3.0
48	-2.0	-4.7	-2.7
54	Not measured	Not measured	
56	0.2	-0.4	-0.6
69	-2.2	-4.0	-1.8
80	0.0	-1.1	-1.1
86	2.9	Not measured	
96	-1.0	-1.9	-0.9
Average	0.2	-2.1	-2.2
SEM	0.60	0.66	0.36

Copying tasks

Figure 2.12 shows the copies made by AC immediately before and after prism adaptation on eight different days. On four days he elaborated on the copying stimulus, for example by adding apples to the tree (day 1, day 52) or curtains to the window (day 11). There are some constructional errors in the day 11 post-test. AC copied more of the picture following prism adaptation on four days (day 44, day 69, day 74 and day 87). On day1 and day 52 he copied less of the picture following prism adaptation. Copying performance was unchanged by prism adaptation on day 11, and on day 80 performance was at ceiling in both sessions.

In the pre-adaptation copying task on day 52 AC drew twice as many windows in his copy of the house than are shown in the Ogden figure. While this may be an elaboration, it may also reflect a bias for preferential processing of the local elements of the figure over the global configuration: the local processing bias. This is relevant because, at eleven months post-stroke, testing of AC using a computerised reaction time (RT) task revealed a local processing bias when identifying global or local levels of hierarchical stimuli, which reduced following adaptation to rightward-shifting prisms (Chapter 4).

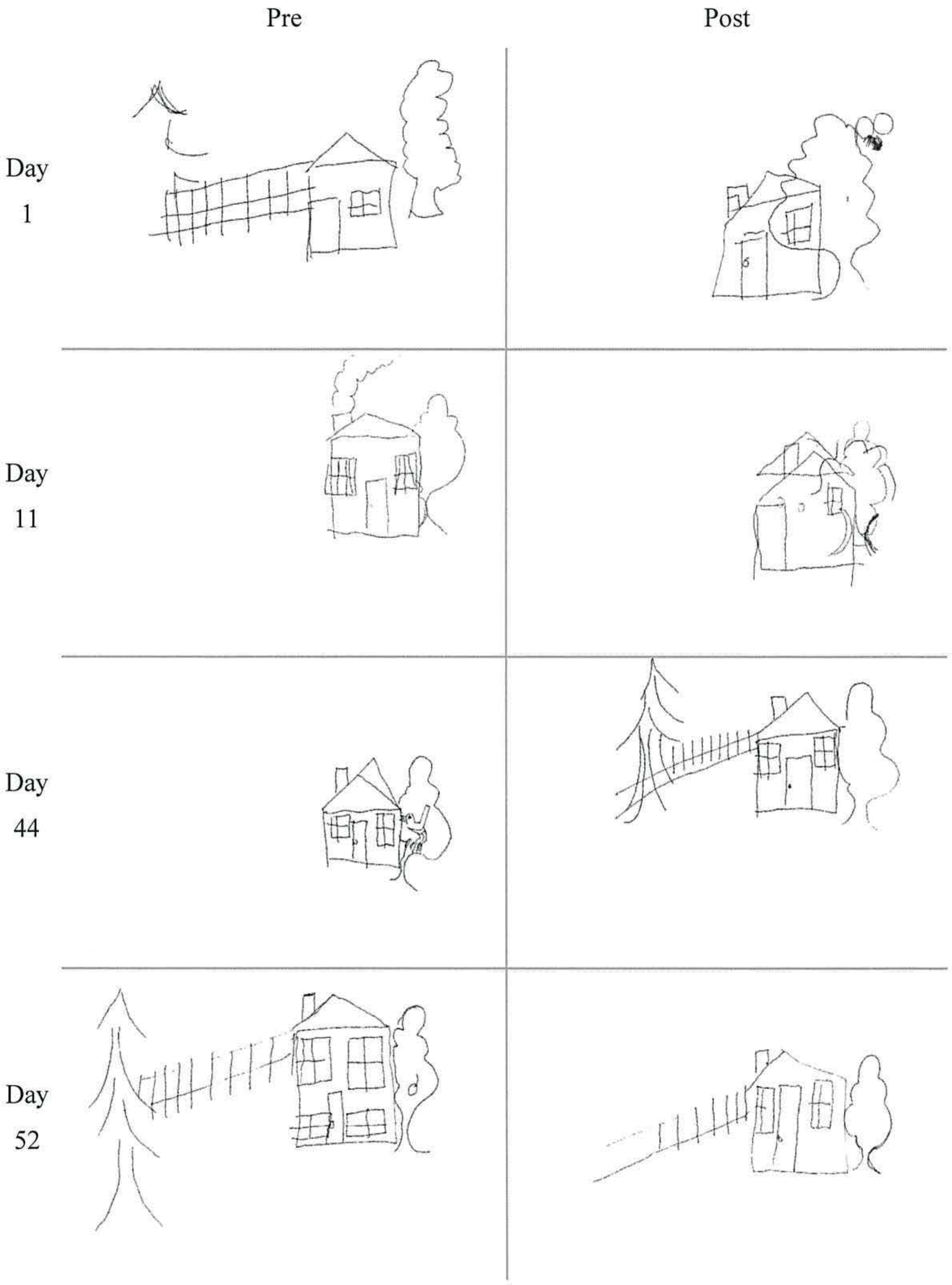

Figure 2.21B. AC's copying performance before and after prism adaptation on four days in the first part of his rehabilitation program.

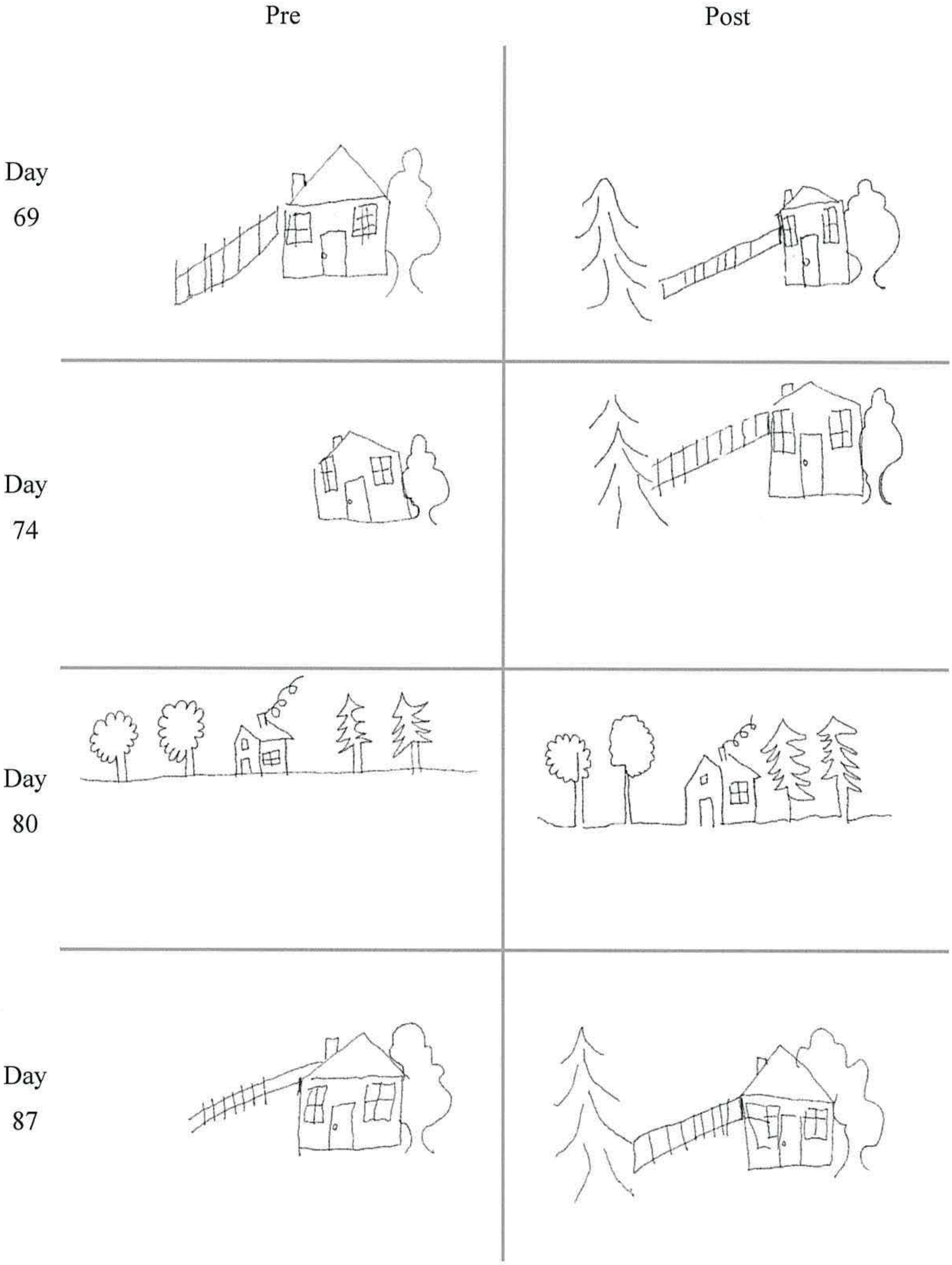

Figure 2.12B. AC's copying performance before and after prism treatment on four days towards later part of his rehabilitation program.

Line Bisection

Mean errors for the four days on which AC was tested on line bisection are shown in Table 2.12. The bisection errors for pre- and post-adaptation testing were pooled across days for analysis. There was no significant difference between mean bisection errors before (*M*=11.3, *SEM*=5.4) and after (*M*=17.7, *SEM*=3.4) prism adaptation ($t(11)=1.7$, $p=0.11$). Analysis of changes in bisection errors across individual sessions was precluded by the low number of lines per session (N=3).

Table 2.12. Average bisection errors made by AC before and after prism adaptation on four days.

Day	Pre	Post	Shift
11	21	11	-10
44	19	18	-1
69	14	22	+8
96	-6	9	+15
Average	12	15	+3

Cancellation

The bells cancellation test was administered on seven days (days 1, 3, 11, 44, 56, 69 and 80, Table 2.13). A chi-squares analysis of the number of targets cancelled pooled over day revealed no significant difference between the pre- and post-tests (40/245 and 32/245 respectively, $\chi^2(1)=1.0$, p=0.307). Individual analyses of targets cancelled before and after prism adaptation on each day also revealed no significant change (*ps*>0.05).

AC also completed subtest B of the Balloons Cancellation task on days 1, 48, 86 and 96 (Table 2.14). A chi-squared analysis of the pooled number of targets cancelled showed no increase following prism adaptation (pre: 16/80, post: 20/80, $\chi^2(1)=0.57$, $p=0.45$). There were also no significant differences in the number of targets cancelled before an after prism adaptation on each day (*ps*>0.05).

Anosognosia

On day 11 anosognosia was assessed immediately before and after prism adaptation using a structured interview based on the Bisiach anosognosia scale. AC's level of awareness of his hemiplegia was evaluated with a series of questions that were initially general ('Why are you in hospital?') and gradually became more specific to make direct reference to the deficit ('Can you move your left arm?'). AC gave no acknowledgement of his hemiplegia before or after prism adaptation, even after he attempted, and failed, to move his arm.

Table 2.13. Number of targets cancelled on the Bells test and Subtest B of the Balloons test by AC before and after prism treatment.

Day	Pre	Post
Bells Test (/35)		
1	3	2
3	2	3
11	4	3
44	5	5
56	10	5
69	6	8
80	10	6
Sum (/245)	40	32
Balloons B (/20)		
1	1	4
48	6	5
86	4	5
96	5	6
Sum (/80)	16	20

Anosognosia was still evident on day 44, at which time AC was confined to bed for most of the day due to two incidents in which he had fallen from his chair after trying to stand up. By day 74 he acknowledged the hemiplegia in his left arm. This was observed as a change between testing days rather than an abrupt change following a treatment session, and is therefore unlikely to be due to prism adaptation. Although anososognosia had improved, some anosodiaphoria was evident: AC failed to recognise the impact that his hemiplegia would have on his ability to return to his previously active and adventurous life, which included hobbies such as climbing and kayaking. This was still the case at the end of his hospital rehabilitation period.

Discussion

Adaptation to rightward-shifting prisms resulted in a small but significant leftward shift in AC's open-loop pointing errors, however there is no evidence that it improved neglect symptoms. Although AC showed improved copying performance after prism adaptation on four out of eight days, his performance on the majority of tests was unchanged. AC's progress was also consistent with the associations between anosognosia and both longer recovery periods and decreased independence following stroke. Over the three-month period of this research, AC showed no recovery of performance on bisection and cancellation tests, although his pusher syndrome resolved during this time. AC was discharged to the care of his wife and daily carers. At eleven months post-stroke AC still showed neglect on standard pen-and-paper tests, although neglect severity had greatly reduced (Chapter 4).

Case 3: A patient with navigational difficulties due to hemianopia and chronic neglect following PCA territory stroke.

To evaluate the usefulness of prism adaptation as a rehabilitation tool it is important to examine whether it can improve the patient's ability to perform tasks that are integral to their daily routine. Individual patients have shown improved wheelchair navigation (Jacquin-Courtois et al., 2008), walking trajectory (Folegatti et al., 2008), lower limb mobility (Bacchini et al., 2006) and obstacle avoidance while walking (two patients; Keane et al., 2006). Tilikete and colleagues (2001) also reported reduction in the rightward postural leaning bias of five left hemiparetic patients following adaptation to rightward-shifting prisms.

Over a two-week period, the effects of five daily sessions each of sham and prism treatment were examined in a patient suffering from chronic functional disability due to neglect and hemianopia.

Methods

Patient

MA, a right-handed 80 year-old lady with a stroke of 30 months' chronicity, was referred for prism adaptation treatment by a community occupational therapist. A CT scan taken five days after her stroke revealed a large region of low-density consistent with a stroke of the right PCA territory. The region incorporated the right occipital lobe (including the calcarine fissure), right medial parietal lobe extending into the precuneus, right posterior corpus callosum, right hippocampus and the dorsomedial thalamic nuclei bilaterally.

MA spent four months at a rehabilitation hospital before being discharged to her home. Medical notes from this time report 'total perceptual inattention' and she was described as having no insight into her perceptual problems. Fifteen months after her stroke the patient underwent visual field testing, which confirmed left hemianopia with macular sparing in the left eye. The ophthalmology report also stated that the patient has decreased visual acuity (6/12 in both eyes).

At the time of the present research, MA lived alone with daily support from carers and her daughter. She demonstrated a high level of functional disability: her carers performed all household tasks, including the preparation of meals and cleaning. However the patient was able to dress herself. She walked with an unsteady gait and the support of a three-wheeled walker. She had great difficulty navigating around her environment and frequently bumped into obstacles on her left side. She had insight into these navigational difficulties, saying that she 'got lost' while she was moving between the rooms of her house.

Formal assessment of MA's visual attention was performed using standard clinical tests. She showed no neglect when drawing a clock from memory, but showed aspects of both spatial and object-based neglect on the Ogden copying task (Figure 2.13). She had an average rightward bisection error of 20% of line length on the Schenkenberg bisection task. She cancelled only 24 of 54 targets in the star cancellation task, and 14 of 35 targets in the bells test. In the Balloons Cancellation task she found more targets in parallel ('pop-out') search (subtest A; 8/20) than in the more attentionally demanding serial search (subtest B, 5/20), indicating that it is highly unlikely that her poor performance can be attributed to hemianopia alone. Based on these results it was concluded that MA suffered from hemispatial neglect and was an appropriate candidate for prism adaptation.

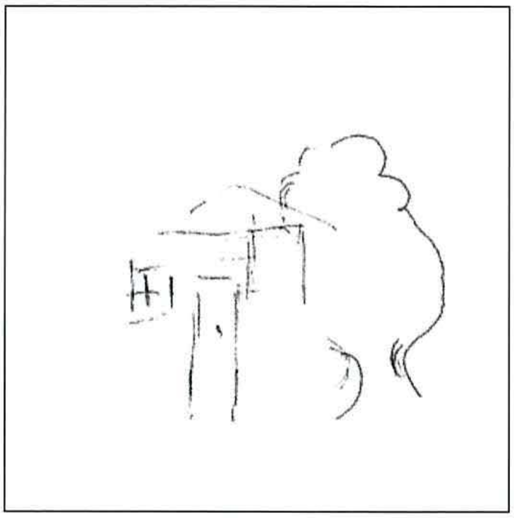

Figure 2.13. A copy of the Ogden scene drawn by MA.

Design and Procedure

Thirteen testing sessions over sixteen days compared the effect of sham treatment (Days 2-6) and prism treatment (Days 9-13) on clinical and functional aspects of neglect, with 90 pointing movements for each treatment session. Neglect symptoms were measured with two sets of standard clinical tests: The Behavioural Inattention Test was administered before and after the thirteen-day testing period, and cumulative effects of multiple treatment sessions were examined using three pen-and-paper tests (Ogden copying task, Schenkenberg line bisection test, Balloons cancellation test subtests A and B) administered on the first, third and fifth day of each treatment condition.

To determine whether prism adaptation resulted in any functional benefits, a spatial navigation task was designed and administered at the beginning and end of the testing period, as well as between the two treatment conditions. The task began with MA seated in a chair in the living room (Figure 2.14). She was asked to rise and, using her walker, to navigate through the hall and into her kitchen, and to then sit in her chair in the kitchen. She then made the return journey. Video recordings were made for later analysis. For each session the time taken was recorded as well as the number and laterality of any neglect-like behaviours (e.g., bumping into the wall, failing to grasp the handle of the walker, etc).

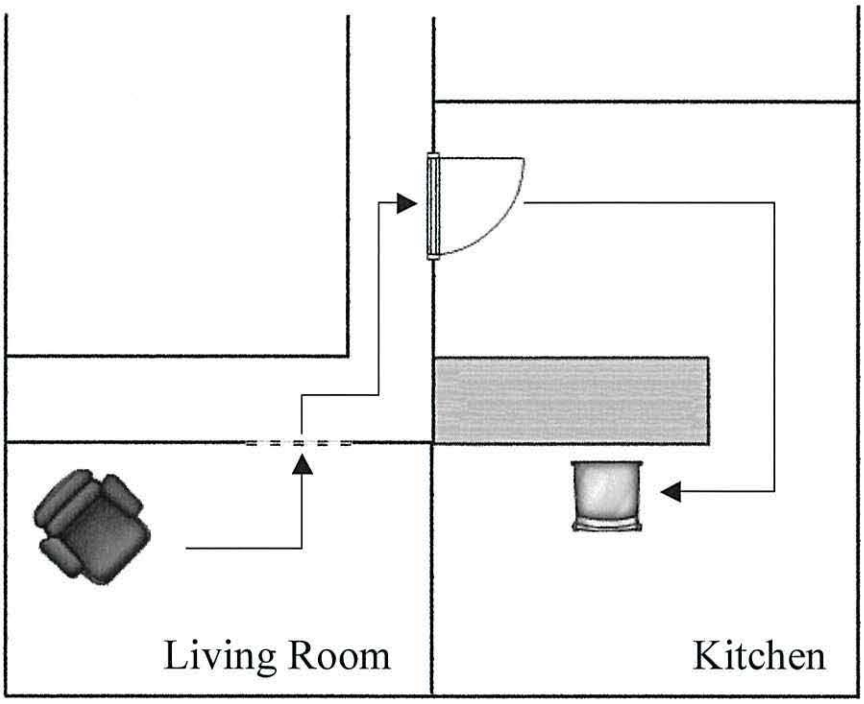

Figure 2.14. A schematic of the portion of MA's house used to test spatial navigation, showing one of the two routes assessed (living room to kitchen).

Results

Prism adaptation. A Treatment (sham, prism) x Session (pre, post) ANOVA of open-loop pointing errors revealed a significant two-way interaction $F(1,236)=117.6, p<0.001$). T-tests showed that there was a leftward shift in pointing error following both sham treatment ($M=2.45°$, $SEM=0.54$, $t(118)=4.5$, $p<0.001$) and prism treatment ($M=5.25°$, $SEM=0.56$, $t(118)=9.45$, $p<0.001$). However, confidence intervals around the pre-post treatment differences revealed that the leftward shift after prism treatment ($CI_{0.95}=[4.14, 6.35]$) was significantly larger than that which followed sham treatment ($CI_{0.95}=[1.38, 3.52]$). Therefore, while MJA showed leftwards shifts in her pointing error after both sham and prism treatment, the significantly larger error following true adaptation suggests that she showed a significant adaptation after-effect.

Behavioural Inattention Test. Prior to prism adaptation the patient scored 94/146 on the conventional BIT and 18/81 on the behavioural BIT. Her poor performance on the behavioural BIT reflects her difficulties in performing everyday activities such as operating a telephone. After the treatment phase, MJA scored 97/146 on the conventional BIT and 11/81 on the behavioural BIT.

Pen-and-Paper Tests.

1) Ogden copying task. In testing sessions on the first day of sham treatment, MA failed to copy the leftmost tree in the pre-test, and then copied the entire picture in the post-test. Complete copies were made in all other sessions.

2) Line bisection. Average bisection error across all sessions was 21.4% to the right of veridical (*SEM*=1.33). A repeated measure ANOVA of bisection error with Treatment (sham, prism), Day (first, middle, late) and Session (pre, post) as factors showed no significant main effects or interactions ($ps>0.05$).

3) Cancellation. The number of targets cancelled by MA for each test and session are shown in Table 2.14. The number of targets cancelled stayed approximately stable across both the sham and prism treatment weeks. Chi-squares tests confirmed that there was no change in the total number of targets cancelled before and after prism adaptation across the three tests for either sham treatment ($\chi^2(1)=0.10, p=0.75$) or prism treatment ($\chi^2(1)=0.42, p=0.52$).

Spatial Navigation. The times taken and descriptions of neglect behaviours shown by MA during each session of the navigation task are shown in Table 2.15. In every session she made major navigational errors, such as overshooting the leftward turn from the hall into the lounge room, after which she would turn around when she reached the end of the hall and retrace her steps to make a rightward turn into the lounge room. There was no evidence of improvements in navigation following five days of prism adaptation, in fact MA took the longest amount of time in this session.

Table 2.14. The number of targets in three tests that were cancelled by MA in the different testing sessions.

	Sham		Prism	
	Pre	**Post**	**Pre**	**Post**
Schenkenberg (/22)				
First	13	14	13	15
Middle	9	16	13	13
Last	16	14	13	12
Sum (/66)	*38*	*44*	*39*	*40*
Balloons Subtest A (/20)				
First	9	5	7	7
Middle	6	5	12	5
Last	9	8	4	4
Sum (/60)	*24*	*18*	*23*	*16*
Balloons Subtest B (/20)				
First	4	3	3	2
Middle	5	4	3	4
Last	3	2	1	1
Sum (/60)	*12*	*9*	*7*	*7*
All tests (summed, /66)				
First	*26*	*22*	*23*	*24*
Middle	*20*	*25*	*28*	*22*
Last	*28*	*24*	*18*	*17*
Grand sum (/186)	***74***	***71***	***69***	***63***

Discussion

No improvements in clinical neglect symptoms or navigational ability were observed after five daily sessions of either sham or prism treatment. It is possible that the effectiveness of prism adaptation in reducing MA's neglect was limited by her hemianopia. Neglect patients with unaffected visual fields showed improved leftward ocular scanning and single word reading, while neglect patients who also had hemianopia showed no improvement (Angeli, Meneghello et al., 2004). Also, a longitudinal study of sixteen patients treated with prism adaptation found that larger occipital lobe involvement related to poorer recovery of oculomotor performance and neglect symptoms. However, the literature provides many examples of patients with hemianopia who have shown improved neglect after prism adaptation treatment with a single-session (Dijkerman et al., 2003), and with multiple sessions (Frassinetti et al., 2002; Nys et al., 2008). In addition to her large occipital lesion, it is also worth noting that MA had bilateral thalamic lesions. As thalamic lesions are associated with both spatial and temporal deficits in attention (Arend, Rafal, & Ward, 2008; Rafal & Posner, 1987), this may have contributed to the lack of improvement following prism adaptation.

Table 2.15. Times taken and descriptions of neglect behaviours shown by MA during each session of the navigation task.

	Baseline	Post Sham	Post Prism
Time taken (s)			
Lounge to kitchen	42	33	46
Kitchen to lounge	55	46	73
Total	*97*	*79*	*119*
Neglect behaviours			
Lounge to kitchen	Misdirected reaching for left handle of walker		
Kitchen to lounge	Collided with left side of kitchen door; missed the left turn from hall to lounge	Missed the doorway from the kitchen to the hall, becoming 'stuck' in the rightmost corner of the kitchen; missed the left turn from hall to lounge	Missed the doorway from the kitchen to the hall, becoming 'stuck' in the rightmost corner of the kitchen

Another possibility is that the five daily prism treatment sessions were insufficient to improve MA's neglect. Three previous studies showed long-term improvement in neglect following repeated sessions of twice-daily treatment for two weeks (Frassinetti et al., 2002; Serino et al., 2005; Serino et al., 2007), while four daily sessions of prism adaptation had no long-term effect on acute neglect symptoms (Nys et al., 2008). However, four daily sessions did result in some immediate, though temporary, reductions in the symptoms of the treated patients compared to controls. This, along with the numerous studies reporting improvements in neglect following a single session of prism adaptation, suggests that the lack of improvement of MA's neglect was not merely due to an insufficient number of treatment sessions. More research comparing the effects of prism adaptation in single and multiple sessions on neglect patients with different lesions may reveal anatomical predictors of the effectiveness of the treatment.

Case 4[1]: Amelioration of right spatial neglect after visuo-motor adaptation to leftward-shifting prisms

As there are hemispheric asymmetries in spatial attention mechanisms, it may be useful to examine whether prism adaptation can produce similar improvements in neglect of the *right* hemispace following left hemisphere damage. The effects of adaptation to leftward-shifting prisms were examined in a patient with mild neglect of the right hemispace following left hemisphere lesion.

Methods

Patient

Patient DS was hospitalised with unintelligible speech, left gaze deviation, right neglect, right facial weakness and hemiplegia with brisk reflexes on the right and bilateral Babinski signs. A CT scan revealed a large left fronto-parietal haematoma due to haemorrhagic infarction.

Three months later, at the time of this investigation, DS was referred for formal neuropsychological testing for neglect after her speech therapist noticed a tendency to leave the rightmost part of her workbooks uncompleted. At this time DS had anomic aphasia with impaired repetition; however her comprehension was relatively preserved and judged sufficient to enable informed consent. She had dense right hemiplegia and completed pen and paper tests for neglect with her left hand. She failed to copy the rightmost detail of the Ogden task (Figure 2.15); showed a mean 8.9% leftward line bisection bias on the line bisection subtest of the BIT; and failed to cancel 2-3 rightmost targets on each of three cancellation tests (Balloons subtests A and B, Bells cancellations test). An MRI scan revealed a large left hemisphere lesion involving the frontal eye field, motor and premotor cortices, cingulate gyrus,

---

[1] A version of this case study has been accepted for publication in Cortex: Bultitude, J.H. & Rafal, R.D. (in press). Amelioration of right spatial neglect after visuo-motor adaptation to leftward-shifting prisms. *Cortex*.

posterior superior temporal gyrus and the parietal lobe (including the superior parietal lobule, precuneus, angular and supramarginal gyri).

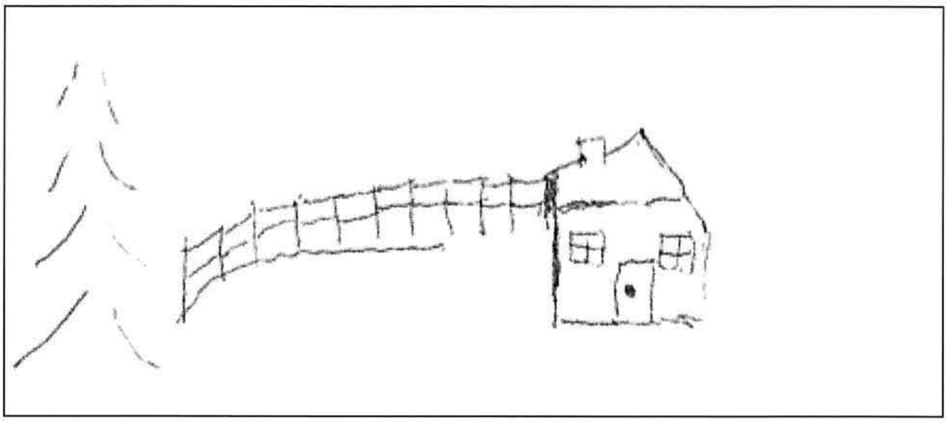

Figure 2.15. A copy of the Ogden scene drawn by DS.

Design and Procedure

A multiple baselines design with eight testing sessions spanning eighteen days was used to examine the effects of adaptation to leftward-shifting prisms on neglect. Effects of both sham treatment (day 2) and prism treatment (day 7) were examined, with fifty pointing movements in each session. In these sessions neglect was assessed using the Ogden copying task, the Bells cancellation task, and a modified version of the line bisection subtest of the BIT. Performance on the copying and cancellation tasks was at ceiling, therefore analyses focused on the results of the line bisection test.

As adaptation to leftward-shifting prisms has been shown to result in rightward shifts in line bisection in healthy participants, comparison data were also collected from eight age- and gender-matched control participants (Mean age=73.4, *SEM*=0.82). The control participants completed the line bisection test in three sessions on one day: at baseline, after sham adaptation, and after prism adaptation. Although all control participants were right-handed, they used their left hand for all tasks, replicating the procedure used for DS.

Adaptation was confirmed by measuring pointing error in four sessions for DS (pre-sham, post-sham, pre-prism and post-prism), and in three sessions for control participants (baseline, post-sham and post-prism).

Results

Prism adaptation

Healthy controls. A repeated-measures ANOVA of pointing error with one factor, session (baseline, post-sham, and post-prism), revealed a significant main effect ($F(2,14)=14.45$, $p<0.001$) where mean pointing error was unchanged between the baseline ($M=0.9$, $SEM=0.67$) and post-sham session ($M=1.9$, $SEM=0.72$; $t(7)=1.124$, $p=0.26$) but shifted significantly rightward after prism adaptation ($M=4.9$, $SEM=0.55$) compared to both baseline ($t(7)=5.37$, $p<0.005$) and post-sham ($t(7)=3.9°$, $p<0.01$) pointing.

DS. A repeated-measures ANOVA of pointing error with two factors, treatment (sham and prism) x session (pre and post), revealed a significant two-way interaction ($F(1,11)=21.9$, $p<0.001$) where pointing error was unchanged following sham treatment (Pre: $M=3.3$, $SEM=0.28$; Post: $M=4.8$, $SEM=0.70$; $t(11)=2.02$, $p=0.07$) but shifted 4.9 rightward following prism treatment (Pre: $M=5.6$, $SEM=0.55$; Post: $M=10.5$, $SEM=0.35$; $t(11)=8.48$, $p<0.001$).

Line bisection

Healthy Controls. There was a decrease in bisection errors across the baseline ($M=-4.68$, $SEM=1.53$), post-sham ($M=-3.66$, $SEM=1.49$) and post-prism sessions ($M=-3.11$, $SEM=1.44$), although a one-way ANOVA revealed no main effect ($F(2,14)=1.63$, p=0.23). Bisection errors were pooled across sessions and a 95% confidence interval around the mean confirmed a significant leftward bias ('pseudoneglect'; $CI_{0.95}=[-5.54, -2.10]$).

DS. Figure 2.16 shows bisection performance across sessions. Bisection errors in all baseline and post-sham sessions were outside the 95% confidence interval for controls, but were within normal bounds in the first two post-prism sessions. The sessions were grouped into three Stages: baseline (day1 and day 2 pre), post-sham (day 2 post, day 6 and day 7 pre), and post-prism (day 7 post, day 8, day 18). A one-way ANOVA revealed a main effect of Stage ($F(2, 93)=7.49$, $p<0.005$). T-tests revealed no difference between baseline ($M=-9.52$, $SEM=1.52$) and post-sham performance (*M*=-10.44, *SEM*=0.97; *t*(58) = 0.58, *p*=0.60). Bisection deviation in the post-prism stage (*M*=-5.46, *SEM*=0.68) was smaller than both baseline (*t*(58)=2.72, *p*<0.01) and post-sham (*t*(70)=4.20, *p*<0.001).

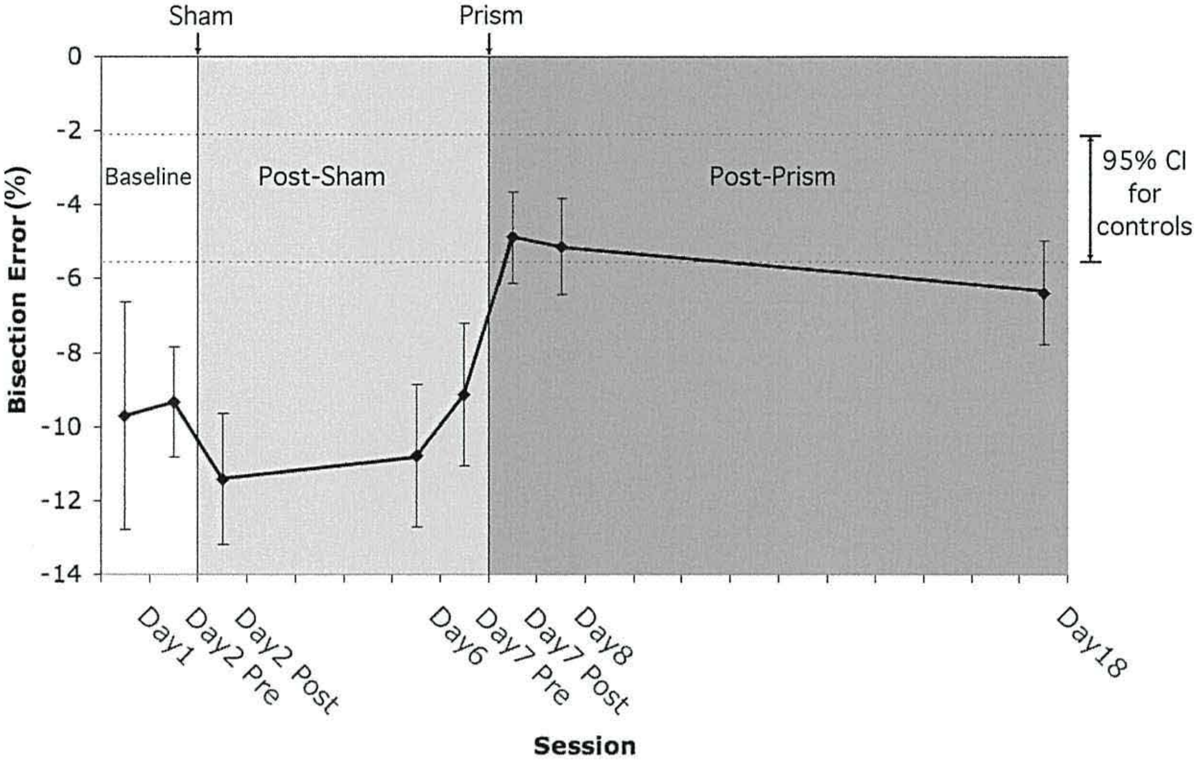

Figure 2.16. Average line bisection errors (±1 *SEM*) of the patient for each session compared to the 95% confidence interval around the mean for healthy control participants. Sessions were grouped into three stages: Baseline, Post-Sham, and Post-Prism as indicated by the shaded areas.

Stability of improvement was evaluated with a one-way ANOVA, which showed no difference between bisection errors in the three post-prism sessions (*F*(2,33)=0.45, *p*=.64), although there appeared to be a trend for a return to baseline. Mean error on day 18 was within one *SEM* of the 95% confidence interval around the mean for the control group, but was also not different from baseline (*t*(34)=1.34, *p*=0.19). Five additional daily adaptation sessions administered after day 18 resulted in no further reduction in bisection error (*M*=-5.58, *SEM*=0.80; not shown in Figure 2.16).

Discussion

To the best of my knowledge, this is the first report of a patient with right spatial neglect to be treated with prism adaptation. In previous work patients with left spatial neglect adapted to rightward- but not leftward-shifting prisms (Rossetti et al., 1998). Leftward-shifting prisms were therefore used to treat this patient with right spatial neglect to induce a rightward visuo-motor after-effect. Prism adaptation was effective both in inducing a rightward after-effect and in improving neglect as measured on a bisection task.

Healthy participants make small but systematic leftward errors in line midpoint estimations ('pseudoneglect'; Bowers & Heilman, 1980). These shift rightward by 1-2% of line length following adaptation to leftward-shifting prisms (Berberovic & Mattingley, 2003; Michel, Pisella et al., 2003) but not always significantly so for manual bisection (Colent et al., 2000). The baseline bisection errors of DS were larger than the controls', and her post-prism error reduction of approximately 5% was greater than the shifts previously reported for healthy participants. These results indicate both the presence of mild neglect, and a reduction of bisection bias after prism adaptation beyond that which would be expected for controls.

Although further studies with greater numbers of patients are needed, the results suggest that the neurological process by which adaptation to rightward-shifting prisms ameliorates left neglect can occur in a similar fashion with leftward-shifting prisms for patients with right neglect. A proposed mechanism for the prism-induced improvements in left spatial neglect involves signals from right cerebellum that influence activity in the left parietal lobe via a network of left and right hemisphere areas (Pisella et al., 2006). These left parietal areas could be recruited for previously right parietal functions (Pisella et al., 2006), or may further influence the right superior parietal lobe via colossal communication (Striemer et al., 2008). Adaptation to leftward-shifting prisms using the left hand may result in a symmetrical process in patients with right spatial neglect, recruiting right parietal areas or influencing spared left hemisphere areas to restore rightward attention.

GENERAL DISCUSSION

Evaluation of both group data from twelve patients and three individual case studies provide little evidence of improvements in left hemispatial neglect following prism adaptation.

One key difference between the prism treatments performed on these patients compared to previous research is that patients adapted to a larger prismatic shift.

Most research on the clinical effects of prism adaptation has used 10° prisms, as this is the largest wedge prism size that can be fixed into glasses and still be comfortably tolerated by the patients. The Risley biprisms and supporting head mount allowed the use of larger visual shifts of 15°. It is conceivable that adaptation to shifts *smaller* than 10° may not induce sufficient leftward reorientation to reduce neglect symptoms; indeed seventeen patients who underwent two weeks of adaptation to 6° prisms showed no improvements in neglect and self-care measures compared to a sham treatment group (Turton, O'Leary, Gabb, & Gilchrist, 2007). It is unlikely, however, that adaptation to shifts *larger* than 10° would reduce the effectiveness of prism adaptation on neglect signs. One argument could be that a visual shift of 15° may be more obvious to patients, resulting in greater use of strategic compensation for the shift, which in turn would reduce the degree of true adaptive realignment. However no patient discussed in this chapter showed awareness of the lateral visual shift induced by prisms. It is therefore unlikely that any patient used a deliberate compensatory pointing strategy during the exposure period. Also, the literature does provide examples of patients with neglect who have shown significant improvements following adaptation to 15° shifting prisms in oculomotor behaviour and centre of gravity (Shiraishi et al., 2008), and functional performance including obstacle avoidance while walking (Keane et al., 2006); although Morris and colleagues (2005) found no improvement in visual search. In summary, although the size of the prismatic shift used to treat the patients in the present study is larger than that used by most other researchers, this is unlikely to have interfered with any clinical effects of prism adaptation.

There is growing evidence for inter-patient variability in the clinical effectiveness of prism adaptation. Dijkerman and colleagues (2004) found that a patient with neglect showed no improvement in star cancellation or bisection following prism adaptation, although her somatosensory function was improved. Sarri and colleagues (2008) also reported no improvement in the cancellation performance of four out of twelve adapted patients. A mixture of symptom improvement, symptom deterioration and no symptom change following prism adaptation have been reported both across patients (Morris et al., 2004; four patients) and for different tests within patients (Dijkerman et al., 2003; three patients). Most significantly, a within-subjects study of ten patients found that single sessions of sham and prism treatment led to no change on tests of reading, bell cancellation, line bisection and scene drawing (Rousseaux et al., 2006). The variability in responses to prism adaptation has led to efforts to identify neuroanatomical and clinical factors that relate to its effectiveness.

In one study prism adaptation increased leftward ocular-motor exploration and reduced reading errors in neglect patients with intact visual fields but not those with hemianopia (Angeli, Meneghello et al., 2004). Lesions involving large parts of the occipital lobe may reduce effectiveness, with evidence for smaller error reduction during prism adaptation, less leftward change in ocular-motor behaviour, and poor recovery of neglect as measured by the BIT (Serino et al., 2005). However Nys and colleagues (2008) found that two patients with hemianopia demonstrated similar patterns of improvement to eight patients without hemianopia. Lesions implicating frontal areas have also been associated with poor neglect recovery after prism adaptation (Sarri et al., 2008; Serino et al., 2005), as well as lesions involving the intraparietal lobe and white matter deep to the intraparietal lobule (Sarri et al., 2007). Striemer and colleagues (2008) also argued that the superior parietal lobe was critical to the clinical effects of prism adaptation, based on evidence that a patient suffering from left hemispatial neglect following asymmetrical bilateral lesions involving both superior parietal lobes showed no improvement following prism adaptation. A large-scale study comparing lesion locations of improved and unimproved patients would be required to fully examine this issue.

Neglect chronicity may impact on the effectiveness of prism adaptation. A distinction can be drawn between the acute neglect shown in the weeks immediately following stroke when symptoms are more severe but some recovery of function can be expected, and chronic neglect where symptoms have stabilised and further spontaneous recovery is unlikely. The differentiation between acute and chronic neglect is often arbitrarily drawn at 3 months post-stroke. The improvements reported by Rossetti and colleagues (1998) were observed in a heterogeneous group of patients with neglect of between 3 weeks and 14 months duration. In contrast, the null findings of the group analysis of the present research as well as those of Rosseaux and colleagues (2006) were observed in patients with predominantly acute neglect (17-102 days post-stroke for Rosseaux and colleagues; 14-106 days in the present study). Also, a randomised double-blind control study comparing the effects of four consecutive days of sham or prism treatment in different patients found that while the treatment group showed slightly greater improvements in bisection and cancellation immediately following treatment, the two groups showed similar levels of improvement at a one-month follow-up (Nys et al., 2006). This is in contrast with longitudinal group studies showing that patients with neglect of at least three month's chronicity who received twice-daily sessions of prism adaptation for two weeks had long-lasting improvements in symptoms compared to controls (Frassinetti et al., 2002; Serino et al., 2005; Serino et al., 2009; Serino et al., 2007). It is notable that the only positive result reported in the present chapter - in a patient with right spatial neglect following adaptation to leftward-shifting prisms - was observed in a patient with neglect of three months' duration (i.e., chronic neglect).

Nys and colleagues (2006) suggested that any benefits of prism adaptation in the weeks immediately following stroke may be negligible compared to the considerable amount of spontaneous recovery that occurs during this time. Another possibility is that patients who are in the acute stages of recovery are unable to point as fast as patients in the chronic stage. Rapid, ballistic pointing movements during adaptation prevent on-line proprioceptive guidance of movement trajectory, which is directed instead by the visual system. This leads to larger proprioceptive realignment and may therefore be more effective in reducing neglect. Where studies of prism adaptation in neglect patients have specified the pointing rate, all describe 'rapid' or 'fast' pointing movements, or asking patients to point 'as quickly as possible'. However the precise speed of 'fast' pointing is limited by the capabilities of the patient.

This argument would be supported by observation of smaller adaptation after-effects in patients with acute neglect compared to those with chronic neglect. Although the patients discussed in this chapter adapted to a prismatic shift that was larger than that used in most previous studies, the adaptation magnitudes were similar. For example, the group analysis of visual target pointing showed an average shift of -3.19°, which is in the upper bounds of the 95% confidence interval around the mean that was obtained in a recent meta-analysis of neglect patient after-effects ($CI_{0.95}$=[-7.09, -1.21]; Sarri et al., 2008). Of seven studies that tested patients with acute neglect, two did not record pointing error (Nys et al., 2008; Vallar, Zilli, Gandola, & Bottini, 2006), and four used proprioceptive straight ahead pointing (Keane et al., 2006; Pisella et al., 2002; Rode, Pisella et al., 2006; Rode, Rossetti, & Boisson, 2001), which confounds the adaptation after-effect with any realignment of egocentric reference frames (Sarri et al., 2008). Rosseaux and colleagues (2006) measured the adaptation after-effect by asking their patients to point two or three times to a remembered visual target with their eyes closed, and found a mean adaptation after-effect of -4.8°. With no direct comparative study available, it is unclear whether patients with acute neglect show smaller shifts in proprioception than those with chronic neglect.

Prism adaptation holds considerable promise as a simple and long-lasting treatment for hemispatial neglect. However the results of the present study add to evidence that single sessions, or a low number of repeated daily sessions, are not beneficial to neglect patients who are in the acute stages of stroke recovery (Nys et al., 2008; Rousseaux et al., 2006).

Evidence that two-weeks of twice-daily treatment result in robust and long-lasting improvements in chronic neglect suggests that acute neglect may be improved by a greater number or frequency of treatment sessions. Studies that directly compare the effects of prism adaptation on acute and chronic neglect, as well as large-scale studies examining the lesions of improved patients compared to those who are unaffected by prism adaptation, may assist in predicting the responsiveness of individual patients to prism adaptation.

Chapter 3

Motor-intentional neglect: Adaptation to leftward-shifting prisms induces a neglect-like withdrawal bias, but not directional hypokinesia, in healthy participants

ABSTRACT

Hemispatial neglect can be observed as a failure to perceive or attend to contralesional stimuli (perceptual-attentional neglect); or as difficulty programming, initiating or performing actions on the contralesional side of space (motor-intentional neglect). Substantial evidence now supports that prism adaptation can reduce the leftward attentional deficit of patients with neglect, or induce neglect-like rightward attentional biases in healthy participants. In contrast, there is only limited evidence that prism adaptation can influence motor-intentional performance beyond that of the visuo-motor after-effect. The aim of this chapter was to examine whether adaptation to leftward-shifting prisms could induce in healthy participants two motor-intentional biases associated with neglect: directional hypokinesia (slowed initiation of leftward movements), and the withdrawal bias (the tendency to make faster withdrawal than approach responses). In Experiment 3.1 RTs for left and right lever movements, and forwards and backwards lever movements, were tested in separate blocks before and after adaptation to leftward- and rightward-shifting prisms. The results showed reduced RTs for withdrawal (backwards) movements in the leftward-shifting prism group only, but RTs for approach (forwards), left and right movements were unchanged. In Experiment 3.2 the effects of prism adaptation on approach and withdrawal was re-examined by asking participants to step towards or away from arrow stimuli presented on a computer monitor. There was an increase in RTs for forward stepping (approach) relative to backward stepping (withdrawal) after adaptation to both leftward- and rightward-shifting prisms. Experiment 3.3 revisited the effects of prism adaptation on leftward and rightward movements. From a central starting position, participants reached to touch buttons to their left or right in response to symbols appearing on a computer monitor. Consistent with the results of Experiment 3.1, there were no changes in initiation and movement times for leftward and rightward reaches after prism adaptation. The results of this chapter suggest that adaptation to leftward-shifting prisms can induce a non-lateralised neglect-like deficit - the withdrawal bias - in healthy participants, but not directional hypokinesia.

Hemispatial neglect can be a disorder of both attention and intention. When a patient with neglect shows difficulty responding to contralesional stimuli this may be because that side of space is the subject of reduced attentional focus and as a result the patient is slower to become aware of the stimuli. Another possibility, first proposed by Heilman and Valenstein (1979), is that contralesional stimuli are registered equally as fast as ipsilesional stimuli but the patient is slower to plan and/or execute responses directed to the neglected side: intentional neglect. Intentional neglect arises not from a decreased ability to register contralesional stimuli, but from problems directing movement or otherwise interacting with the contralesional side of space.

Attentional and intentional causes are not mutually exclusive and both deficits contribute to the biased behaviour of some patients. Individual patients have, however, been classified as having predominantly attentional or intentional neglect based on their performance under conditions in which motor and sensory task demands are decoupled (Figure 3.1). Bisiach, Geminiani, Berti and Rusconi (1990) asked patients to indicate the midpoint of horizontal lines by moving a pointer that was attached to a pulley device such that its lateral displacement required a movement of the patient's hand in the same or the opposite direction (Figure 3.1A). When pointer and hand movement direction were incongruent, rightward bisection error was reduced in thirteen of fifteen patients, two of whom made leftward bisection errors under these conditions. Tegnér and Levander (1991) used a 90° angle mirror to reverse visual feedback on the horizontal plane for patients completing a line cancellation task (Figure 3.1B). Four of 18 patients cancelled lines only in the right hemispace (left side of vision), and ten patients cancelled lines only in the left hemispace (right side of vision). A similar dissociation between intentional and attentional neglect was found when patients viewed their cancellation performance through a closed circuit television with the camera inverted so that hand movement on table and on the monitor were in opposite directions (Figure 3.1C; Na et al., 1998).

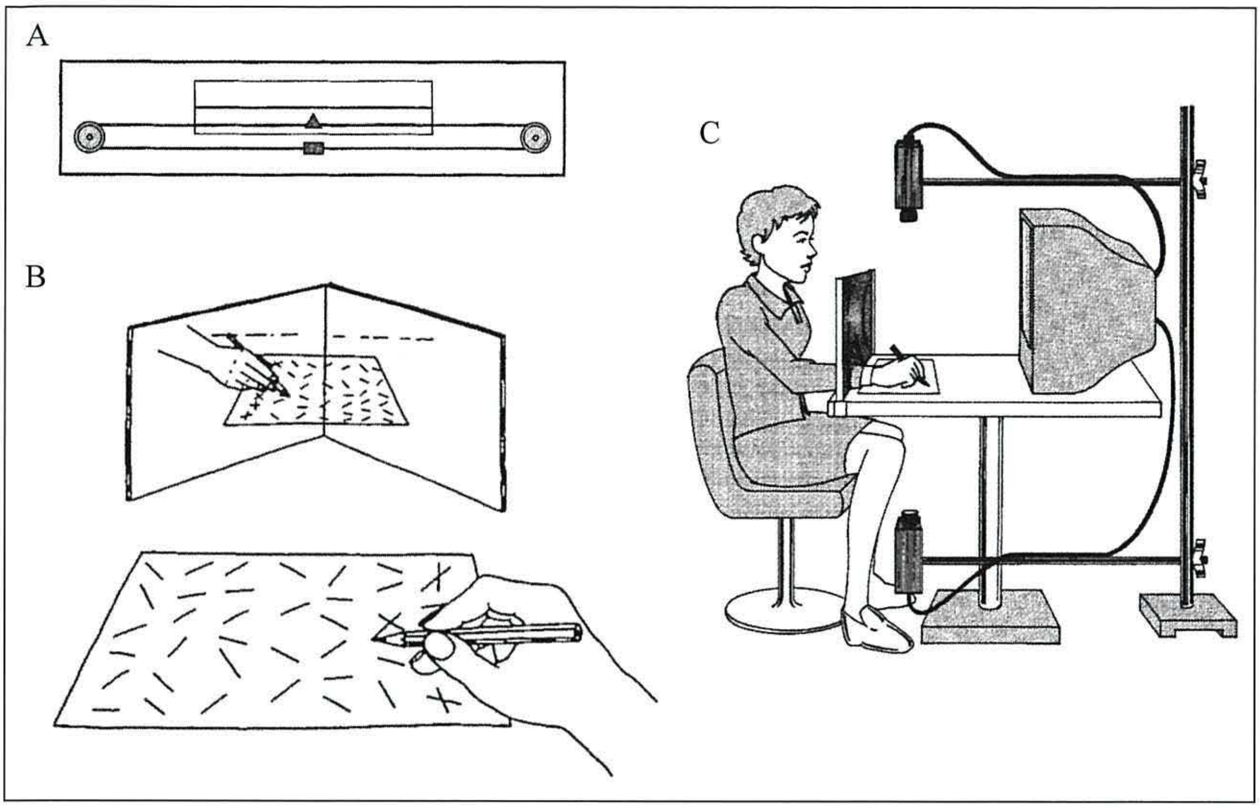

Figure 3.1. Procedures for decoupling perceptual-attentional and motor-intentional contributions to neglect. Using Bisiach pulley device (A), patients indicated line midpoint by moving the triangular marker (congruent condition) or by manipulating the location of the marker by holding the rectangular section (incongruent condition). Tegnér and Levander (1991) compared cancellation performance with normal visual feedback, or when viewed with 90° angle mirrors that reversed visual feedback around the vertical axis (B). Using closed-circuit television (C), patients performed a cancellation task while viewing input from a camera positioned above (congruent) or below (incongruent) the workspace (Na et al., 1998).

One well-documented type of motor-intentional neglect is directional hypokinesia: slowness in initiating movements to the contralesional side of space. Directional hypokinesia was first described by Heilman and colleagues (1985), who showed that patients with neglect following right hemisphere lesions were slower to initiate leftward movements of a handle along a fixed linear pathway, even when the entirety of this movement was performed in the right space. Mattingley, Bradshaw and Phillips (1992) showed that this slowing of movements occurred in patients with either left or right hemisphere lesions, but only when the lesions had resulted in neglect. Patients with right hemisphere lesions resulting in neglect also showed slowed leftward movement *execution* ('directional bradykinesia'), but this was not present in neglect patients with left hemisphere lesions.

A lesser-studied motor-intentional bias that has been described in neglect patients is the withdrawal bias. Denny-Brown argued that the frontal lobes mediate withdrawal-related behaviours, while the parietal lobes mediate approach-related behaviours (Denny-Brown, 1956, 1958; Denny-Brown & Chambers, 1958). Based on extensive observations of brain-lesioned patients and ablated monkeys, he argued that lesions to the parietal lobe, such as those that are often associated with neglect, led to the loss of approach behaviours and the 'transcortical release' of the frontally-mediated withdrawal behaviours. This can be observed at the level of reflexive withdrawal of the contralesional limb from tactile stimuli, but also as a generalised retraction from all forms of stimuli and a lack of exploration and utilisation behaviour (Denny-Brown & Chambers, 1958). The withdrawal bias should not be confused with the radial spatial neglect that has been reported in patients with right hemisphere lesions: Radial neglect is reported as a performance bias *away from* the body while completing pen-and-paper tasks (Gold, Shuren, & Heilman, 1994; Halligan & Marshall, 1993; Kori & Geldmacher, 1999), and the withdrawal bias also describes a more comprehensive response to stimuli and the environment. In fact, Denny-Brown even likened anosognosia to a kind of mental withdrawal behaviour (Denny-Brown, 1956).

According to Denny-Brown's description, the withdrawal bias is a non-lateralised motor-intentional deficit: that is, performance of patients is equally affected in the left and right hemispace (although, see Kodsi & Heilman, 2002, for evidence of contribution of contralesional avoidance to right bisection errors in a neglect patient). While the defining symptom of neglect is the lateralised spatial deficit in responding to left-sided stimuli, neglect is also associated with several non-lateralised spatial and non-spatial symptoms that are thought to contribute to the patient's disability (see Husain & Rorden, 2003, for a review). Patients with neglect show a tendency to be fixated on local details in preference to the global configuration of a scene, indicating a local processing bias (Marshall & Halligan, 1995; Rafal & Robertson, 1995). They also show a pathologically large attentional blink, indicating impaired selective attention (Husain, Shapiro, Martin, & Kennard, 1997; Van Vleet & Robertson, 2006). A third example is that when completing cancellation tasks, patients revisit previously cancelled targets and perceive these as new targets, suggesting a deficit in spatial working memory (Husain et al., 2001; Malhotra et al., 2005; Malhotra, Mannan, Driver, & Husain, 2004).

Many of the studies examining the effects of prism adaptation on neglect symptoms have used tests that do not differentiate between perceptual-attentional and motor-intentional neglect. For example, standard clinical tests of neglect such as drawing, cancellation and reading involve arm and eye movements. However several studies using highly controlled computerised experiments have shown benefits to perceptual-attentional components of neglect isolated from motor-intentional performance by requiring patients to hold constant fixation and indicate responses verbally or with a keypress. In healthy participants, Loftus and colleagues (2009) recently demonstrated reduced pseudoneglect following adaptation to leftward-shifting prisms on the greyscales task, which requires verbal judgements about the relative darkness of two briefly presented mirror-reversed luminance gradients while fixation is held constant. There is therefore evidence that prism adaptation can change perceptual-attentional performance in both neglect patients and healthy controls.

Although less extensive, there is also evidence that prism adaptation can influence motor-intentional performance in neglect patients independent of perceptual-attentional factors. Patient CS was asked to haptically explore a circular groove while blindfolded before placing her finger in the perceived centre of the circle (McIntosh et al., 2002). Prism adaptation reduced her rightward error on this task, but her radial error was unchanged. Patients who were asked to reach for a centrally located ball and throw it into a basket to their left or right were slower to initiate the first movement to acquire the ball if the subsequent throw was to the left, but this asymmetry was reversed after prism adaptation (Rossetti et al., 2005, as cited in Pisella et al., 2006). Only one study provides evidence for changes in motor-intentional performance in healthy participants following adaptation to leftward-shifting prisms (Girardi et al., 2004), with an induction of a neglect-like rightward error in the haptic circle centring task of McIntosh and colleagues (2002), but no change in the radial direction.

The research described in this chapter examined the effect of prism adaptation on motor-intention. Specifically, the aim was to determine if adaptation to leftward-shifting prisms could induce directional hypokinesia or a withdrawal bias in healthy participants. Three experiments examined the effects of prism adaptation on initiation and/or movement times for leftward vs rightward or forward vs backward movements using different motor tasks. In Experiment 3.1 both directional hypokinesia and approach-withdrawal behaviour were measured using two similar tasks in which participants moved a lever left or right, or forwards or backwards. Experiment 3.2 examines the effects of prism adaptation on the participants' initiation times when they approached or withdrew their body from stimuli by stepping towards or away from the display screen. Finally, Experiment 3.3 re-examines whether prism adaptation can induce directional hypokinesia using a directional reaching task.

GENERAL METHODS

Participants

The participants for all four studies were neurologically healthy students studying at Bangor University. All participants had normal or corrected-to-normal vision and were right-handed. Participants received course credits or £6 per hour of participation and gave informed consent in accordance with the ethical standards of Bangor University and the Declaration of Helsinki.

Apparatus

A 90cm wide x 35cm high x 70cm deep prism adaptation box was constructed based on that described by Berberovic and Mattingley (2003). The box was open at two opposite ends and was fitted with a lid that had lines drawn on the upper surface radiating out at -10°, 0° and +10° from the participant's position. Identical lines were drawn on the inner base of the box. These lines served as targets for visual target pointing and prism adaptation. During adaptation participants wore welding goggles fitted with Risley biprisms that were adjusted to shift the visual field 15° to the left or right. Visual stimuli for the motor tasks were programmed using Eprime software in a Windows XP operating system and presented on a 17" CRT monitor set at 1280 x 1024 resolution and refresh rate of 75 Hz.

Procedure

Each experiment had the same general procedure. One or more motor tasks were performed before and after a session of prism adaptation. Half the participants adapted to leftward-shifting prisms and half adapted to rightward-shifting prisms. Visuomotor adaptation was confirmed using a visual target pointing task which was performed three times: First, baseline pointing errors were obtained immediately before prism adaptation (pre-test); Second, the presence of an adaptation after-effect was confirmed by measuring visual target pointing errors immediately after prism adaptation (post-test); Finally, to confirm that the after-effect was maintained throughout the entire post-adaptation testing period, pointing errors were measured after the completion of the second set of motor tasks (late-test). Participants kept their eyes closed between tasks to minimise deadaptation.

Analyses

Data for each experiment were analysed using repeated-measures ANOVAs and follow-up paired-subjects t-tests with Bonferroni-corrected alpha levels.

EXPERIMENT 3.1: THE EFFECTS OF PRISM ADAPTATION ON HORIZONTAL AND RADIAL ARM MOVEMENTS

To examine whether adaptation to leftward-shifting prisms could induce neglect-like directional hypokinesia or the withdrawal bias described by Denny-Brown, two groups of healthy participants moved a lever in separate blocks, either left or right, or forwards or backwards, in response to visual stimuli before and after prism adaptation. The duration of adaptation after-effects have been shown to decrease with movement, even when no visual feedback of the arm is provided (Beckett & Melamed, 1980). As the experimental tasks required movement, the following measures were employed to maximise the duration of adaptation and the potential for inducing a motor-intentional effect: 1) vision of the hand during the lever tasks was prevented using a panel positioned under the participant's chin, 2) An extended (20 minute) prism adaptation period was used based on the finding that the magnitude of the adaptation after-effect is increases with longer exposure times (Efstathiou, 1969); 3) during adaptation participants received visual feedback of only the last 2-3 cm of their pointing movement (terminal feedback), a condition that has been shown to maximise the generalisation of the adaptation after-effect (Cohen, 1967).

To control for any direct influence of the adaptation-after-effect, half the participants completed the lever tasks using their right (adapted) and half used their left (unadapted) hand. While inter-manual transfer of the adaptation after-effect can occur, any motor bias in unadapted limb would be smaller than in the adapted limb (Choe & Welch, 1974). Therefore changes in performance that are due to the low-level motor after-effect would present differently in participants using their left and right hands, while changes due to higher-level cognitive influences of prism adaptation would occur equally across the two groups.

Method

Participants

Forty participants were randomly allocated to the leftward-shifting prism group (Mean age=20 years, *SEM*=0.34, 8 Males), or the rightward-shifting prism group (Mean age=21 years, *SEM*=0.48, 9 Males).

Apparatus

Motor performance was measured using a custom-built joystick with an 11.5cm long handle.

Stimuli and Procedure

Participants completed two motor tasks measuring directional hypokinesia and approach/withdraw behaviour before and after prism adaptation. All participants used their right hand for the adaptation phase, but prism direction (left or right) and hand used for the motor tasks (left or right) were manipulated between subjects in a completely crossed design.

Prism Adaptation

Participants were seated at one open end of the prism adaptation box with their chin resting on the top edge of the box. During adaptation participants wore the prism goggles while pointing their arms under the target lines such that their finger emerged from under the arced edge of the lid and they could see the final 2-3cm of their pointing movement (terminal feedback). All participants pointed with the index finger of their right arm during the adaptation phase. Participants were asked to fully extend their elbow when pointing under the target and to return their hand to rest in front of their torso between each pointing movement. The order of pointing target was left-middle-right-middle, repeated for 20 minutes with participants resting their arm as required. To help maintain constant pointing speed participants pointed in time with a metronome set to 0.5 Hz.

Pre- post- and late-test visual target pointing errors were recorded in the following way: An additional panel was placed on top of the box to completely occlude the participant's arm from their view. Participants then pointed their arm under each of the target lines four times in pseudorandom order as directed by the experimenter, returning their hand to rest in front of their torso between each pointing movement. Pointing error was measured by the experimenter to the nearest 0.5 degree using markings on the underside of the lid, where negative and positive values indicate leftward and rightward errors respectively.

Motor Tasks

Similar stimuli and procedures were used for the directional hypokinesia and approach/withdraw tasks (Figure 3.2). Participants were seated 80cm from the computer screen and rested their chins in a chinrest such that their eyes were level with the middle of the computer screen. The joystick was positioned with the lever 15cm to the left or right of their body midline, depending on whether they were using their left or right hand to complete the task. Stimuli were presented on the screen as black figures on a white background. Each trial began with the appearance of a 0.11° x 0.11° central fixation cross. After 1000 ms, this cross was replaced by a 0.11° x 0.13° arrowhead. In the directional hypokinesia block, the arrowhead pointed to the left or right and the participant was asked to move the handle of a joystick as quickly as possible to the left or right respectively. In the approach/withdraw block the arrows pointed up or down and the participant moved the joystick forward (approach) or backward (withdraw).

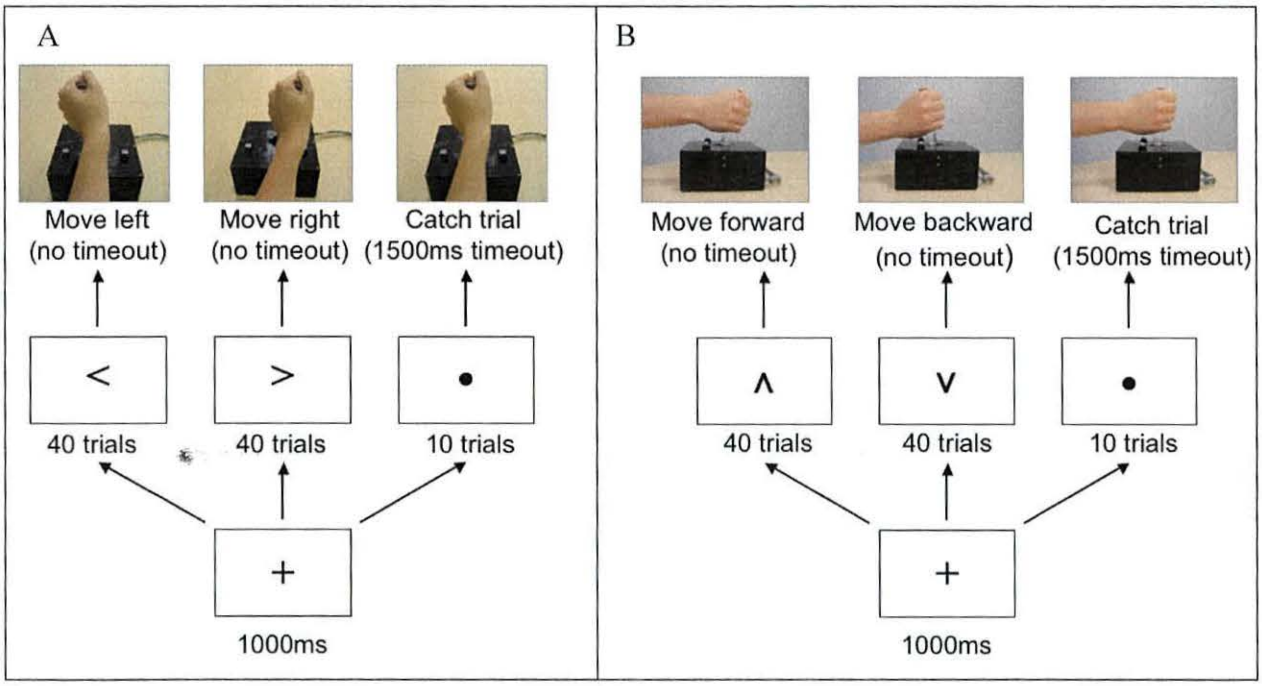

Figure 3.2. Task stimuli and responses for the directional hypokinesia (A) and approach-withdrawal task (B) tasks.

The arrowhead remained on the screen until the participant responded, with a time-out of 1500ms. The time between the appearance of the arrow and the end of the movement was recorded with the participant's response ending the trial. Each block consisted of 80 movement trials as well as 10 catch trials in which the fixation cross was replaced by a 0.11° diameter circle and participants were instructed not to move the joystick. The order of motor tasks was counterbalanced between subjects with practice trials provided before the pre-adaptation session as required.

Results

Prism Adaptation

There was a significant Group x Session interaction (*F*(2, 76)=604.7, *p*<0.001), which reflected significant adaptation after-effects for both groups, which were maintained to the late-test (see Tables 3.1 and 3.2 below).

Table 3.1: Summary of the pointing errors for the leftward-shifting prism group in Experiment 3.1.

Session	M	SEM	t (compared to baseline)	p
Pre	-0.39	0.41	-	-
Post	8.85	0.34	21.56	<0.001
Late	8.01	0.46	17.77	<0.001

Table 3.2: Summary of the pointing errors for the rightward-shifting prism group in Experiment 3.1.

Session	M	SEM	t (compared to baseline)	p
Pre	-0.35	0.42	-	-
Post	-7.90	0.47	20.33	<0.001
Late	-6.73	0.51	15.63	<0.001

Motor tasks

Leftward-shifting prism group

Analysis of mean RTs for the directional hypokinesia task revealed no significant main effects or interactions, other than a trend for faster reaction times after prism adaptation (*M*=469.36, *SEM*=10.77) compared to baseline (*M*=490.38, *SEM*=13.74); *F*(1,19)=4.31, *p*=0.052. In contrast, the analysis of mean RTs for the approach/withdraw task revealed a main effect of Session for the leftward-shifting prism group (*F*(1,19)=6.275, *p*<0.05), with significantly faster reaction times after prism adaptation (*M*=484.13, *SEM*=14.14) compared to baseline (*M*=505.93, *SEM*=15.12). There was also a significant Session x Action interaction, which is plotted in Figure 3.3 (*F*(1,19)=7.67, *p*<0.05). Withdraw actions were significantly faster after prism adaptation (M=480.9, *SEM*=13.2) than before prism adaptation (*M*=511.3, *SEM*=15.3); *t*(19)=3.52, *p*<0.005. In contrast, there was no significant difference between reaction times for approach actions before prism adaptation (*M*=510.8, *SEM*=15.5) and after prism adaptation (*M*=499.9, *SEM*=13.6), *t*(19)=1.11 *p*=0.28. There were no further significant main effects or interactions in the analysis of mean RTs for the leftward-shifting prism group (*ps*>0.05) .

In summary, adaptation to leftward-shifting prisms did not induce directional hypokinesia, but did induce a withdrawal bias.

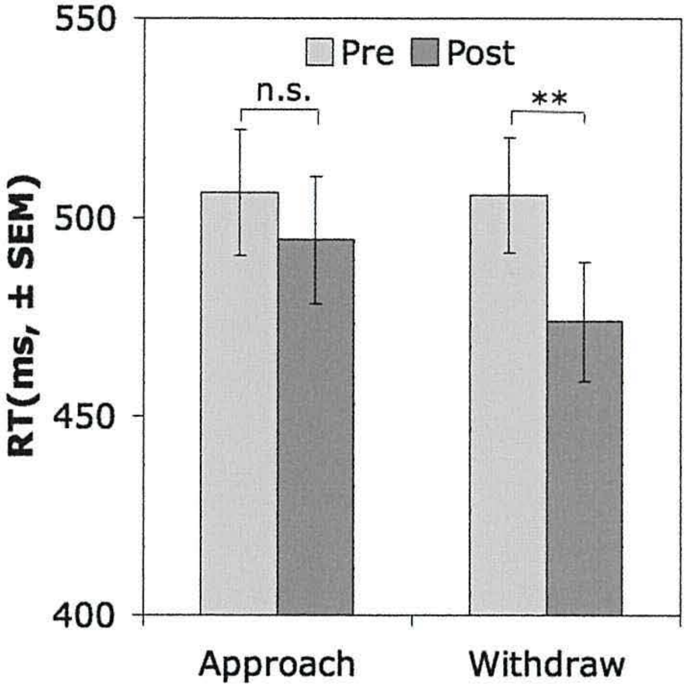

Figure 3.3. Mean RTs for the performance of the leftward-shifting prism group in the approach/withdrawal task before and after prism adaptation. Significance levels for paired t-test comparisons between conditions are indicated by the number of asterisks (** indicates $p<0.005$; n.s. indicates $p>0.05$).

Rightward-shifting prism group

Analysis of the mean RTs for the directional hypokinesia task revealed no main effects or interactions involving Session, therefore lateral movement was not influenced by prism adaptation. There was, however, a significant main effect of Direction which was driven by a significant Direction x Hand interaction (see Figure 3.4; $F(1,18)=14.26$, $p<0.005$). Participants performing the motor tasks with their right hand were significantly faster to make leftward movements (M=430.6, SEM=20.7) than rightward movements (M=483.2, SEM=23.3); $t(9)=4.26$, $p<0.005$. In contrast there was no significant difference in reaction times for leftward (M=438.6, SEM=16.5) and rightward (M=424.2, SEM=12.4) movements for the participants using their left hand ($t(9)= 1.13$, $p=0.28$).

Adaptation to rightward-shifting prisms did not influence approach or withdrawal behaviour, with no significant main effects or interactions in the analysis of the mean RTs for this task ($ps>0.05$).

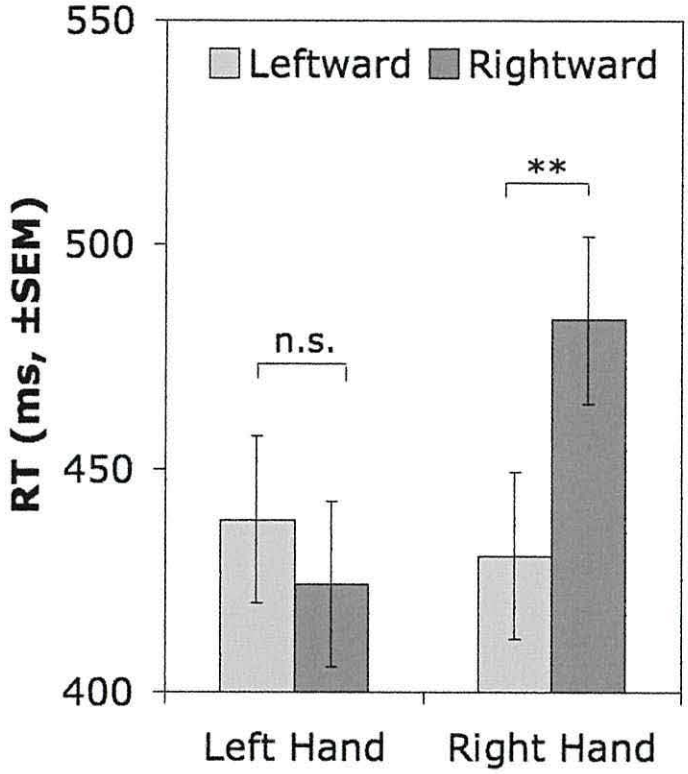

Figure 3.4. Mean RTs for the performance of the rightward-shifting prism group for leftward and rightward movements of the left or right hand. Significance levels for paired t-test comparisons between conditions are indicated by the number of asterisks (** indicates $p<0.005$; n.s. indicates $p>0.05$).

Discussion

The main result of Experiment 3.1 was that adaptation to leftward-shifting prisms decreased reaction times for pulling a lever towards the body in response to neutral stimuli, which can be likened to the withdrawal bias that Denny-Brown observed in neglect patients and parietal lesioned monkeys. Leftward prism adaptation did not, however, induce directional hypokinesia. The withdrawal bias in the leftward-shifting prism group occurred regardless of whether participants used their adapted or unadapted hand for the motor task, and therefore cannot be attributed to the influence of the motor after-effect itself but some higher-level influence of prism adaptation.

Denny-Brown described a withdrawal bias in patients with parietal lobe lesions that generalised from their reflexive withdrawal from light touch, to withdrawal from awareness of their disability (anosognosia). An improvement in such a pervasive deficit after prism adaptation may explain why the treatment has been so successful in improving clinical symptoms and functional recovery (Keane et al., 2006). Further research examining approach and withdrawal behaviour in neglect patients before and after prism adaptation would shed light on this possibility.

For the rightward-shifting prism group there was no change in performance as a result of prism adaptation in either task. There was, however, a significant Hand x Direction interaction in the directional hypokinesia task, reflecting rightward movements that were 53ms slower than leftward movements for participants who used their right hands to perform the task (compared to a 14ms rightward movement *advantage* for participants using their left hand). In light of this finding I re-examined the performance of the leftward-shifting prism group and discovered that they too showed a tendency, albeit a non-significant one, for slower rightwards compared to leftwards movements, which was more evident for participants using their right hand (16ms difference) than those using their left hand (7ms difference). Why it would take longer for participants to make rightward movements with their right hand is unclear. I can only speculate that in some individuals the accustomed pronated posture of the right hand for writing may create a bias against supination that is not expressed in the left hand, and that this was true for more participants in the rightward-shifting prism group than in the leftward-shifting prism group.

Denny-Brown associated the general behavioural withdrawal of neglect patients with the reflexive withdrawal of the hand that can be observed in patients with parietal lesions upon light tactile stimulation of the outstretched hand. More recently, withdrawal has been examined within the field of social cognitive neuroscience. Researchers within this field have drawn associations between a person's evaluation of or attitude about an object and the behaviour they direct towards that object (Solarz, 1960). There is now considerable evidence that the automatic evaluation of stimuli predispose behaviour consistent with the evaluation. One such evaluation-behavioural link is that positive evaluations predispose flexion responses (e.g. pulling a desired object closer to us) and negative evaluations predispose extension responses (e.g. pushing noxious objects away from us; Da Gloria, Pahlavan, Duda, & Bonnet, 1994; Duckworth, Bargh, Garcia, & Chaiken, 2002). This was first demonstrated by Chen and Bargh (1999), who showed that participants were faster to respond to negatively valenced stimuli when pushing a lever away than when pulling it towards them, but were faster to respond to positively valenced stimuli by pulling than by pushing the lever. These associations can be bi-directional: Cacioppo, Priester and Berntson (1993) found that participants who were asked to evaluate meaningless ideographs while pushing upwards with their hand on the undersurface of a table (requiring flexion) subsequently ranked the ideographs more positively than those that they evaluated while pushing downwards with their hand on the top of a table (requiring extension).

The evidence that positive and negative appraisals are associated with flexion and extension of the arm respectively is in direct contradiction to Denny-Brown's description of withdrawal in monkeys and patients with parietal lobe injury as a pulling away of the limbs and body. His classification of the withdrawal bias would predict faster retraction of the limb, or arm flexion, following adaptation to leftward-shifting prisms, which is indeed the pattern reflected in the results of this experiment. However, in conflict with this Chen and Bargh (1999) associated flexion with responses to positive stimuli - approach responses. One important difference between these authors is that when approach and withdrawal is studied within the field of social cognitive neuroscience, it is in the context of emotional elicitors or participant appraisal of the stimuli. In these studies the flexion response association for withdrawal is absent when the participant makes no stimulus evaluations. Rotteveel and Phaf (2004) found that the flexion and extension associations that Chen and Bargh (1999) demonstrated for emotionally valenced stimuli were not observed when stimuli were not under conscious evaluation. Similarly, Cacioppo and colleagues found that flexion and extension responses only influenced later evaluations of meaningless ideographs if participants were also asked to evaluate them during the original motor task.

Further studies in social cognitive neuroscience have found that the specific linking of positive and negative evaluations to flexion and extension can be reversed when contextual factors or action consequences are changed. Wentura, Rothermund and Bak (2000) showed that participants were faster to push a button in response to positive compared to negative stimuli (an approach response requiring push/extension) and were faster to release the button in response to negative compared to positive stimuli (a withdrawal response requiring pull/flexion). Markman and Brendl (2005) showed that the associations between flexion or extension and approach or withdrawal depended on the consequences of the action and the participants' representation of themselves in space. Participants were faster to move the lever in the direction that moved negatively valenced words away from a representation of themselves on the computer monitor, regardless of whether the action required was flexion or extension. Similarly, for positively valenced words participants were faster to move the lever in the direction that moved the word towards the representation of themselves, irrespective of the action required (see also Eder & Rothermund, 2008; Lavender & Nosaka, 2008). These results show that the meaning or consequence of motor responses is intrinsic to the behavioural predispositions evoked by emotional-motivational states.

In summary, social cognitive research has associated withdrawal emotions with arm extension. This association is dependent on both the evaluation of the stimulus by the participant, and the meaning or outcome of the action; and it can be eliminated or reversed by changing the task requirements. In contrast, the withdrawal bias described by Denny-Brown is a motor-intentional bias that is not intrinsically tied to evaluations of external stimuli, but is a generalised behavioural response to visual and tactile stimuli, irrespective of the emotional valence. As the approach-withdrawal task in Experiment 3.1 involved no emotional elicitors or evaluative judgments, I argue that the finding of faster flexion observed in the leftward-shifting prism group is a withdrawal bias like that which Denny-Brown observed in patients with parietal lobe injury. Nonetheless, due to the conflicting associations between extension or flexion and the withdrawal response, a second experiment was conducted in which the effects of prism adaptation on approach and withdrawal were re-examined using a task in which the implication of the required action was more apparent.

EXPERIMENT 3.2: THE EFFECT OF PRISM ADAPTATION ON APPROACH AND WITHDRAWAL STEPPING.

The affects of prism adaptation on approach and withdrawal were examined using a task in which participants stepped towards or away from arrow stimuli displayed on a monitor. To encourage a strong cueing of approach and withdrawal, stimuli were arrows that were drawn to give the illusion of verging into or out of the computer screen (Figure 3.5). If prism adaptation induces a withdrawal bias, a decrease in backwards step initiation time would be observed in participants who had adapted to leftward-shifting prisms.

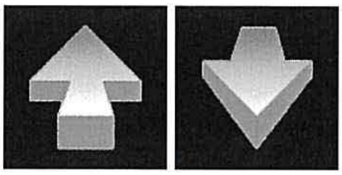

Figure 3.5. Arrow stimuli for the forwards (approach) and backwards (withdrawal) conditions (Maxwell & Davidson, 2007).

Method

Participants

Fourteen male and 26 female participants were recruited for the study (Mean age =22 years, *SEM*=0.55; handedness=-0.875, *SEM*=0.03).

Apparatus

A schematic of the stepping platform is shown in Figure 3.6. Step initiation times were recorded via two 1cm x 1cm microswitches positioned towards the centre of the board. Stimuli were presented on a 16” monitor that was positioned in an elevated position such that the centre of the screen was 156.5cm above the ground. At this height the vertical screen centre was approximately level with the participant’s eye level (Mean level of eyes above the ground=159.0, *SEM*=1.6, range=149 to 180cm).

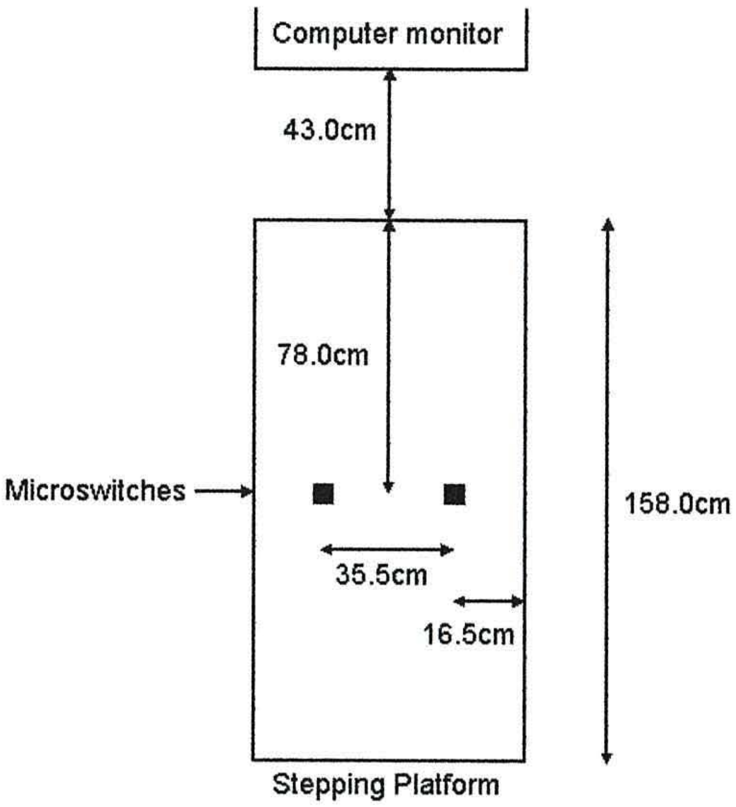

Figure 3.6. Schematic of the stepping platform used for the stepping task, viewed from above (not to scale).

Stimuli and Procedure

Experiment 3.1 used a long prism adaptation period (20 minutes). Since the results showed a robust after-effect in the late-test phase a more conventional adaptation period was used in Experiment 3.2 (2.5 minutes). This shorter adaptation period also allowed the use of a faster, ballistic, pointing rate (1Hz), which has been shown to increase the magnitude of adaptation after-effect (Redding & Wallace, 1992). The final change to the adaptation procedure was that participants received visual feedback of the second half of their pointing movement (continuous feedback) rather than just the terminal 2-3cm. This maximises the proportion of adaptive realignment that is due to alteration of proprioceptive (compared to visual) references (Cohen, 1967): a measure that may be more likely to produce higher-level motor-intentional effects. Aside from these changes, the procedure for the prism adaptation was identical to that used for Experiment 3.1.

Stepping task

Stimuli for the stepping task were presented as greyscales figures on a black background. At the beginning of each trial participant stood on the stepping platform with the balls of their feet over each of the microswitches such that the microswitches were depressed. Once they were in position the experimenter initiated the trial by pressing a mouse button. A 0.6° x 0.6° fixation cross appeared. After a pause that varied randomly between 1000 and 3000 ms the fixation cross was replaced by a 1.6° x 1.6° arrow (Figure 3.3). The arrows were based on those used by Maxwell and Davidson (2007) and were designed to strongly suggest an illusion of moving into the screen or verging out of the screen. The participant's task was to step in the direction consistent with the arrow direction. They were asked to take a large step with each foot such that their body moved towards or away from the stimuli. The arrow remained on the screen until one of the switches was released, after which it was replaced by a blank screen. To keep the stepping as natural as possible, participants were not instructed to use any particular foot as their leading foot, however the foot with which the step was initiated was recorded for each trial. Participants completed 30 forward and 30 backward trials in pseudorandom order for each pre- and post-adaptation block.

Results

Prism Adaptation

There was a significant Group x Session interaction (*F*(2, 68)=107.28, *p*<0.001), which reflected significant adaptation after-effects for both groups, which were maintained to the late-test (see Tables 3.3 and 3.4 below).

Table 3.3. Summary of the pointing errors for the leftward-shifting prism group in Experiment 3.2.

Session	M	SEM	t (compared to baseline)	p
Pre	0.14	0.48	-	-
Post	4.26	0.59	9.89	<0.001
Late	2.80	0.60	7.14	<0.001

Table 3.4. Summary of the pointing errors for the rightward-shifting prism group in Experiment 3.2.

Session	M	SEM	t (compared to baseline)	p
Pre	0.07	0.56	-	-
Post	-4.45	0.78	8.28	<0.001
Late	-3.56	0.74	7.67	<0.001

Stepping Task

The proportion of trials that were initiated with the left compared to right foot were analysed and there were no significant main effects or interactions (*ps*>0.05). There were also no main effects or interactions involving Foot Preference when this was included in a preliminary analysis of RTs, therefore data were collapsed across this variable for further analysis.

Leftward-shifting prism group

The analysis revealed a main effect of Session (*F*(1,17)=8.71, *p*<0.01), with faster step initiation times in the pre-adaptation stepping task (*M*=586.3, *SEM*=20.9) than the post-adaptation stepping task (*M*=612.7, *SEM*=24.8). There was also a main effect of Direction (*F*(1,17)=8.53, *p*<0.05) reflecting faster initiation times for forward stepping (*M*=579.0, *SEM*=26.5) than backward stepping (*M*=620.0, *SEM*=20.2). The most relevant finding, however, was a significant Session x Direction interaction (*F*(1,17)=6.67, *p*<0.05), which is plotted in Figure 3.7. Before prism adaptation participants showed faster step initiation times for forward stepping (*M*=558.2, *SEM*=24.0) compared to backward stepping (*M*=614.3, *SEM*=19.4); *t*(17)=4.47, *p*<0.001. After prism adaptation there was no significant difference between RTs for forward stepping (*M*=599.8, *SEM*=30.0) and backward stepping (*M*=625.6, *SEM*=21.9); *t*(17)=0.158. That is, the difference between the time taken to initiate withdrawal versus approach responses decreased following prism adaptation.

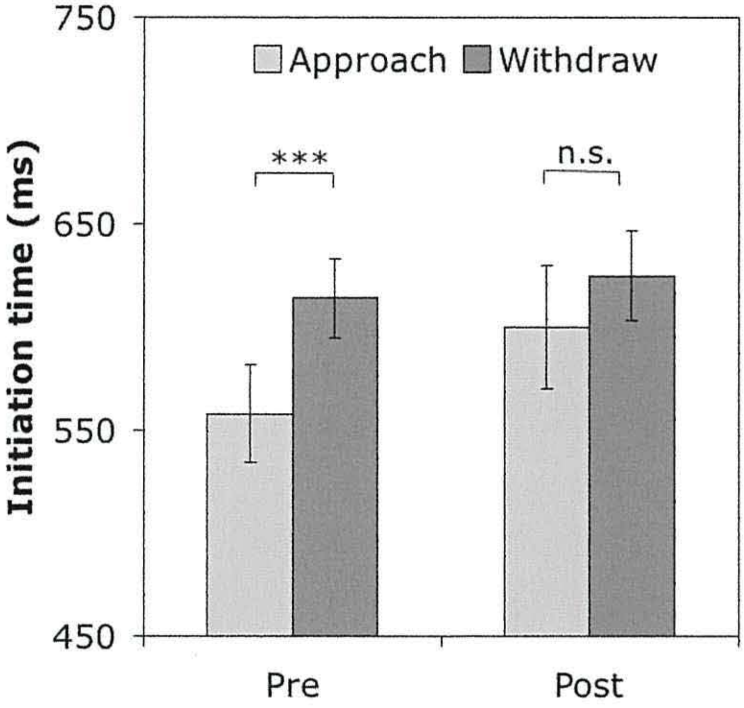

Figure 3.7. Mean initiation times for forward (approach) and backward (withdrawal) stepping of the leftward-shifting prism group before and after prism adaptation (*** indicates $p<0.001$; n.s. indicates $p>0.05$)

Rightward-shifting prism group

As was revealed for the leftward-shifting prism group, there were significant main effects of Session ($F(1,17)=7.96$, $p<0.05$) and Direction ($F(1,17)=8.82$, $p<0.01$) reflecting faster step initiation times before prism adaptation ($M=555.2$, $SEM=18.8$) than after prism adaptation ($M=577.9$, $SEM=21.8$), and for forward movements ($M=537.5$, $SEM=25.2$) than backward movements ($M=595.6$, $SEM=18.9$). There was also a significant Session x Direction interaction ($F(1,17)=8.38$, $p<0.05$), which is plotted in Figure 3.8. There were faster initiation times for forward steps ($M=518.0$, $SEM=24.1$) than backwards steps ($M=591.5$, $SEM=17.8$) before prism adaptation ($t(17)=3.74$, $p<0.005$). Following prism adaptation this difference was reduced, although a trend remained for faster RTs for forwards steps ($M=556.0$, $SEM=27.3$) compared to backward steps ($M=600.0$, $SEM=20.7$); $t(17)=2.09$, $p=0.052$).

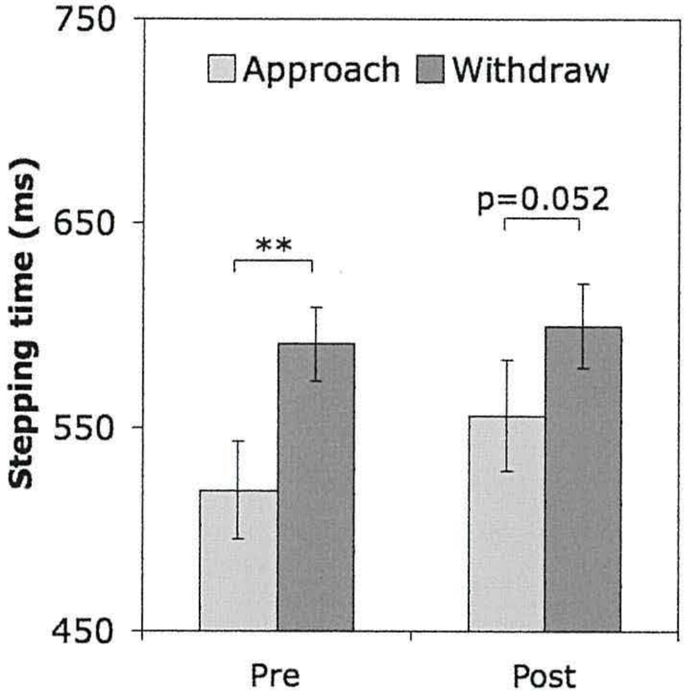

Figure 3.8. Mean initiation times for forward (approach) and backward (withdrawal) stepping of the leftward-shifting prism group before and after prism adaptation (** indicates $p<0.005$).

Comparison of leftward- and rightward-shifting prism groups

Since both the leftward- and rightward-shifting prism groups demonstrated a reduction in the RT difference for the initiation of forward compared to and backward stepping, a further analysis was performed to directly compare the performance of the two groups. For each participant the mean increase in RT was calculated for both stepping directions by subtracting the pre-adaptation RT from the post-adaptation RT. These were subjected to a two-way ANOVA of Prism (left, right) x Direction (forwards, backwards). A main effect of Direction ($F(1,34)=5.9$, $p<0.05$) indicated that RTs increased more for approach stepping ($M=12.7$, $SEM=5.7$) than for withdrawal stepping ($M=4.4$, $SEM=5.0$). However, the interaction of Prism and Direction was not significant ($F(1,34)=0.14$, $p=0.71$), indicating no difference between RT changes for the two groups.

Discussion

Before prism adaptation participants were faster to initiate forwards than backwards stepping. For both groups this difference decreased following prism adaptation. A larger RT increase for forward stepping compared to backward stepping is consistent with an approach deficit (i.e., a relative withdrawal bias) following prism adaptation. However, these data do not indicate differential effects of adaptation to leftward- and rightward-shifting prisms. Therefore, one interpretation is that some influence of practice, boredom or fatigue influenced stepping such that RTs for the forward and backward directions were equal in the second block. A second possibility is that prism adaptation significantly perturbed approach and withdrawal behaviour for this particular task, regardless of the direction of prismatic shift. Distinguishing between these explanations is not possible with these data, but requires a sham adaptation condition in which participants perform the stepping task before and after 'adaptation' to neutral lenses.

While acknowledging that the changes observed in the stepping task could be explained by effects of practice or fatigue, it unlikely that they were a direct result of the low-level adaptation after-effect. The adaptation after-effect is highly specific to the limb used for adaptation and the movement that was performed during the adaptation period. For example, Morton and Bastian (2004) showed that adaptation of target reaching does not generalise to walking.

There is no published research on the affect of prism adaptation on step initiation. In healthy participants, prism adaptation produces asymmetrical locomotor after-effects in healthy participants, with larger errors in walking trajectory following adaptation to leftward-shifting prisms than to rightward-shifting prisms. In single-case studies of neglect patients, prism adaptation has reduced the leftward bias in the walking trajectory (Folegatti et al., 2008) and improved kinematic and kinetic measures of gait (Bacchini et al., 2006). Prism adaptation also influenced lateral postural control in patients with right hemisphere lesions (Tilikete et al., 2001) and neurologically healthy participants (Michel, Rossetti, Rode, & Tilikete, 2003). The lead leg of the participants in Experiment 3.2 stepping was unchanged by prism adaptation, and did not influence the speed of forward or backward stepping, which could be expected if locomotor and postural control had a major influence in this task. If the observed changes in RTs for forward stepping are due to higher-level influences of leftward and rightward- prism adaptation, they could not be attributed to these asymmetrical locomotor and postural changes.

As explained in the introduction to this chapter, the aim of this research was to examine whether adaptation to leftward-shifting prisms could induce two neglect-like motor-intentional biases in healthy participants: directional hypokinesia and the withdrawal bias. The results of Experiment 3.1 showed a prism-related change in performance for forwards and backwards movements, but no change on the lateral movement task. This may have been because the lever task required only small movements of the hand, which held a centrally attached object (the lever) throughout the entire task. Experiment 3.3 re-examined whether prism adaptation would influence lateral movements in healthy participants using a reaching task that required larger movements.

EXPERIMENT 3.3: THE EFFECT OF PRISM ADAPTATION ON LEFTWARD AND RIGHTWARD REACHING MOVEMENTS

Participants were tested on a directional reaching task that was based on that used by Sapir and colleagues (2007). In their task, participants reached from a starting button positioned on a table in front of them to touch targets that appeared on the left or right of a computer monitor. In the present study participants responded to arrows that appeared on the computer screen by reaching to unseen buttons positioned on the table forwards and to the left or right of a central starting button. Unlike the task described in Experiment 3.1, this required more obvious directional movements, and the release of one object and acquisition of another (the buttons). If prism adaptation can induce directional hypokinesia in healthy participants then faster leftward responses would be expected in participants who had adapted to leftward-shifting prisms.

Method

Participants

Participants were 16 males and 24 females (Mean age=24 years, *SEM*=0.96; handedness=-0.85, *SEM*=0.021).

Apparatus

For the directional reaching task a three-button array was arranged in front of a computer monitor. Each button measured 4.8 x 4.8 cm. One was placed in line with the participant's midline with a distance of 17.5cm between the edge of the table and the closer edge of the button. The two remaining buttons were placed 11cm to the left and right of the participant's midline respectively, with a distance of 34cm between the edge of the table and the closer edge of the button.

Stimuli and Procedure

Prism adaptation

The prism adaptation procedure was identical to that described for Experiment 3.2 above.

Directional reaching task

Participants were seated 60cm from the computer screen and rested their chin in a chinrest such that their eyes were level with the middle of the computer screen. Visual stimuli were similar to that used for the directional hypokinesia task in Experiment 3.1. Each trial began with the presentation of a 0.11° x 0.11° central fixation cross, with a simultaneous 500Hz tone that sounded for 500ms. At the sounding of this tone the participants were required to press and hold the central button. After a period that varied randomly between 750 and 1500ms, a 0.11° x 0.13° arrowhead was presented pointing to the left or right. Participants were required to release the central button and reach to press and hold the indicated button as quickly as possible. The arrow disappeared once the starting button was released. Participants held the button until the tone sounded for the beginning of the next trial, which happened with an inter-trial interval that varied randomly between 750 and 1500ms. In each of the pre- and post-adaptation blocks participants completed a total of 40 trials for each of the left or right reaching directions in pseudorandom order. Two measures were recorded for later analysis: the time between the appearance of the arrow and the release of the starting button ('initiation time') and the time between the release of the starting button and the depression of the left or right button ('movement time').

Results

Prism Adaptation

There was a significant Group x Session interaction (*F*(2,76) = 144.169, *p*<0.001), which reflected significant adaptation after-effects for both groups, which were maintained to the late-test (see Tables 3.5 and 3.6 below).

Table 3.5: Summary of the pointing errors for the leftward-shifting prism group in Experiment 3.3.

Session	M	SEM	t (compared to baseline)	p
Pre	0.14	0.45	-	-
Post	4.23	0.36	11.0	<0.001
Late	2.40	0.52	4.58	<0.001

Table 3.6: Summary of the pointing errors of the rightward-shifting prism group in Experiment 3.3.

Session	M	SEM	t (compared to baseline)	p
Pre	0.80	0.45	-	-
Post	-4.43	0.44	11.05	<0.001
Late	-3.13	0.52	10.45	<0.001

Directional Reaching Task

Leftward-shifting prism group

There were significant interactions between Hand and Reach Direction in both the analysis of initiation time ($F(1,18)=12.45$, $p<0.005$) and movement time ($F(1,18)=30.82$, $p<0.001$), which are plotted in Figure 3.9 A and B below.

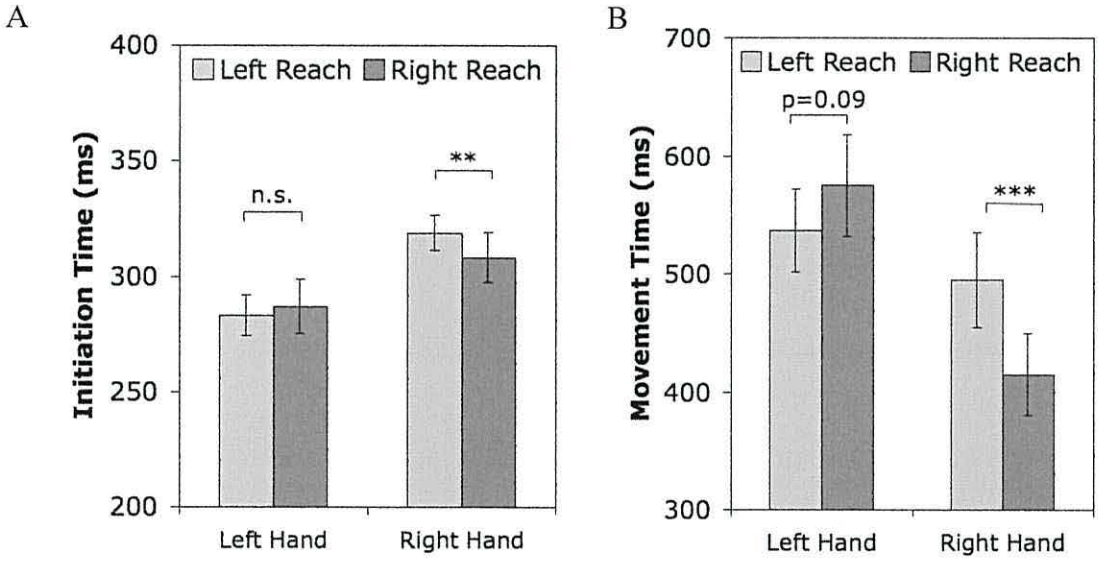

Figure 3.9. Mean initiation times (A) and movement times (B) for left and right reaching movements made by participants in the leftward-shifting prism group using the left or right hand (** indicates $p<0.005$; *** indicates $p<0.001$; n.s. indicates $p>0.05$).

For participants completing the reaching task with their left hand, there was no significant difference between initiation times for leftward reaches (*M*=283.3, *SEM*=8.79) compared to rightward reaches (*M*=287.3, *SEM*=7.63); $t(9)=1.193$, $p=0.26$. However participants completing the task with their right hand were significantly faster to initiate rightward reaches (*M*=308.3, *SEM*=10.7) compared to leftward reaches (*M*=318.8, *SEM*=11.8); $t(9)=4.40$, $p<0.005$.

Similarly, in the analysis of movement times there was a non-significant trend for faster RTs for leftward movements (*M*=537.0, *SEM*=35.1) compared to rightward movements (*M*=574.6, *SEM*=40.0) for participants completing the task using their left hand ($t(9)=2.31$, $p=0.09$). Participants who were using their right hand were significantly faster to make rightward reaching movements (*M*=415.3, *SEM*=35.3) compared to leftward reaching movements (*M*=495.3, *SEM*=43.3); $t(9)=5.92$, $p<0.001$).

There were no further significant main effects in the analysis of initiation and movement times for the left prism group.

Rightward-shifting prism group

The analysis of initiation times revealed no significant main effects or interactions ($ps>0.05$). For the analysis of movement times there was a significant main effect of Reach Direction ($F(1,18)=11.57$, $p<0.005$), reflecting faster movement times for rightward reaches (*M*=434.6, *SEM*=33.6) compared to leftward reaches (*M*=473.1, *SEM*=30.5). This was driven by a significant Hand x Reach Direction interaction ($F(1,18)=42.28$, $p<0.001$) which is plotted in Figure 3.10 below. This interaction reflected a similar pattern as that shown by the leftward-shifting prism group. That is, there was no significant difference between movement times for leftward reaches (*M*=459.8, *SEM*=51.5) compared to rightward reaches (*M*=494.9, *SEM*=61.2) for participants who were using their left hand to complete the task ($t(9)=1.65$, $p=0.133$), but participants who were using their right hand were significantly faster to make reaching movements towards the right side (*M*=374.3, *SEM*=27.8) compared to the left (*M*=486.4, *SEM*=32.6); $t(9)=14.3$, $p<0.001$.

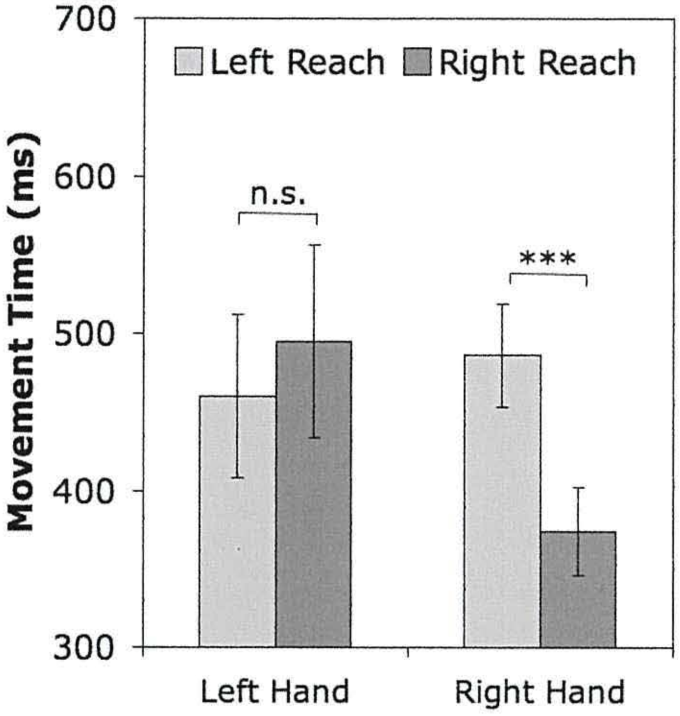

Figure 3.10. Mean movement times for left and right reaching movements made by participants in the rightward-shifting prism group using the left or right hand (*** indicates $p<0.001$; n.s. indicates $p>0.05$).

Discussion

The initiation and movement times of the participants were unchanged by prism adaptation indicating that, as with Experiment 3.1, adaptation to leftward-shifting prisms did not induce directional hypokinesia or bradykinesia. There were also findings of interactions between Hand and Reach Direction in the analyses of initiation time (leftward-shifting prism group only) and movement times (leftward- and rightward-shifting prism groups). These interactions appear to reflect a compatibility effect that is greater in the right (dominant) hand: participants were faster to initiate and execute movements to the buttons on the same side of their body as the hand they were using to make the movement. This is in contrast with the Hand x Movement Direction interaction found in the directional hypokinesia task for Experiment 3.1, which reflected *longer* RTs for rightward movements with the right hand. This may be because of the different movement tasks used for the two experiments.

The results of Experiments 3.1 and 3.3 provided no evidence that adaptation to leftward-shifting prisms can induce directional hypokinesia in healthy participants, in contrast to the neglect-like patterns of performance that have been induced by prism adaptation on tasks that have perceptual-attentional demands. Colent and colleagues (2000) found that changes in line bisection performance after prism adaptation were larger for a 'perceptual' version of the test that did not involve overt arm movements (i.e. the Landmark Test) than for a manual version, however this may be due to the greater sensitivity of this test in detecting spatial bias (Jewell & McCourt, 2000).

The failure to induce slower leftward movement in healthy participants contrasts with the results of Rossetti and colleagues (2005; in Pisella et al., 2006), who found that neglect patients who showed slowness in picking up a ball if their instruction was to throw it to the left had a reversal of this bias following adaptation to rightward-shifting prisms. These results suggest that adaptation to rightward-shifting prisms can improve directional hypokinesia. Significant effects of prism adaptation in neglect patients where no change is found on similar aspects of performance in healthy participants is not unprecedented. Berberovic and colleagues (2004) found that prism adaptation improved the performance of neglect patients on a temporal order judgements task, although the performance of healthy participants was unchanged. Prism adaptation may therefore influence the performance of neglect patients through different mechanisms, or to a greater extent, than its influence on healthy participants.

GENERAL DISCUSSION

The research presented in this chapter examined the effect of prism adaptation on motor-intentional performance in healthy participants. The results suggest that adaptation to leftward-shifting prisms can induce a withdrawal bias similar to that observed in patients with parietal lobe lesions (Experiments 3.1). However, adaptation to leftward-shifting prisms did not induce neglect-like directional hypokinesia (Experiments 3.1 and 3.3).

Some consideration must be given as to why a withdrawal bias but not directional hypokinesia was observed following adaptation to leftward-shifting prisms. Although little is known about the neurological mechanisms of the visuo-spatial effects of prism adaptation in healthy participants, a reasonable hypothesis is that prism adaptation alters activity in cortical areas that are also associated with neglect. Whether prism adaptation can induce other neglect-like symptoms may depend on the neural substrates of these behaviours.

Denny-Brown (1958) noted that withdrawal behaviour was particularly pronounced in patients with lesions of the lateral parietal lobe, an area that is also heavily implicated in both neglect (Vallar & Perani, 1986) and prism adaptation. Through systematic ablation of frontal and parietal areas in monkeys, he localised the posterior parietal cortex as an area that when lesioned produced withdrawal from both tactile and visual stimuli. In contrast, lesions to the cingulate gyrus and areas 6 and 8 of the frontal lobe (equivalent to the human frontal eye field) abolished the avoiding response and resulted in inappropriate approach behaviours (Denny-Brown and Chambers, 1958). If the changes in the visuo-spatial performance of healthy participants following prism adaptation is mediated by modification of parietal lobe activity, then it is possible that adaptation-induced perturbation of parietally-mediated activity could inhibit approach behaviour and release the withdrawal behaviour of the anterior areas, leading to the faster withdrawal responses displayed by the participants in Experiments 3.1.

For many years directional hypokinesia, or 'premotor' neglect, was thought to stem from lesions to frontal lobe areas (see Vallar, 2001, for a review). However this observation was challenged by evidence for slowed initiation of leftward reaches in patients with right IPL lesions, but not in patients with lesions to the right inferior frontal lobe (Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Mattingley, Husain, Rorden, Kennard, & Driver, 1998). Recently, clarification of the neural correlates of directional hypokinesia was provided by by Sapir and colleagues (2007), who compared the lesions of 52 neglect patients with and without directional hypokinesia. Areas that were uniquely implicated in the directional hypokinesia group were restricted to subcortical areas, specifically the ventral lateral putamen, claustrum and the white matter underneath the frontal lobe. These subcortical structures may be beyond the direct influence of prism adaptation, which would explain the failure to induce directional hypokinesia in healthy participants in the present study. This holds implications for the use of prism adaptation to treat directional hypokinesia in patients with neglect.

Denny-Brown described an association between the withdrawal bias and neglect, however two of the areas he associated with an approach bias (areas 6 and 8) are also frequently lesioned in neglect patients (Heilman & Valenstein, 1972b; Husain & Kennard, 1996; Vallar, 2001). Heilman (2004) argued that a contralesional approach bias may partially explain 'ipsilateral' neglect: a paradoxical deficit demonstrated by some patients with right frontal lobe lesions in which their performance is biased towards the *left* side of space. Further study of approach and withdrawal behaviour in neglect patients with parietal and frontal lobe injuries may provide new insights into neglect.

Although the bias away from the left side is the most definitive feature of neglect, emphasis has also been placed on the role of deficits that are no worse on one side of space than the other (Husain & Rorden, 2003). These 'non-lateralised spatial' and 'non-spatial' deficits include impaired spatial working memory (Husain et al., 2001), sustained attention (I. H. Robertson et al., 1997), and spatial updating (Pisella & Mattingley, 2004) and may contribute as much to the disability of neglect patients as their leftward inattention. The induction of a withdrawal bias in healthy participants suggests that prism adaptation, which for so long was thought to operate on strictly low-level processes, may be beneficial not only to the left inattention of neglect patients, but also to the associated non-lateralised spatial deficits. Indeed, benefits to such mechanisms may explain why prism adaptation has been a much more successful treatment technique than previously investigated methods.

Chapter 4

Prism adaptation reverses the local processing bias in patients with right temporo-parietal junction lesions

[2]ABSTRACT

Lesions to the right temporo-parietal cortex commonly result in hemispatial neglect. Lesions to the same area are also associated with hyperattention to local details of a scene and difficulty perceiving the global structure. This local processing bias is an important factor contributing to neglect and may contribute to the higher prevalence of the disorder following right compared to left hemisphere strokes. The present investigation provides evidence that prism adaptation reduces the local processing bias. In two experiments, five patients with right temporal-parietal junction lesions completed tests of hierarchical processing before and after visuomotor adaptation to rightward-shifting prisms. In Experiment 4.1, patients identified the global or local level of hierarchical figures in separate blocks (directed attention). In Experiment 4.2, they identified targets that could appear at either the global or local level on any given trial (divided attention). The results of Experiment 4.1 showed that before prism adaptation patients had difficulties ignoring the local elements when identifying the global component. This pattern reversed following prism adaptation. In contrast, the results across both experiments showed that patients were no different to control participants in the relative speed with which they identified local or global levels, a pattern that was unchanged by prism adaptation. Therefore the results show that, where patients had pathologically biased local processing, performance improved following prism adaptation. The results suggest that prism adaptation may improve non-lateralised spatial deficits that contribute to the neglect syndrome.

---

[2] A version of this chapter has been published in Brain: Bultitude, J.H., Rafal, R.D. & List, A. (2009). Prism adaptation reverses the local processing bias in patients with right temporo-parietal junction lesions. *Brain, 132(6)*, 1669-1677.

Neglect commonly follows lesions to the right temporo-parietal junction, or TPJ (Friedrich, Egly, Rafal, & Beck, 1998; Karnath, Huimmelback, & Küker, 2003). Right TPJ lesions are also associated with hyperattention to local details of a scene and difficulty perceiving global structure. Right hemisphere damage was first associated with global processing deficits by Delis and colleagues (1986) who asked patients with unilateral lesions to copy pictures in which identical smaller components are arranged to form larger shapes (so-called 'hierarchical' figures). Patients with large right hemisphere lesions such as those that lead to neglect tended to draw many copies of the local element in a disorganized arrangement, failing to reproduce the global structure (Figure 4.1A). In a later study Marshall and Halligan (1995) reported a patient with a large right hemisphere lesion who was able to identify the global form of hierarchical stimuli but when instructed to cross out all the local elements only crossed out targets on the right side, suggesting that she could not sustain a representation of the global form (Figure 4.1B). Similarly, a patient who failed to copy the left side of a figure following a right hemisphere lesion transposed the left-sided local details to the copied right side (Figure 4.1C), implying some processing of these local elements (Halligan, Marshall, & Wade, 1992). This local processing bias - or global processing deficit - was localised to the right TPJ through a series of reaction time studies involving patients with different focal lesions, with left TPJ deficits resulting in a local processing deficit (L. C. Robertson, Lamb, & Knight, 1988).

Although the local processing bias is not uniquely observed in patients with neglect, it is an important factor contributing to the disorder and may be one reason for the higher prevalence of neglect following right compared to left hemisphere damage (Rafal & Robertson, 1995). Patients can get locked onto small parts of the scene and fail entirely to perceive the critical big picture. Neglect severity is reduced under conditions that encourage the patients to deploy their attention more globally. For example, bisection bias is smaller when the to-be-bisected stimulus is a square rather than a line, probably because the rightward vertical side of the square enhances the right hemisphere's global processing capacity (Halligan & Marshall, 1994).

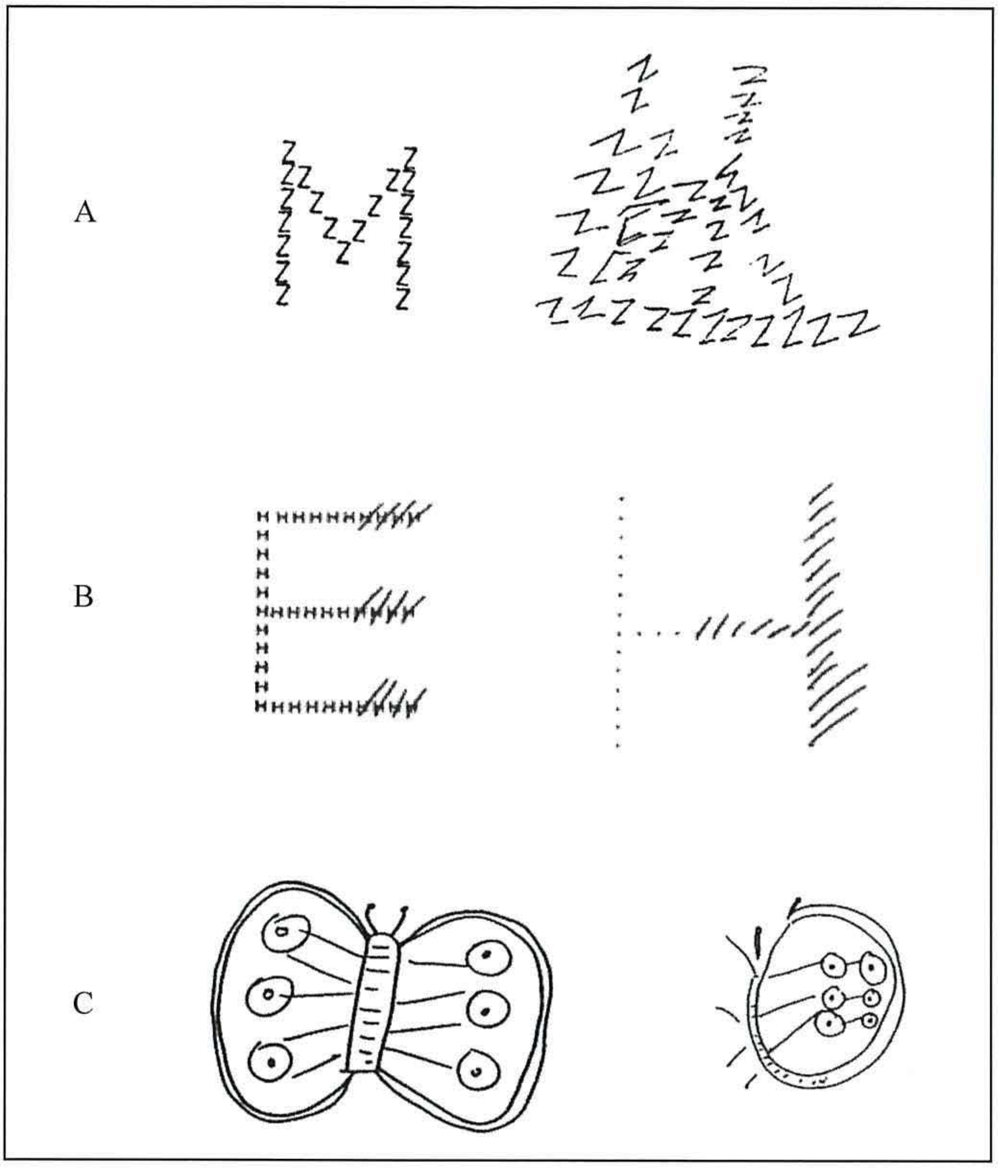

Figure 4.1. Examples of biased local processing in patients with right hemisphere lesions: A) a patient's copy (right) of a hierarchical figure (left) shows local elements arranged into an incorrect global form (Delis et al., 1986); B) a patient with neglect cancelled only the right-sided local elements of correctly identified global figure (Marshall & Halligan, 1995); C) A patient's copy (right) shows neglect of the stimulus figure (left), with left-sided local details transposed to the right (Halligan et al., 1992).

Similarly, performance is improved under conditions that reduce the number of local elements available to capture attention. Line cancellation performance is better when patients erase lines, eliminating the capture of attention by right-sided detail, than when they cancel over them (di Pellegrino, 1995; Mark, Kooistra, & Heilman, 1988). When a neglect patient was asked to place numbers on a clock face with all numbers on a single dial she showed the classic pattern of compressing all numbers to the right side, but she had accurate number placement with no spatial bias when instructed to place each number on a separate dial (di Pellegrino, 1995). Ishai and colleagues (1996) found that neglect patients could correctly discriminate between complete and incomplete pictures of daisies, but omitted left-sided detail when performing the more attentionally demanding task of copying complete daisies. These studies suggest that the capture of attention to right-sided local detail contributes to the severity of neglect.

Over the past decade, prism adaptation has emerged as a promising treatment for neglect, with benefits demonstrated on tests of visual perception, tactile perception, somatosensation, haptic exploration, and wheelchair navigation (Dijkerman et al., 2004; Jacquin-Courtois et al., 2008; Maravita et al., 2003; McIntosh et al., 2002; Pisella et al., 2002; Rossetti et al., 1998). Explanations for the clinical benefits of prism adaptation have generally described a leftward realignment of attention, for example through a resetting of the ocular-motor system (Serino, Angeli, Frassinetti, & Làdavas, 2006). The research in this chapter investigates another possibility: that adaptation to rightward-shifting prisms could improve neglect symptoms by alleviating the local processing bias. The effects of adaptation to rightward-shifting prisms on hierarchical processing were tested in five patients selected on the basis of right TPJ lesions using a directed attention task (Experiment 4.1) and a divided attention task (Experiment 4.2).

EXPERIMENT 4.1: THE EFFECT OF PRISM ADAPTATION ON HIERARCHICAL PROCESSING IN A DIRECTED ATTENTION TASK.

In separate blocks patients identified the global or local levels of hierarchical stimuli in which large S's and A's were formed out of small S's or A's (Figure 4.2). The stimuli could be congruent (e.g., a large S built of small S's) or incongruent (e.g., a large S built of small A's). This hierarchical processing task, first used by Navon (1977), allows measurement of the extent to which participants are able to ignore the information at one level while directing their attention to another. Navon found that healthy participants showed relative superiority of global processing. Participants had difficulty inhibiting their processing of the global form, with slower RTs for incongruent compared to congruent stimuli in the local block. In contrast, interference of the local form during the global block was absent. Participants also had faster overall responses to global than local targets.

It was predicted that before prism adaptation patients would show deficits in ignoring the local stimuli when identifying global forms relative to their ability to ignore global stimuli when identifying local forms. If adaptation to rightward-shifting prisms reduces the local processing bias, then this would be reflected by significantly smaller local interference and/or greater global interference after prism adaptation.

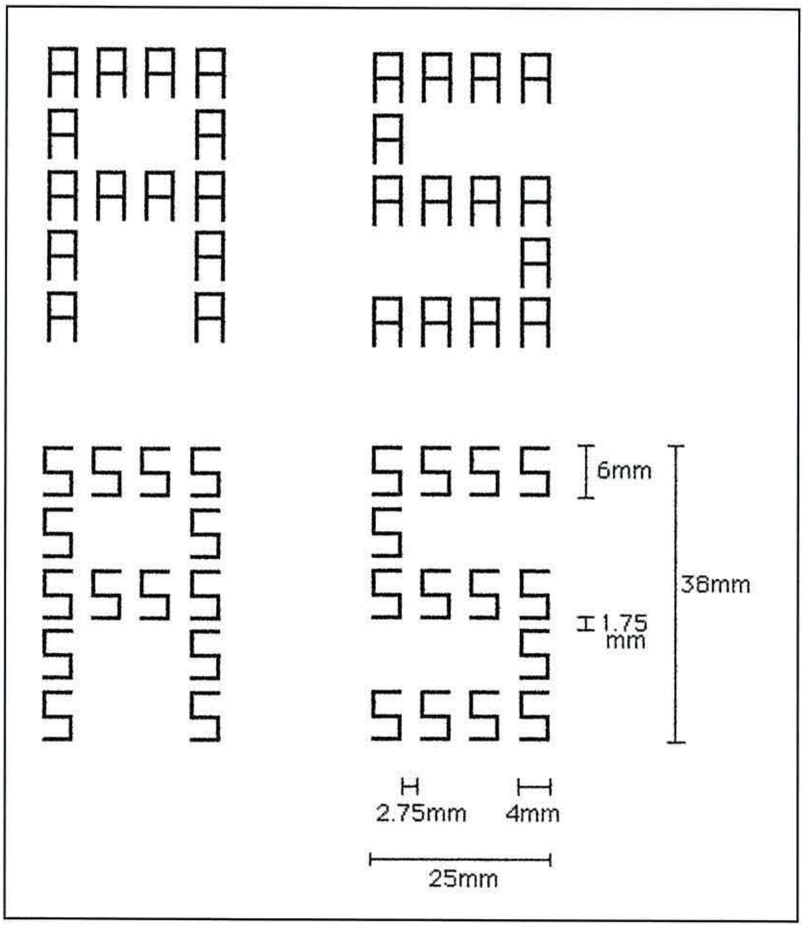

Figure 4.2. The experimental stimuli for the directed attention task, based on Navon (1977).

Methods

Participants

Patients

Five patients (mean age = 57 years, *SEM*=4.68) with chronic lesions to the right TPJ and intact visual fields were recruited and gave informed consent to participate in a research protocol approved by hospital and university ethic committees according to the Declaration of Helsinki. The clinical details of these patients are shown in Table 4.1 and their lesion locations are shown in Figure 4.3. Three patients (AC, GS and NB) showed visual extinction on neurological confrontation testing. Patients GS and JD had previously suffered from neglect, which had resolved by the time of testing. One patient, AC, showed neglect at the time of testing based on the results of standard pen-and-paper tests (see Table 4.2). This patient had also shown anosagnosia for his hemiplegia in the weeks immediately following his stroke, and some anosodiaphoria remained at the time of the present study (see Chapter 2, Case 2). In addition to the main experimental task he completed three pen-and-paper tests for neglect (Wilson et al., 1987) and showed improved performance only on the line bisection task (pre-adaptation: 14.6% vs. post-adaptation 0.3% rightwards error).

Table 4.1. Clinical details of the patients who participated in the study.

Patient	**Age**	**Sex**	**Type of stroke**	**Weeks since stoke**	**Handedness**	**Limb weakness‡**	**Visual extinction‡**	**Visual neglect‡**
AC	72	M	Ischemic	47	R	*	*	*
GS	62	M	Ischemic	111	L	*	*	§
NB	55	M	Subarr. Haem.	252	R		*	
JD	49	F	Ischemic	181	R	§	§	§
DB	46	M	Ischemic	31	R	§		

‡=based on standard neurological examination
*=present at time of testing, §=previously present but resolved

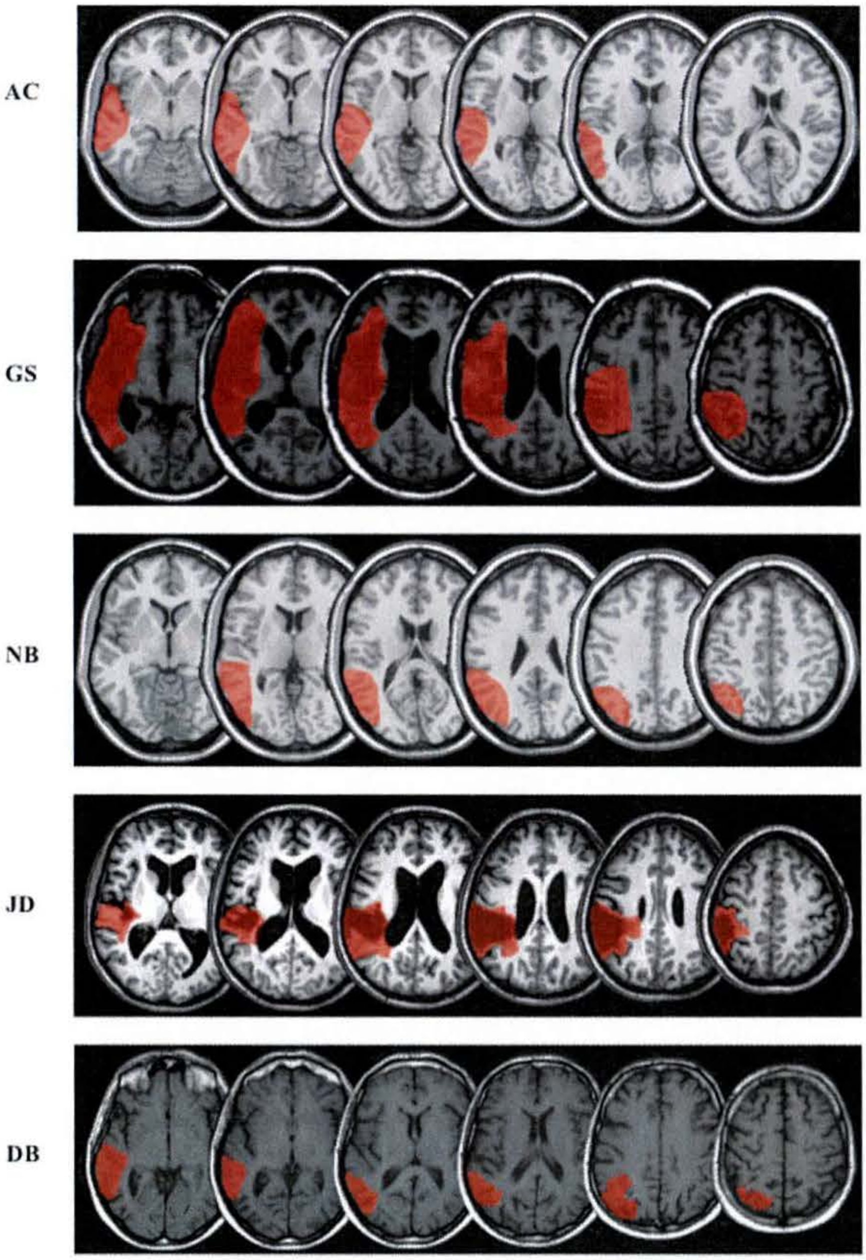

Figure 4.3. Axial MR slices showing lesions for the five patients. Images are presented in radiological format (the right side of the brain presented on the left side of the image) with affected areas in red. No MRI scans were available for patients AC or NB so lesions for these patients were drawn from CT scans onto a normal template brain. Note that AC's stroke progressed after the CT scan was taken, and his lesion is probably much more extensive than that shown in the reconstruction. For example, the figure shows preserved motor cortex and internal capsule, but the patient exhibited dense left-sided weakness and sensory loss.

Control Participants

Ten age- and gender-matched control participants were tested on the hierarchical processing task to provide a baseline with which to compare the pre- and post-adaptation performance of the patients. The control group had a mean age of 56 years (*SEM* = 3.0), and scored an average of -0.88 (*SEM*= 0.05) on the Edinburgh Handedness Inventory (where -1 denotes extreme right-handedness and +1 denotes extreme left handedness; Oldfield, 1971).

Table 4.2. Assessment of AC.

Test	Initial assessment (1 week before testing)	Pre-adaptation	Post-adaptation
Copying *	Neglected leftmost detail	Not tested	Not tested
Star Cancellation § (% hits)	92.7	Not tested	Not tested
Letter Cancellation § (% hits)	67.5	85.0	87.5
Line Bisection ‡ (% rightward error)	10.1	14.6	0.3
Article Reading ‡ (% words read)	19.4	82.7	77.7

* Marshall and Halligan (1993), § Wilson and colleagues (1987), ‡ adapted from Wilson and colleagues (1987)

Stimuli and Procedure

The patients completed the following sequence of tasks: 1) Pre-adaptation directed attention task, 2) Pre-adaptation open-loop pointing, 3) Prism adaptation, 4) Post-adaptation open-loop pointing, 5) Post-adaptation directed attention task. The control participants completed the directed attention task only, i.e., they did not undergo any prism adaptation.

1) Pre-adaptation directed attention task

A hierarchical processing task was designed based on the results of a pilot study with twelve healthy older participants such that approximately equal RTs and interference effects were obtained for global and local stimuli. Stimuli were presented on a computer screen positioned 60cm from the participant's eyes. Each participant identified target letters at the global or local levels of hierarchical stimuli in two separate blocks ('globally-directed' and 'locally-directed'), with practice provided prior to each block as required. The order of events for each trial is shown in Figure 4.4. The trial began with a 500Hz tone presented for 500ms. After a further delay of 100ms a 3mm x 3mm central fixation cross appeared. Participants were instructed to look at the cross throughout the entire trial. After 500ms the fixation cross was joined by a hierarchical stimulus (Figure 4.2) presented in the left or right visual field such that there was 24mm between the fixation cross edge and the inner edge of the hierarchical stimulus. The stimuli consisted of eleven small 4mm wide x 6mm high S's or A's (the local forms) arranged to form large 25mm wide x 38mm high S's or A's (the global form). The identity of the local and global forms could be identical (congruent) or different (incongruent), resulting in four stimuli. There were 16 repetitions of each of the four stimuli within each visual field, with a total of 128 trials per global and local block. These were presented in one block per attended level for all patients (counterbalanced between patients) except AC, who completed two global and two local blocks of 64 trials per block before and after prism adaptation in local-global-global-local order.

The stimulus remained on the screen for 500ms for patient AC and 200ms for all other participants, after which time it was replaced by a blank screen. In the locally-directed block the participants identified the local form. In the globally-directed block the participants identified the global form. Participants indicated their decision (S or A) by pressing one of two buttons on a standard mouse with the index and middle fingers of their right hand (that is, the patients' ipsilesional hand). Button assignment was counterbalanced between participants, who practiced the response mapping prior to the commencement of the experiment. The participants were instructed to respond as quickly and as accurately as possible. The participant's response ended the trial, with a timeout after 3000ms. There was an inter-trial interval of 1000ms.

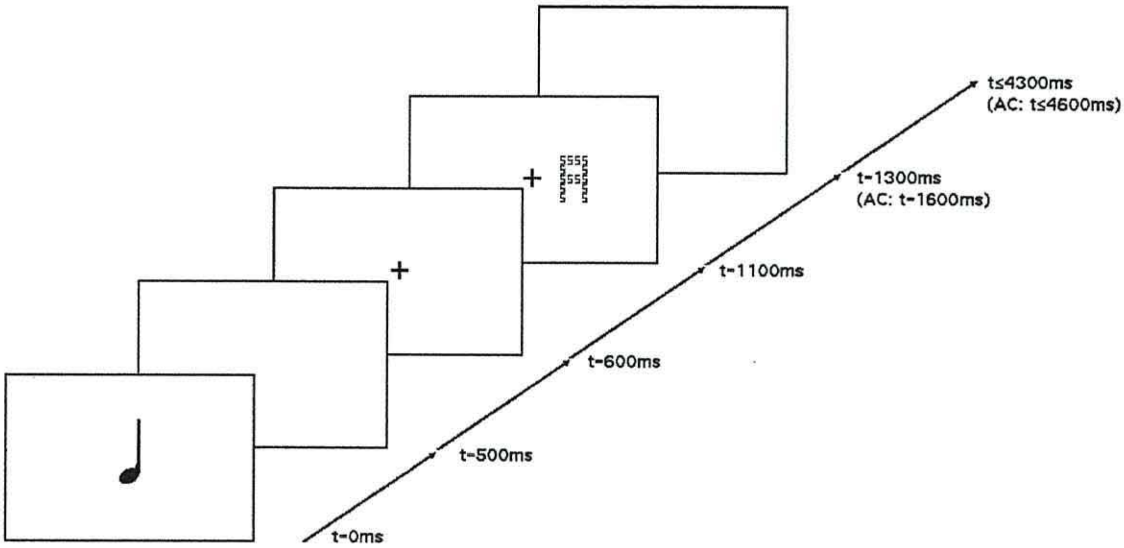

Figure 4.4. The timecourse of events for the hierarchical processing task. This example shows the stimulus appearing in the right visual field, however stimuli also appeared in the left visual field.

2) Pre-adaptation open-loop pointing

The patients' open-loop pointing errors were measured with the aid of a semi-circular panel (radius = 59 cm) that occluded their pointing arm from their vision. Three target lines were drawn on the visible upper surface of the panel radiating out at -10°, 0° and +10° from the patient's body midline. The panel was held under the patient's chin while they pointed their arm under each of the target lines four times in a pre-determined pseudorandom order, returning their hand to rest in front of their torso between each pointing movement. Pointing error for each of the twelve trials was measured by the experimenter to the nearest 0.5 degrees with the aid of markings drawn on the underside of the panel.

3) Prism adaptation

The panel was removed and the patients were fitted with prism glasses that had been constructed by inserting two adjustable Risley biprisms into optician's trial frames. These were set to induce a 15° rightward shift for all patients. The patients pointed with their right hand to visual targets held at eye level and arm's length 10° alternately to the left and right of body midline. The construction of the prism glasses was such that the first half of the patient's pointing movement was occluded from their view. They made 50 pointing movements as fast as possible, returning their hand to their torso in between each pointing movement.

4) Post-adaptation open-loop pointing

To confirm adaptation an open-loop pointing session was conducted immediately after prism adaptation using the same procedure as described above (2) for the pre-adaptation open-loop pointing.

5) Post-adaptation directed attention task

Patients completed the global and local processing tasks using the same procedure as described above (1).

Results

Prism Adaptation

The control participants were not tested with prisms and therefore no adaptation after-effect was measured. One-sample t-tests revealed that patients NB, JD and DB showed pre-adaptation pointing errors that erred significantly leftward ($p<0.001$). These errors were within the range of individual variability in open-loop pointing errors made by healthy control participants under similar conditions (for example, in Experiment 3.2 of Chapter 3 pre-adaptation open-loop pointing errors for individual participants ranged from -3.79° to +4.42°). Paired-samples t-tests comparing pre- and post-adaptation pointing errors for each individual confirmed that each of the five patients showed significant leftward after-effects ($p<0.001$; Figure 4.5). The average shift magnitude was 4.08°.

Hierarchical Processing

Analysis of hit rates

The healthy controls showed a 99% response rate, of which 96% of the responses were accurate. The response rates and accuracy of patients NB, GS, JD and DB were also at ceiling, with an average of 96% of trials responded to and 94% accuracy. Such low error rates precluded meaningful analyses.

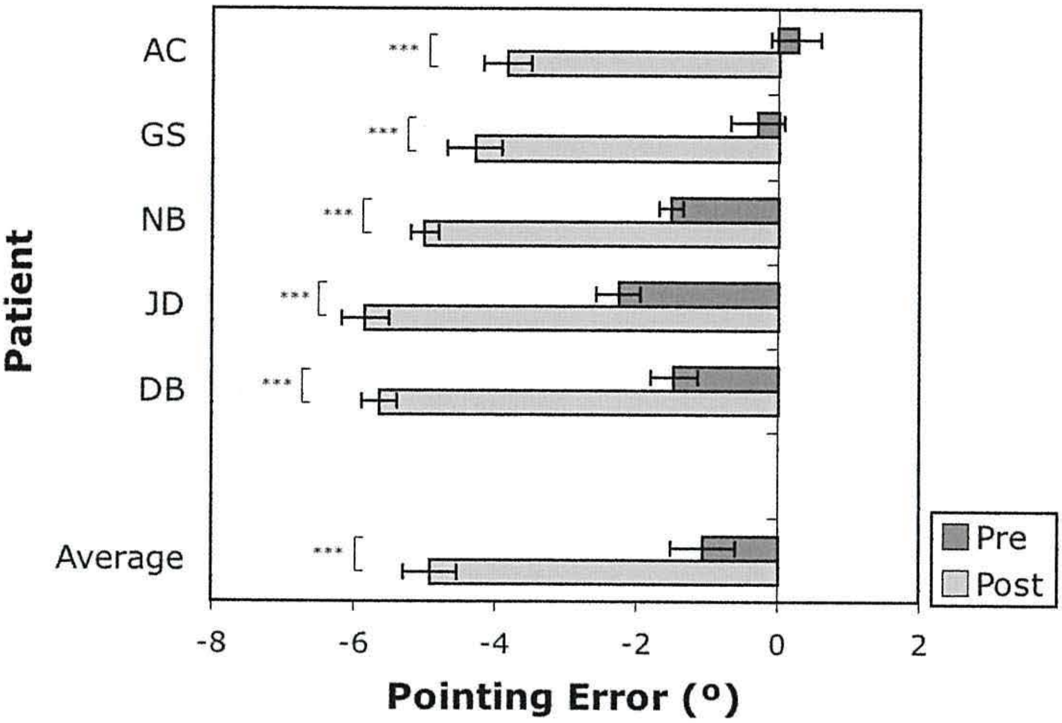

Figure 4.5. Pointing errors of the individual patients before and after prism adaptation. Error bars represent one *SEM*; *** indicates $p<0.001$.

Because AC showed a dramatically different pattern, with a response rate more than three standard deviations less than the mean for the other four patients, his response and error rates were analyzed separately. AC had a lower response rate (59% of all trials) and accuracy rate (87% of responded-to trials). Many more of his accurate responses were in the Right Visual Field (RVF; 83% of all RVF trials) than Left Visual Field (LVF;19% of all LVF trials). His accurate responses were therefore pooled over visual field for further analysis. AC's accuracy was at ceiling for the congruent trials (>95% of responded-to trials), however chi-squared analyses were performed to determine whether his accuracy for incongruent trials in the globally- and locally-directed tasks changed as a result of prism adaptation. Accuracy for incongruent trials in the locally-directed task before adaptation was at ceiling (97.5%), precluding statistical analysis, but it is of note that this dropped to 89.4% following prism adaptation, consistent with increased interference of the global form. In contrast there was a significant increase in accuracy for incongruent trials in the globally-directed task from 43.2% to 77.1% following prism adaptation ($\chi^2=8.59$, $p<0.005$), consistent with decreased interference of local information.

Analysis of RTs

Preliminary analysis. As AC responded to only 19% of LVF stimuli a preliminary omnibus analysis of Session (pre, post) x Visual Field (left, right) x Target (S, A) x Level (global, local) x Congruency (congruent, incongruent) was performed on the data from the four other patients. A main effect of Target (F(1,3)=25.7, p<0.05) indicated significantly faster responses to the target A (M=780.8, *SEM*=24.5) than the target S (M=842.3, *SEM*=39.2). A Visual Field x Target interaction (F(1,3)=11.6, p<0.05) showed that the reaction time advantage for A compared to S was larger in the left visual field (110ms advantage) than in the right visual field (13ms advantage). There were no further interactions involving Target, and although inspection of individual patient data reveal a general pattern of right visual field advantage (Table 4.3), there was no main effect and no further interactions involving Visual Field (*ps*>0.05). Data were therefore collapsed across visual fields and target identity for both the control and patient group analyses.

Table 4.3. Patient RTs for the left and right visual field across session. No data are provided for patient AC due to his low response rate to LVF stimuli (19%).

	Pre-adaptation			**Post-adaptation**		
	LVF	**RVF**	**RVF-LVF**	**LVF**	**RVF**	**RVF-LVF**
GS	876	796	80	920	797	123
NB	742	827	-84	694	795	-101
JD	762	723	39	747	725	22
DB	897	885	12	851	812	40
Mean	**819**	**808**	**12**	**803**	**782**	**21**

Control participants. The mean RTs for the control participants are shown in Table 4.4. A two-way repeated measures ANOVA was performed with Level (global, local) and Congruency (congruent, incongruent) as within-subjects factors. There was a 43ms main effect of congruency ($F(1,9)=22.9$, $p<0.001$), with significantly faster RTs for congruent (*M*=631.8, *SEM*=31.3) than incongruent (*M*=674.5, *SEM*=28.0) stimuli. The RT cost for incongruent compared to congruent stimuli was larger for the locally-directed task (49ms) than the globally-directed task (36ms), however this difference was not significant ($F(1,9)=0.01$, $p=0.92$). There were no further significant main effects or interactions (*ps*>0.05).

Table 4.4. Control RTs for the directed attention task.

	Global Target			**Local Target**		
	Congruent	**Incongruent**	**Local Interference**	**Congruent**	**Incongruent**	**Global Interference**
C1	586	672	86	537	586	50
C2	532	621	89	545	598	53
C3	796	819	23	743	774	31
C4	745	762	17	670	803	133
C5	575	688	113	454	440	-13
C6	679	649	-31	854	865	11
C7	531	523	-8	690	709	19
C8	585	624	39	576	616	39
C9	543	585	42	557	630	73
C10	648	641	-7	793	887	94
Mean	**622**	**658**	**36**	**642**	**691**	**49**

Patients. The RTs for the pre- and post-adaptation performance of the patient group are shown in Tables 4.5 and 4.6. A three-way repeated-measures ANOVA was performed with Session (pre, post), Level (global, local) and Congruency (congruent, incongruent) as within-subjects factors. There was a significant main effect of Congruency (81ms, $F(1,4)=15.8$, $p<0.05$), reflecting faster RTs for congruent stimuli ($M=822.9$, $SEM=49.9$) than incongruent stimuli ($M=893.7$, $SEM=64.3$). No other main effects were significant ($ps>0.05$).

Table 4.5. Patient RTs for the pre-adaptation directed attention task.

	Global Target			**Local Target**		
	Congruent	**Incongruent**	**Local Interference**	**Congruent**	**Incongruent**	**Global Interference**
AC	994	1128	134	969	1013	45
GS	859	937	78	728	746	18
NB	714	849	135	788	791	3
JD	712	762	50	710	786	75
DB	639	669	30	1214	1282	68
Mean	**784**	**869**	**85**	**882**	**924**	**42**

Table 4.6. Patient RTs for the post-adaptation directed attention task.

	Global Target			**Local Target**		
	Congruent	**Incongruent**	**Local Interference**	**Congruent**	**Incongruent**	**Global Interference**
AC	1111	1260	149	874	1105	231
GS	916	945	28	746	788	43
NB	732	740	8	727	772	46
JD	704	748	43	695	798	103
DB	626	634	7	1000	1122	122
Mean	**818**	**865**	**47**	**808**	**917**	**109**

The important finding for the purposes of this study, however, was a significant Session x Level x Congruency interaction (*F*(1,4)=14.5, *p*<0.05). This interaction reflects that the amount of global and local interference changed after prism adaptation (see Figure 4.6). *A priori* t-tests were used to examine global and local interference before and after prism adaptation. Prior to prism adaptation there was significant local interference in the globally-directed task, with RTs 86ms faster for congruent stimuli (*M*=783.6, *SEM*=63.6) than incongruent stimuli (*M*=868.9, *SEM*=78.6); *t*(4)=4.00, *p*<0.05. There was also significant global interference on responses in the locally-directed task, with RTs 42ms faster for congruent stimuli (*M*=881.8, *SEM*=94.8) than incongruent stimuli (*M*=923.6, *SEM*=101.1); *t*(4)=3.00, *p*<0.05. The RT cost of incongruent compared to congruent global information in the locally-directed task was more than twice the interference effect in the globally-directed task, although this difference was not significant (*F*(1,4)=0.16, *p*=0.71).

This pattern was reversed following prism adaptation. The pre-adaptation 85ms local interference effect decreased to 47ms and was not significant: congruent (*M*=818.2, *SEM*=87.4) compared to incongruent (*M*=865.3, *SEM*=110.8,); *t*(4)=1.79, *p*=0.15. In comparison, the pre-adaptation 42ms global interference effect reliably increased to 109ms: congruent (*M*=808.3, *SEM*=56.9) compared to incongruent (*M*=917.1, *SEM*=80.3); *t*(4)=3.17. *p*<0.05. Post-adaptation, the global interference in the locally-directed task was also significantly larger than the local interference in the globally-directed task (*t*(4)=3.58, *p*<0.05). Comparisons of the pre- to post-adaptation interference levels indicated that the 38ms decrease in local interference in the globally-directed task was not significant (*t*(4)=1.56, *p*=0.19), however global interference in the locally-directed task increased significantly by 67ms (*t*(4)=2.21, *p*<0.05).

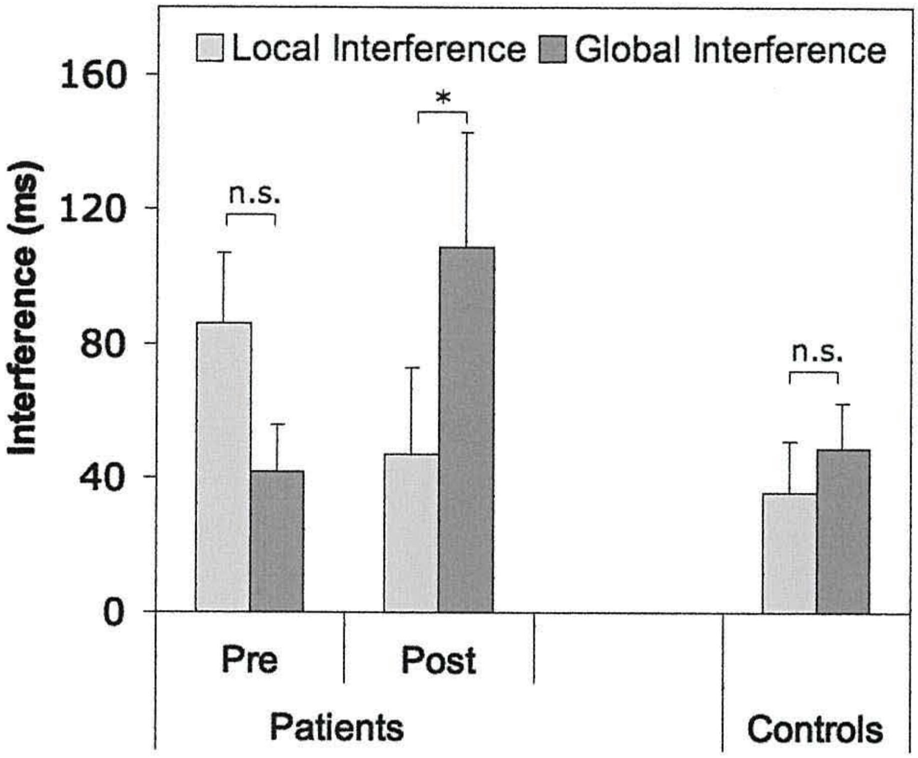

Figure 4.6. Global and local interference for patients before and after prism adaptation, and age-matched controls. Error bars represent +1 *SEM*; * indicates p<0.05; n.s. indicates *ps*>0.05.

Comparison of the control participants and patients. This investigation was motivated by the hypothesis that reduced global processing and exaggerated local interference in patients with right TPJ lesions would be reduced by prism adaptation. To assess the effects of prism adaptation on the balance between global and local processing, local-to-global interference ratios were calculated for the pre- and post-adaptation performance of each patient and each control participant. The interference was calculated as the difference between congruent and incongruent RTs: Local interference (LI) was calculated as the effect of task-irrelevant incongruent local information when identifying global targets, whereas global interference (GI) was calculated as the effect of task-irrelevant incongruent global information when identifying local targets. The balance between local and global interference was computed as the interference ratio LI/GI, where a value less than one indicated greater global than local interference, and a value greater than one indicated greater local than global interference.

The interference ratios for each patient were compared to the 95% confidence interval (CI) constructed around the control group ratios (Table 4.7). As a group, the patients' mean ratio was 10.57 in the pre-adaptation phase, whereas it decreased to 0.39 in the post-adaptation phase. The mean for the control group was -0.60, with the 95% CI ranging from -2.79 to 1.59. Prior to prism adaptation AC, GS and NB showed local-to-global interference ratios that were outside the upper boundary of the 95% confidence interval around the control mean. This indicates that local interference was significantly larger than global interference for these three participants compared to controls. After prism adaptation, however, the local-to-global interference ratios for these three patients were within normal range. The interference ratios for patients JD and DB also decreased after prism adaptation, but were within normal range in both sessions.

Table 4.7. Local-to-global interference ratios for each patient. Ratios falling outside the 95% confidence interval of the results from the control participants are underlined.

Patient	Pre-adaptation	Post-adaptation
AC	3.02	0.65
GS	4.40	0.66
NB	44.34	0.17
JD	0.66	0.42
DB	0.45	0.06
Average	**10.57**	**0.39**
Controls	**95% CI = $-2.79 \leq X \leq 1.59$**	

Discussion

In a test of hierarchical processing using directed attention, healthy older controls showed similar levels of global and local interference. When this same task was presented to five patients with right TPJ lesions before and after rightward prism adaptation, the results demonstrate a reduction in their local processing bias. Prior to prism adaptation, the patients had numerically greater local than global interference as a group, and individually three of these patients showed local-to-global interference ratios that differed significantly from the age-matched controls. This is consistent with previous literature linking right TPJ lesions with deficits in filtering out and disengaging from local detail in comparison to the global form. This pattern reversed following prism adaptation: as a group the patients showed greater global than local interference and individually none of the five patients had local-to-global interference ratios that were different from controls'.

Although no sham treatment condition was used, it is unlikely that a placebo would induce such specific, reciprocal changes in local and global interference. Similarly, the consistency of the changes across the five individual patients suggests that the observed improvement was not the product of spontaneous performance fluctuations.

Furthermore, these changes in hierarchical processing occurred without a concomitant change in lateralised spatial attention; no reliable effects of prism adaptation on visual field were found. This is most likely because the patients, who were selected on the basis of lesion location and not behavioural performance, did not show a robust RVF bias before prism adaptation. Importantly, it highlights the possibility that prism adaptation affects more than just lateralised spatial functions.

One interpretation is that the greater local interference prior to prism adaptation was due to a lateralised bias in the allocation of attention within each stimulus, which interfered with perception of the global level. In this case the changes in interference effects after prism adaptation would be explained by improvement in the lateralised object-based allocation of attention rather than modification of hierarchical processing per se. Two points militate against this possibility. First, responses to global targets were faster than to local targets in both sessions (although not significantly so), which is contrary to the pattern predicted by a lateralised bias selectively impairing global identification. Second, both target letters (S and A) are readily discriminable based on right-sided information alone. For these reasons, the data are better explained by modified hierarchical processing following prism adaptation.

Although there were significant changes in local and global interference, there was no interaction between Level and Session, indicating that prism adaptation did not affect patients' average RTs to the global or local levels when they were required to monitor only one at a time. In Experiment 4.2, a divided attention test of hierarchical processing was used that provides an indication of any preferential processing of one level over the other when participants monitor both simultaneously. The task was used to determine whether adaptation to rightward-shifting prisms would influence the patients' relative allocation of attention to local compared to global levels.

EXPERIMENT 4.2: THE EFFECT OF PRISM ADAPTATION ON HIERARCHICAL PROCESSING IN A DIVIDED ATTENTION TASK.

Patients completed two blocks of a divided attention task before and after adaptation to rightward-shifting prisms, with the same general procedure as for Experiment 4.1. Within each block hierarchical stimuli were presented with one of two assigned targets at either the local or global level on any given trial. Stimuli were eight hierarchical figures (Figure 4.7) constructed with two target letters (S or A) at the global or local level and two distracter letters (H and E) at the other level. It was expected that the patients would show preferential processing of the local level, as indicated by faster RTs for local compared to global targets. A reduction in the local processing bias by prism adaptation would be reflected by a smaller difference in RTs for local and global targets.

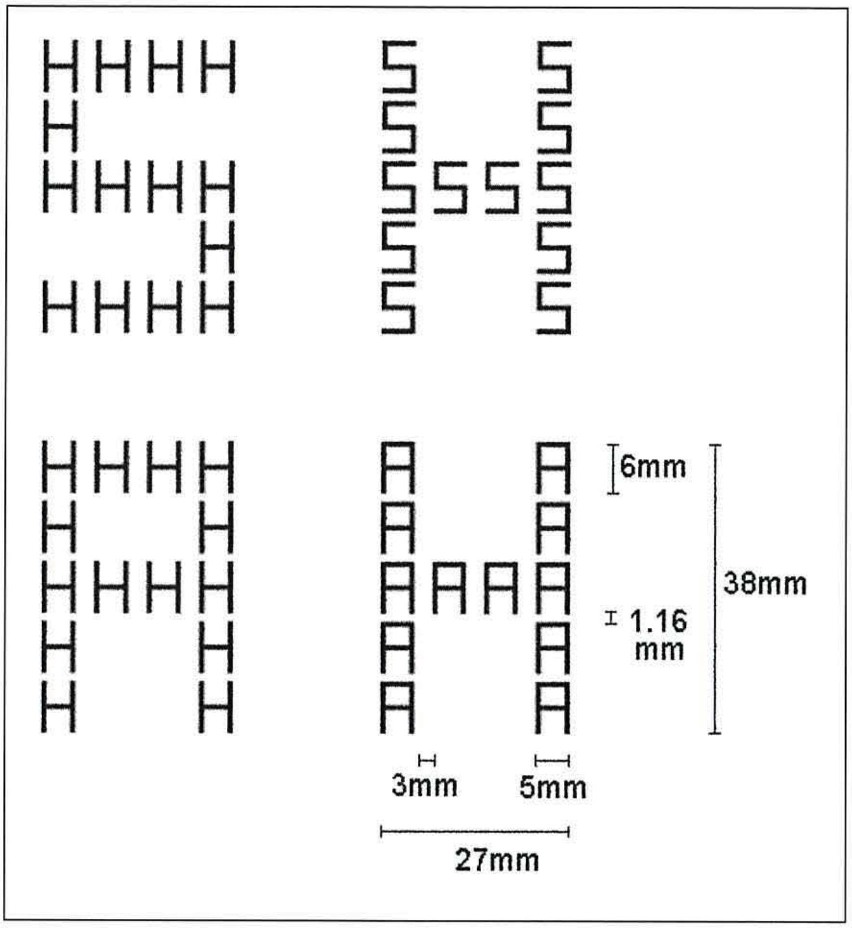

Figure 4.7. Four of the eight stimuli for the divided attention task, with targets S (top row) and A (bottom row) present at the global (left column) and local (right column) levels. Stimuli with E distractor are omitted from the figure.

Methods

Participants

Patient and control participants were the same as those who took part in Experiment 4.1.

Stimuli and Procedure

An average of 110 days intervened between the patients' participation in Experiments 4.1 and 4.2 (range=8 to 227 days), while control participants completed the tasks for the two experiments on the same day. Patients underwent prism adaptation as well as pre- and post-adaptation open-loop pointing with the same procedures as for Experiment 4.1. Hierarchical processing was examined with a divided attention task pre- and post-adaptation for the patients, but controls participants did not undergo prism adaptation and completed only one set of the divided attention task.

Divided attention task

The timecourse and stimuli were similar to those for the directed attention task of Experiment 4.1 (Figure 4.4). After a 500ms tone a central fixation cross appeared for 500ms and was then joined by one of eight hierarchical stimuli (Figure 4.7). The stimuli were presented in the left or right visual field such that there was a 24mm gap between the fixation cross edge and the inner edge of the stimulus. The target letter (S or A) appeared at the local level in half the stimuli and at the global level in the other half, with the distracter letters (H and E) appearing at the other level. The stimulus remained on the screen for 750ms for AC, and 500ms for all other participants. The participants were instructed to identify the target letter regardless of whether it appeared at the local or global level. They indicated their decision (S or A) by pressing one of two buttons on a standard mouse with the index finger and middle finger of their right hand. Individual button assignment was assigned as in Experiment 4.1. The participant's response ended the trial, with a timeout of 3000ms and an inter-trial interval of 1000ms

All patients except for AC completed two blocks of 128 trials per block before and after prism adaptation, with sixteen repetitions of each stimulus per visual field per block. AC completed blocks of 96 trials, with twelve repetitions per visual field per block. Control participants did not undergo prism adaptation, so completed only two blocks of 128 trials.

Results

Prism Adaptation

One-sample t-tests revealed that pre-adaptation pointing errors for patient AC erred significantly rightward ($p<0.05$), while all other patients showed significant leftward pointing errors at baseline ($p<0.001$). These were within the normal range of pre-adaptation pointing errors shown by control participants under similar conditions (e.g., Experiment 3.2 of Chapter 3). Paired samples t-tests comparing pre- and post-adaptation pointing errors for each patient confirmed significant leftward after-effects (*p*<0.05; Figure 4.8), with an average leftward shift magnitude of 4.46°.

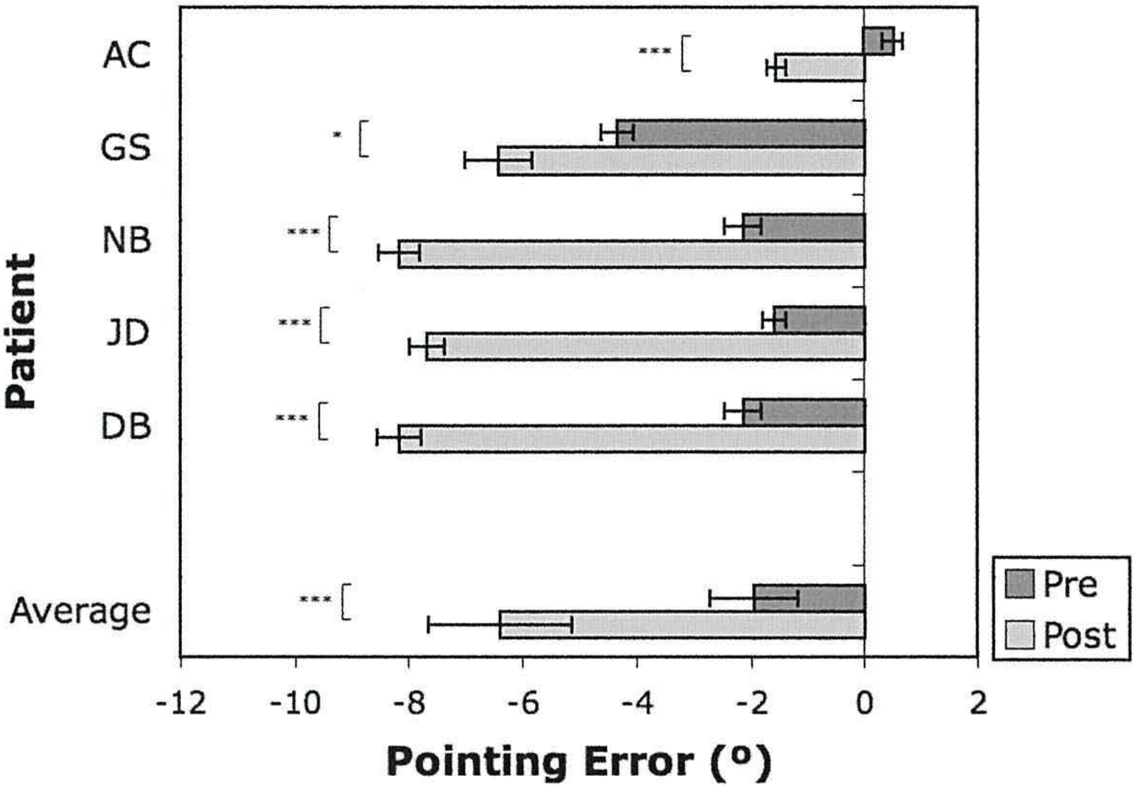

Figure 4.8. Pointing errors of the individual patients before and after prism adaptation. Error bars represent ±1 *SEM*; *** indicates *p*<0.001, * indicates *p*<0.05.

Hierarchical Processing

Analysis of hit rates

As was found for Experiment 4.1, the accuracy rates were at ceiling for the healthy controls (responses=100%, accuracy=92%), and for all patients except for AC (responses=99.6%, accuracy=93%), precluding meaningful analysis. AC had a response rate more than three standard deviations less than the mean for the other patients (65%), of which 97% were accurate. He made a greater number of responses in the RVF than LVF both before (80% versus 49%; $\chi^2(1)=20.5$, p<0.001) and after prism adaptation (89% versus 46%; $\chi^2(1)=39.7$, p<0.001). He also responded to a significantly greater number of local- than global-target trials both before (73% versus 56%; $\chi^2(1)=5.8$, $p<0.05$) and after prism adaptation (77% versus 57%; $\chi^2(1)=8.5$, $p<0.005$). The number of responses made by AC for local compared to global targets did not change between sessions.

Analysis of RTs

Preliminary analysis. Since AC responded to fewer than 50% of left visual field trials a preliminary omnibus ANOVA was conducted on reaction times for the four other patients, with Session (pre, post), Visual Field (left, right), Target (S, A) and Level (global, local) as within-subjects factors. As for the directed attention task in Experiment 4.1, there was no consistent pattern of RVF advantage in individual patient data (Table 4.8). There were no significant main effects or interactions involving either Visual Field or Target, therefore data were collapsed across visual fields and target identities for both the control and patient group analyses.

Table 4.8. Patient RTs for the left and right visual field across session. No data are provided for patient AC due to his low response rate to LVF stimuli (<50%).

	Pre-adaptation			**Post-adaptation**		
	LVF	**RVF**	**RVF-LVF**	**LVF**	**RVF**	**RVF-LVF**
GS	1038	1036	-2	1036	901	-136
NB	1250	1256	6	1131	1161	31
JD	822	888	66	803	887	84
DB	888	907	19	738	728	-10
Mean	**1000**	**1022**	**22**	**927**	**919**	**-8**

Control participants. Table 4.9 shows individual control RTs for global and local targets, as well as local advantage values, which were calculated by subtracting the local RT from the global RT for each participant. A paired samples t-test comparing mean RTs for global and local targets revealed a 58ms trend for faster responses to local targets (M=855.9, SEM=48.8) compared to global targets (M=914.2, SEM=58.5); $t(9)=2.24$, $p=0.05$.

Table 4.9. Control RTs for the divided attention task.

	Global	Local	Local Advantage
C1	934	768	167
C2	910	868	42
C3	1225	999	226
C4	1087	1090	-3
C5	789	770	19
C6	1074	1023	51
C7	871	771	100
C8	556	558	-3
C9	823	852	-29
C10	873	860	13
Mean	**914**	**856**	**58**

Patients. Individual patient RTs for global and local targets before and after prism adaptation are provided in Table 4.10, along with local advantage values (i.e., local minus global RTs). A repeated-measures ANOVA was performed on mean RTs with Session (pre, post) and Level (global, local) as within-subjects factors. There was a trend for a main effect of Session (*F*(1,4)=7.0, *p*=0.06), suggesting faster responses after prism adaptation (*M*=997.3, *SEM*=101.7) compared to before prism adaptation (*M*=1072.9, *SEM*=93.2). Although responses to local targets were numerically faster than to global targets both before and after prism adaptation, there was no significant main effect of Level or Session x Level interaction (*ps*>0.05). Therefore, prism adaptation did not influence hierarchical processing under conditions of divided attention.

Table 4.10. Patient RTs for the divided attention task before and after prism adaptation.

	Pre-adaptation			Post-adaptation		
	Global	Local	Local Advantage	Global	Local	Local Advantage
AC	1487	1154	333	1395	1200	195
GS	1092	983	110	1002	932	69
NB	1153	1353	-200	1045	1246	-201
JD	955	755	200	941	749	191
DB	899	895	4	743	721	22
Mean	**1118**	**1028**	**89**	**1025**	**970**	**56**

Comparison of control participants and patients. To compare the performance of individual patients and controls, the local advantage value for each patient was compared to the 95% CI around the mean local advantage for control participants ($CI_{0.95}$=[-0.46, 117.06]). As a group, patients had a mean local advantage of 89ms before prism adaptation and 56ms after prism adaptation, both of which were within the normal range. Also, local advantage values of individual patients (Table 4.10) relative to controls did not change between sessions. Both before and after prism adaptation AC and JD showed advantages for local targets that were outside the upper boundary of the 95% CI for the control participants, indicating significant local processing biases that were not normalised after prism adaptation (although the local advantage for AC did reduce from 333ms to 195ms). GS and DB had RT advantages for local targets that fell within the normal range, while NB showed a significant *global* advantage in both sessions. In summary, evaluation of group and individual data provide little evidence that patients' RTs to local compared to global stimuli were significantly different from controls', and there was no change in performance following prism adaptation.

Discussion

In a divided attention test of hierarchical processing, healthy older controls showed a non-significant trend for faster RTs to local than to global targets. Prior to prism adaptation the patients with right TPJ lesions also showed faster RTs to local than to global targets, however this difference was not significant. Individually, only two of the five patients had RT advantages for local targets. These results show that, overall, the allocation of attention was not significantly biased to the local or global level for either the control participants or the patients. Also, patients' RTs to local compared to global targets did not differ between pre- and post-adaptation sessions. That is, there was no evidence that adaptation to rightward-shifting prisms reduced the local processing bias of patients with right TPJ lesions under conditions of divided attention.

The absence of significant local processing bias in patients completing divided attention tasks has been reported previously. A group of patients suffering hemispatial neglect following lesions to a variety of right hemisphere areas showed no significant difference between RTs to global and local targets during a divided attention test (Lux, Marcshall, Thimm, & Fink, 2008). Also, Robertson, Lamb and Knight (1988) found that, for reasons unknown, patients with right TPJ lesions showed a larger local advantage than controls when the target was an S and not when the target was an H. It is also relevant that there was high variability across individual patients in the present study, with JD and AC showing a local advantage compared to controls, DB and GS showing no significant difference to controls, and NB showing a global advantage. The reason for this variability is unclear. One possible source is differences in the patients' lesions, which all involve the right TPJ but are otherwise heterogeneous in size and precise extent. Comparison of these lesions, however, provides no anatomical groupings that are consistent with the behavioural differences. For example, no lesion sites that are common to JD and AC were also preserved in DB and GS.

Prism adaptation did not influence RTs for local compared to global targets. This replicates the results of Experiment 4.1, in which prism adaptation was followed by changes in local and global interference, but not overall local and global RTs. These null findings may simply be because, for both the directed and divided attention tasks, patients showed no overall pathological bias to the local level compared to controls. In line with this, it may be relevant that the only patient with neglect at the time of testing was also the only patient to show a (non-significant) reduction in local advantage in the divided attention task after prism adaptation. Further research with patients who show a pathologically large RT advantage for local targets in divided attention tests of hierarchical processing may reveal improvements following prism adaptation.

GENERAL DISCUSSION

Robertson, Lamb and Knight (1988) conducted a series of studies examining the effects of temporo-parietal lesions with different foci on aspects of hierarchical processing. Lesions centred on the posterior STG resulted in larger than normal global RT advantages for left hemisphere lesions, and local RT advantages for right hemisphere lesions, both when tested under conditions of directed (Lamb, Robertson, & Knight, 1989) and divided attention (Lamb, Robertson, & Knight, 1990; L. C. Robertson et al., 1988). These lesions did not, however, result in analogous hemisphere-specific deficits in global and local interference. Rather, an analysis of pooled data from patients with lesions to the left or right hemisphere showed that unilateral STG lesions led to eradication of both global and local interference on a directed attention task (Lamb, Robertson & Knight, 1989). This was also reflected in interference from distracter letters of varying similarity to the targets of a divided attention task when the responses of patients with left and right STG lesions were analysed separately (Robertson, Lamb and Knight, 1990; although unlike the left hemisphere group, the patients with right hemisphere lesions also had damage to the right inferior parietal lobule). Overall their results demonstrated that lesions to the posterior STG differentially influenced the speed of identification of global and local levels, and the amount of interference from the unattended level.

Lesions to the IPL did not disrupt the normal global RT advantage and global interference in patients with left or right hemisphere lesions who completed a directed attention test (Lamb, Robertson & Knight, 1989), or in patients with left hemisphere lesions who completed a divided attention test (Robertson, Lamb & Knight, 1988). However, when the probability of targets appearing at the local or global level in a divided attention task was varied, patients with left IPL lesions were unable to modify their allocation of attention to favour the more probable level (Robertson, Lamb & Knight, 1988). This was initially interpreted as a deficit in controlling the allocation of attention between levels, however a reanalysis of these data showed that the results can be better accounted for by an absence of level priming, indicating that patients were deficient in keeping track of which level had been identified in the previous trial (L. C. Robertson & Lamb, 1991). No data is available for the effects of discrete right IPL lesions on this attentional control, as the right hemisphere lesioned patients in the same study could not be analogously subdivided into STG and IPL groups. These patients showed no difference to controls in their ability to modify attention to favour the more probable level.

Overall, the results of these studies suggest that distinct processes are involved in identifying global and local levels, disregarding the irrelevant level, and maintaining attention at the level of the previous target. Discrete lesions to the STG and IPL differentially influence these processes (see Robertson and Lamb, 1991, for a discussion of evidence for separate subsystems for different aspects of hierarchical processing). Like the right hemisphere group tested by Robertson and colleagues (1988), the five patients described in this chapter had lesions involving both the posterior STG and the IPL. The patterns of performance of these two groups are very similar: For their divided attention task Robertson and colleagues (1988) report a non-significant 91ms RT advantage for local targets when there was equal probability of the targets appearing at the global and local levels ($t(5)=1.08$, $p=0.33$), which is comparable to the 89ms baseline local RT advantage shown by the patients in Experiment 4.2.

In comparison to the local RT advantage and eradication of global interference resulting from discrete right STG lesions, the patients in this chapter showed no local RT advantage for either the directed or divided attention tasks, but did have increased local interference and diminished global interference in the directed attention task. This pattern of increased local interference and/or decreased global interference in the absence of a local RT advantage has been reported previously for patients with right anterior temporal lobe lesions (Doyon & Milner, 1991) and for patients with neglect following right hemisphere lesions to a variety of cortical areas (Lux et al., 2006; although in this study the data from healthy controls also reflected significant local interference with no global interference). Although it is likely that different cortical mechanisms are involved in producing the global/local RT advantage and global/local interference, these would be best examined in larger groups of patients with more homogenous or discrete lesion locations than those described in this chapter.

In Experiment 4.1 adaptation to rightward-shifting prisms reduced local interference and increased global interference in patients with right TPJ lesions. In both Experiments 4.1 and 4.2 there was no change in RTs to local compared to global targets after prism adaptation, however this may be because patients showed no local

RT advantage in baseline performance for either task. Therefore, where patients showed a pathological local processing bias, performance normalised after prism adaptation. Specifically, the results suggest that the patients were impaired in ignoring local level information, and this improved following prism adaptation.

Research into the rehabilitation of neglect is a high priority as the disorder is associated with poor functional outcome and decreased independence (Jehkonen et al., 2006). Unfortunately it has proven difficult to identify an intervention that is brief and simple enough to administer to stroke patients, that provides long-lasting benefits, and which generates improvements that generalise to activities outside the treatment setting (see Luauté, Halligan, Rode, Rossetti, & Boisson, 2006, for a review of treatment methods). However, a single session of prism adaptation can ameliorate a wide range of sensory and cognitive manifestations of spatial neglect for as much as one week post-treatment. Evidence from two longitudinal studies show that these improvements can be sustained for as many as 5 weeks (Frassinetti et al., 2002) or even 6 months (Serino et al., 2007) following a two-week program of *repeated* adaptation sessions. The existing literature therefore suggests that prism adaptation is a promising treatment for neglect.

Although the defining symptom of neglect is difficulty attending to the contralesional hemispace, there are a number of other deficits associated with neglect that are not more pronounced on one side of space than the other. These include 'non-lateralised spatial' deficits - such as impaired spatial working memory (Husain et al., 2001), and hyperattention to local detail in preference to global scenes (the local processing bias; Marshall & Halligan, 1995) - as well as 'non-spatial' deficits such as impaired sustained attention (I. H. Robertson et al., 1997), Although these deficits are not necessarily specific to neglect, they may increase neglect severity and reduce the potential for recovery (Husain & Rorden, 2003). For example, neglect patients with sustained attention deficits are less likely to recover than those without (Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998), and vigilance training aimed at improving sustained attention also benefits neglect symptoms (I. H. Robertson et al., 1995). It is worth noting that in Experiment 4.1, the three patients who had local interference ratios exceeding controls' before prism adaptation were also the only three who had clinical signs of hemi-inattention at the time of testing.

Rode and colleagues (2006) reported the case of a neglect patient who showed improved spatial dysgraphia following adaptation to rightward-shifting prisms. Improvements were observed in both lateralised and non-lateralised spatial symptoms: there was a reduction in the patient's tendency to restrict writing to the right side of the page as well as in the degree of visuo-constructional abnormalities such as exaggerated word spacing, graphic errors and line sloping. Similar improvements in neglect and constructional apraxia were reported in two patients who copied complex figures before and after prism adaptation (Rode, Klos, Courtois-Jacquin, Rossetti, & Pisella, 2006). The amelioration of non-lateralised spatial deficits such as constructional apraxia and the local processing bias by prism adaptation may explain why the technique appears to be more successful than many other treatment methods.

It is of interest to consider the neurological process through which prism adaptation may improve both hemispatial neglect and the local processing bias. One explanation is that it may restore the balance of activation levels between the two cerebral hemispheres. Kinsbourne (1970; 1993) argued that the left and right hemispheres direct attention contralaterally in a mutually opposing fashion. Damage to the right hemisphere results in disinhibition of left hemisphere function; hence neglect can also be considered a hyperattention to the right hemispace rather than impaired leftward attention. Similarly, right hemisphere damage leads to impaired global processing but also hyperattention to local detail as a result of left hemisphere disinhibition.

Restoring the balance of activity between the two hemispheres by increasing right hemisphere activation improves neglect symptoms. For example, performance on a cancellation task improves if patients simultaneously make small repetitive movements with their left hand (I. H. Robertson & North, 1992). Bilateral hand movements result in no benefits in neglect symptoms (I. H. Robertson & North, 1994), suggesting that the activation of the damaged right hemisphere relative to the left is the restorative factor. Limb activation therapy, in which patients are trained to move their contralesional arm at regular intervals is a treatment based on these findings (I. H. Robertson, Hogg, & MacMillan, 1998). Improvements in left inattention can even be observed when left limb movement is merely implied rather than actually performed: activation of the right hemisphere by presenting an object in the display that affords action by the left hand - a teacup with a handle pointing to the left - also reduced visual extinction, even though the teacup and the direction of its handle was irrelevant to the task (di Pellegrino, Rafal, & Tipper, 2005). Finally, when repetitive transcranial magnetic stimulation (rTMS) is applied over the left hemisphere, inhibiting activity in the stimulated areas, neglect symptoms improve in patients with right hemisphere lesions (Fierro, Brighina, & Bisiach, 2006; Shindo et al., 2006).

Changes in relative hemispheric activity have already been proposed as a mechanism for the clinical effects of prism adaptation by Pisella and colleagues (2006). They put forward a hypothesis, based partially on their studies of visuo-motor adaptation in patients with lesions to the cerebellum (Pisella et al., 2005) and the parietal lobe bilaterally (Pisella et al., 2004; see also Newport and Jackson, 2006) that visual error signals caused during prism exposure lead to the generation of a bottom-up signal in the right cerebellum that is transferred via a network of left and right hemisphere areas to ultimately modify activity in the left parietal lobe. They suggest that this may lead to the recruitment of left hemisphere areas for functions that would usually be served by the damaged right hemisphere, however their model could just as easily provide for a reduction in left hemisphere activity. Reduction of left PPC activity by adaptation to rightward-shifting prisms could improve both the leftward inattention and the local processing bias by restoring the activation balance of the two hemispheres.

There is now substantial evidence that prism adaptation improves the spatial attention bias of neglect as manifested on a wide range of tests. The present results extend this evidence to include hierarchical processing. They suggest a promising avenue for future investigation: examining the effects of prism adaptation on non-lateralised spatial deficits other than the local processing bias, as well as non-spatial deficits such as reduced sustained attention. If prism adaptation ameliorates a wide range of non-lateralised spatial and non-spatial symptoms, then this may explain its greater effectiveness for reducing spatial neglect symptoms compared to other treatment methods.

Chapter 5

Adaptation to leftward-shifting prisms reduces the global processing bias of healthy participants

ABSTRACT

When healthy participants are presented with figures in which small letters are arranged to form a large letter, they are quicker to identify the global level and have difficulty ignoring global information when identifying the local level. The global RT advantage and global interference effects imply biased processing of global level information in the normal brain. This contrasts with the local processing bias demonstrated following lesions to the right TPJ, such as those that lead to hemispatial neglect. Visuo-motor adaptation to prismatic visual shifts can affect the performance of healthy participants and patients with neglect on tests of lateralised spatial attention. In Chapter 4, evidence was presented that adaptation to rightward-shifting prisms, which ameliorates neglect symptoms, also improved the local processing bias of patients with right TPJ lesions. The present investigation provides evidence that adaptation to leftward-shifting prisms can induce a neglect-like reduction in the global processing bias of healthy participants. The effects of adaptation to leftward- and rightward-shifting prisms on hierarchical processing were compared in two groups of forty participants under conditions of directed (Experiment 5.1) and divided attention (Experiment 5.2). The results revealed a reduction in global interference following adaptation to leftward-shifting prisms. The influence of prism adaptation on the performance of healthy participants therefore extends beyond that of low-level visuo-motor changes and spatial reorientation.

In his landmark study, Navon (1977) showed that when healthy participants were presented with figures in which small letters are arranged to form a large letter they were quicker to identify the global level than the local form. Furthermore, when the identity of the local and global levels differed, requiring participants to inhibit the response indicated by the unattended level, there was a significant RT cost for responses to locally-directed stimuli but not for globally-directed stimuli. That is, healthy participants showed a global processing bias reflected by both an overall global RT advantage and global interference on local target identification.

This global processing bias has since been replicated many times (Heinze & Munte, 1993; M. Martin, 1979a; Pomerantz, 1983; Proverbio, Minniti, & Zani, 1998) and can be reduced or reversed by perceptual manipulations that decrease the relative discriminability of the global level, such as by increasing the visual angle of the stimulus (Kinchla & Wolfe, 1979; Lamb & Robertson, 1988; Lamb et al., 1990) the eccentricity of stimulus presentation (Amirkhiabani & Lovegrove, 1996; Pomerantz, 1983) or the spacing between the local elements (M. Martin, 1979b). However, none of these perceptual influences can completely explain the global processing bias. An attentional contribution to this bias is suggested by several studies. For example, when participants identified the local or global level of hierarchical stimuli in separate blocks ('directed' attention task), threshold probe gratings that were presented intermittently between stimuli were detected at a lower intensity if the gratings have a similar spatial frequency to the target level (Shulman & Wilson, 1987). Also, when participants identified global and local targets presented randomly within the same block ('divided' attention task), responses to a target appearing at a given level were faster both when the target had appeared at the same level in the previous trial (Ward, 1982), and if there was a higher probability of targets appearing at that level across the entire block (Kinchla, Solis-Macias, & Hoffman, 1983). Both perceptual and attentional factors therefore contribute to the global processing bias shown by healthy participants.

Studies of patients with unilateral brain lesions have provided evidence for preferential processing of global and local level information by the left and right hemispheres respectively (Delis et al., 1986; Marshall & Halligan, 1995). This asymmetry has also been supported by behavioural and neurophysiological studies of healthy participants. RTs to lateralised hierarchical stimuli indicate that healthy participants show a larger global bias for left visual field stimuli than right visual field stimuli (e.g., Hübner, 1998; M. Martin, 1979a; Sergent, 1982; Van Kleeck, 1989; but see Alivisatos & Wilding, 1982; Boles, 1984). ERP, PET and fMRI investigations of cortical activity during hierarchical processing suggest that preferential processing of global and local levels arise in early visual areas of the left and right hemispheres and are mediated by attentional control from the temporo-parietal cortices (Fink et al., 1996; Fink et al., 1997; Han et al., 2002), which are themselves differentially activated during pre-stimulus allocation of attention to global and local levels (Weissman & Woldorff, 2005; Yamaguchi, Yamagata, & Kobayashi, 2000). This neurophysiological evidence for the specialisation of left and right temporo-parietal areas for the attentional control of local and global respectively is consistent with research localising local and global processing deficits in brain-lesioned patients to damage of these areas (Lamb et al., 1989, 1990; L. C. Robertson & Lamb, 1991; L. C. Robertson et al., 1988).

In Chapter 4 I presented evidence that adaptation to rightward-shifting prisms, which has previously been shown to improve neglect symptoms, also reduced the local processing bias of five patients with right TPJ lesions. This amelioration of both neglect and the local processing bias - two deficits strongly associated with right TPJ lesions - suggests that prism adaptation can influence both lateralised and non-lateralised spatial deficits associated with neglect.

Adaptation to leftward-shifting prisms results in neglect-like rightward biases in healthy participants on tests of line bisection, mental representation of numbers, and haptic exploration. In comparison, performance on the same tasks is unchanged by adaptation to rightward-shifting prisms. The similarity between the prism-induced errors made by healthy participants and those evident in neglect, the non-motor nature of some of the tests used, and the asymmetrical influences of leftward- and rightward-shifting prisms, have led to the suggestion that prism adaptation can have a higher-level influence on the performance of healthy participants reminiscent of that created by a right hemisphere lesion. The aim of this chapter is to examine whether adaptation to leftward-shifting prisms can induce the local processing bias in healthy participants. In two experiments hierarchical processing was measured before and after prism adaptation under conditions of directed (Experiment 5.1) and divided (Experiment 5.2) attention.

EXPERIMENT 5.1: THE EFFECTS OF PRISM ADAPTATION ON HIERARCHICAL PROCESSING IN HEALTHY PARTICIPANTS PERFORMING A DIRECTED ATTENTION TASK

In separate blocks forty healthy participants identified the global or local levels of hierarchical stimuli before and after adaptation to leftward-shifting prisms (experimental group) or rightward-shifting prisms (control group). Stimuli could be congruent or incongruent. It was expected that before prism adaptation participants would show significant global interference during the locally-directed block. If adaptation to leftward-shifting prisms increases processing of local-level information relative to global-level information then participants in the experimental group would show significantly smaller global interference and/or larger local interference after prism adaptation, while no change would be expected for the control group.

Methods

Participants

Forty neurologically healthy undergraduates were recruited for the experiment (16 males, mean age = 24 years, *SEM* = 0.81). Each had normal or corrected-to-normal vision and were right-handed according to the Edinburgh Handedness Inventory (mean = -0.93, *SEM* = 0.015, where -1 denotes exclusive right-handedness). Informed consent was obtained in accordance with guidelines approved by the university ethics committee and the 1964 Declaration of Helsinki. Participants received course credits or a payment of £6 for the one-hour session.

Stimuli and Procedure

The procedure was similar to that used with the brain-lesioned patients in Experiment 4.1 of Chapter 4. Participants completed the following sequence of tasks: 1) Pre-adaptation directed attention task, 2) Pre-adaptation open-loop pointing, 3) Prism adaptation, 4) Post-adaptation open-loop pointing, 5) Post-adaptation directed attention task 6) Late open-loop pointing. Throughout the experiment participants were seated in a standard computer chair that could be wheeled and rotated between the computer and adaptation box by the experimenter as required for each task.

1) Pre-adaptation directed attention task

Stimuli were generated by Eprime software on a Dell PC running Windows XP. Black-on-white figures appeared on a 17-inch monitor running at 85Hz, positioned 60cm from the participant's eyes. Participants identified the global and local levels of hierarchical figures in separate blocks, with the order of task completion counterbalanced between participants. Stimuli were identical to those that were presented to patients with right TPJ lesions in Experiment 4.1 of Chapter 4. Each stimulus consisted of eleven 4mm wide x 6mm high local letters (S's or A's) arranged to form 27mm wide x 39mm high global letters (an S or A). Each block started with four practice trials that were excluded from the analysis. The order of events for each trial is shown in Figure 5.1. The trial began with a 500Hz tone that was presented for 500ms. After a further delay of 100ms a 3mm x 3mm central fixation cross appeared. Participants were instructed to look at the cross throughout the entire trial. After 500ms the fixation cross was joined by one of four hierarchical stimuli presented in the left or right visual field such that there was 24mm between the cross and inner edge of the stimulus. Each stimulus was presented sixteen times in each visual field in pseudorandom order, resulting in a total of 128 trials.

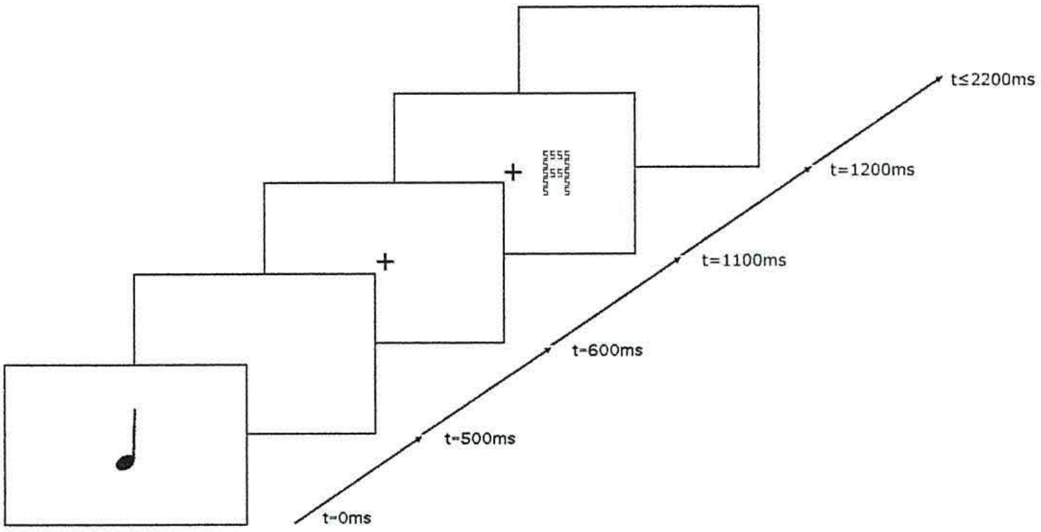

Figure 5.1. The timecourse of the directed attention task. This example shows the stimulus appearing in the right visual field, however stimuli also appeared in the left visual field.

The stimulus remained on the screen for 100ms and was replaced by a blank screen. Participants indicated their response, S or A, by pressing one of two buttons on a standard keyboard with the index and middle fingers of their right hand. Key assignment was counterbalanced between participants, who practiced response mapping prior to the commencement of the experiment. Participants were instructed to respond as quickly and as accurately as possible. The participant's response ended the trial, with a timeout of 1000ms. There was an inter-trial interval of 1000ms.

2) Pre-adaptation open-loop pointing task

Without rising, participants turned their chair to face a 90cm wide x 35cm high x 70cm deep prism adaptation box that was constructed based on that described by Berberovic and Mattingley (2002). The box was open at two opposite ends where the participant and experimenter were positioned. For the open-loop pointing task a lid was placed on the box with lines drawn on the upper surface radiating at angles of -10°, 0° and +10° from the participant's body midline. These served as target lines for the open-loop pointing task. Participants rested their chin on the top of the box and pointed their arm under each of the target lines four times in pseudorandom order as directed by the experimenter, returning their hand to rest in front of their torso between each pointing movement. Pointing error was measured by the experimenter to the nearest 0.5 degree with the aid of markings drawn on the underside of the lid.

3) Prism adaptation

The lid was removed from the box and three 1.5cm diameter targets were placed on the base of the box at arms length from the participant and at angles of -10°, 0° and +10° from their body midline. Participants were fitted with welding goggles that had been adapted to contain Risley biprisms that were adjusted to shift the visual field 15° to the left or right. While resting their chins on the edge of the box participants reached out to touch the targets in a pre-determined sequence (left-middle-right-middle) that was repeated for 150 pointing movements, returning their hand to rest in front of their torso between each. Pointing was performed in time with a metronome set to 1Hz to encourage a constant ballistic pointing speed. Participants closed their eyes at the end of the adaptation session and between each task for the remainder of the experiment to minimise deadaptation.

4) Post-adaptation open-loop pointing

The prism goggles were removed and adaptation was confirmed with an open-loop pointing session using the same procedure as described above (2) for the pre-adaptation open-loop pointing.

5) Post-adaptation divided attention task

Participants completed the divided attention task using the same procedure as described above (1).

6) Late open-loop pointing

A third open-loop pointing task was performed to determine if the adaptation after-effect had been sustained throughout the entire post-adaptation directed attention task, using the same procedure as described above (2). Participants were then paid and debriefed.

Results

Data from two participants were excluded from analysis: one had missing data due to experimenter error and the other had low accuracy (<10%) for incongruent stimuli in the local processing task, suggesting a failure to comprehend the task instructions. The results for the analysis of pointing errors and reaction times of the remaining 38 participants are as follows.

Prism adaptation

A Prism (left, right) x Session (pre, post, late) repeated-measures ANOVA revealed a significant Prism x Session interaction ($F(2,72) = 194.61, p<0.001$), which confirmed significant adaptation after-effects in both both the leftward- and rightward-shifting prism groups that were maintained to the late-test (see Tables 5.1 and 5.2).

Table 5.1: Open-loop pointing errors for the leftward-shifting prism group in Experiment 5.1.

Session	M	SEM	t (compared to baseline)	p
Pre	0.61	0.53	-	-
Post	5.62	0.52	11.60	<0.001
Late	3.80	0.57	11.80	<0.001

Table 5.2: Open-loop pointing errors for the rightward-shifting prism group in Experiment 5.1.

Session	M	SEM	t (compared to baseline)	p
Pre	-0.31	0.53	-	-
Post	-5.75	0.52	11.4	<0.001
Late	-4.38	0.57	7.2	<0.001

Hierarchical processing

Accuracy was at 96%, precluding meaningful analysis. Incorrect trials and trials with RTs less than 200ms were excluded from analysis (<5% of data). To examine for any Target effects a preliminary 6-way ANOVA of mean RTs was conducted with Prism (left, right) as a between-groups factor and Session (pre, post), Visual Field (left, right), Target (S, A), Level (global, local) and Congruency (congruent, incongruent) as within-groups factors. The significant influences of Target on RTs were as follows: There was a main effect of Target ($F(1,36)=25.13$, $p<0.001$), with faster responses to S ($M=563.40$, $SEM=13.33$) than to A ($M=585.90$, $SEM=12.90$). A significant Target x Congruency interaction ($F(1,36)=14.38$, $p<0.005$) revealed that when stimuli were incongruent, responses were significantly faster for target S ($M=581.11$, $SEM=13.53$) than for the target A ($M=613.22$, $SEM=13.68$), $t(37)=3.97$, $p<0.001$. When stimuli were congruent there was no difference in RTs to S ($M=545.70$, $SEM=13.28$) than to A ($M=558.59$, $SEM=12.63$) , $t(37)=0.88$, $p=0.39$. This suggests that, regardless of the target level, S interfered more on the identification of the target A than A's interference on the identification of target S. This may be due to differences in the discriminability of the two letters. However t-tests comparing congruent to incongruent RTs for each target separately confirmed significant congruency effects ($ps<0.001$).

A Prism x Target interaction ($F(1,36)=5.81$, $p<0.05$) reflected that, for reasons unknown, responses to the letter S were faster than to the letter A for participants in the leftward-shifting prism group ($M=542.78$ and 576.09, $t(18)=6.21$, $p<0.001$), but not for those in the rightward-shifting prism group ($M=584.03$ and 595.72, $t(18)=1.62$, $p=0.12$). As there were no interactions between Session and Target, data were collapsed over target type for further analysis.

The significant main effects and interactions that did not involve Target included a 4-way interaction of Prism x Visual Field x Level x Congruency ($F(1,36)=6.54$, $p<0.05$). Therefore RTs from the leftward- and rightward-shifting prism groups were analysed separately with two 4-way repeated measures ANOVAs of Visual Field, Level and Congruency, as well as Session as an *a priori* factor of interest.

Leftward-shifting prism group

There were significant main effects of Session (*F*(1,18)=21.91), $p<0.001$, Visual Field (*F*(1,18)=5.91, $p<0.05$) and Congruency (*F*(1,18)=133.00, $p<0.001$). These reflected faster responses in the post-adaptation session (*M*=542.74, *SEM*=11.39) compared to the pre-adaptation session (*M*=575.14, *SEM*=11.82), to right visual field stimuli (*M*=553.72, *SEM*=11.22) compared to left visual field stimuli (*M*=564.16, *SEM*=11.35), and to congruent stimuli (*M*=536.32, *SEM*=10.67) compared to incongruent stimuli (*M*=581.56. *SEM*=11.81).

Significant interactions of Visual Field x Level (*F*(1,18)=11.93, $p<0.005$) and of Visual Field x Level x Congruency (*F*(1,18)=9.71, $p<0.01$) reflected the differential specialisation of the two hemispheres for global and local processing. Comparisons of overall RTs for global and local stimuli in each visual field showed that responses to local targets were significantly faster in the right visual field (*M*=560.97, *SEM*=14.62) than in the left visual field (*M*=584.04, *SEM*=16.30), consistent with the left-hemisphere bias for local processing (*t*(18)=3.38, $p<0.005$). However, there was no significant difference between responses to global targets in the left visual field (*M*=544.28, *SEM*=11.64) and right visual field (*M*=546.46, *SEM*=12.65), *t*(18)=0.53, $p=0.60$.

To further examine the Visual Field x Level x Congruency interaction, global and local interference effects were calculated for each visual field by subtracting RTs for congruent stimuli from RTs for incongruent stimuli (Figure 5.2). Interference of irrelevant global information on local target identification was significantly greater in the left visual field (*M*=60.28, *SEM*=9.52) than in the right visual field (*M*=40.19, *SEM*=6.81; *t*(18)=2.82, $p<0.05$), consistent with the preferential global processing of the right hemisphere. Local interference was greater in the right visual field (*M*=44.00, *SEM*=6.22) than in the left visual field (*M*=36.51, *SEM*=5.11), however this difference was not significant (*t*(18)=1.49, $p=0.15$).

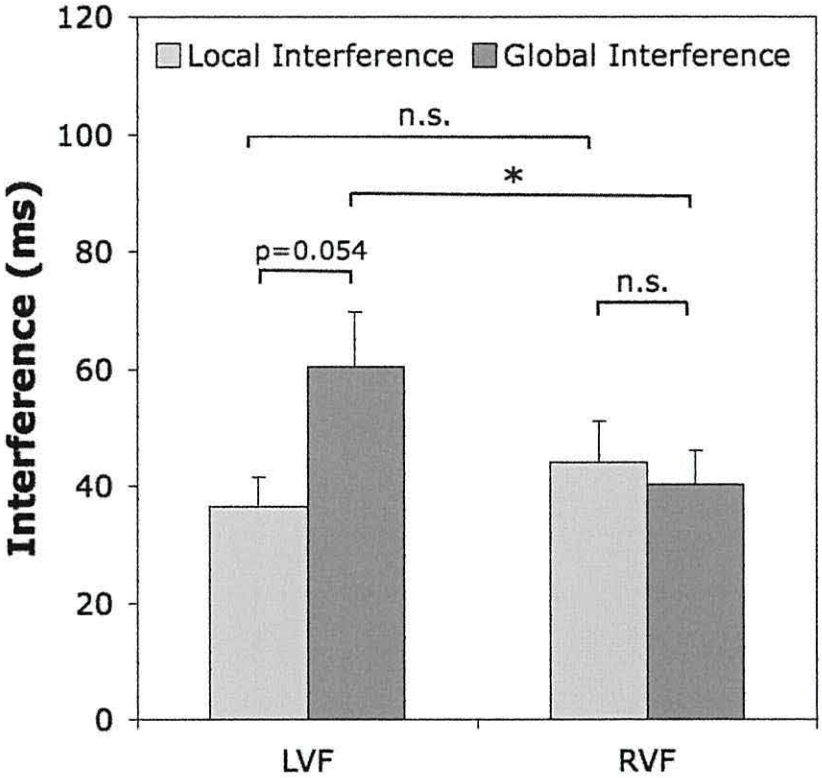

Figure 5.2. Global and local interference in the left and right visual fields for the leftward-shifting prism group. Error bars represent +1 *SEM*; * indicates $p<0.05$; n.s. indicates $ps>0.05$.

The most relevant finding, however, was a trend for an interaction of Session x Level x Congruency ($F(1,19)=3.51$, $p=0.077$; Figure 5.3). T-test comparisons of congruent compared to incongruent RTs confirmed significant interference in both the global and local blocks before and after prism adaptation ($p<0.05$). To examine whether prism adaptation changed the relative interference of global and local levels *a priori* t-tests were performed on interference values before and after prism adaptation. There was a significant 15ms decrease in global interference following prism adaptation from 58ms (*SEM*=9.64) to 43ms (*SEM*=5.60), $t(18)=1.83$, $p<0.05$. There was a simultaneous 7ms increase in local interference from 37ms (*SEM*=6.63) to 44ms (*SEM*=5.60), however this difference was not significant ($t(18)=1.07$, $p=0.30$). The analysis therefore suggests that following adaptation to leftward-shifting prisms there was a decrease in global interference on local target identification.

There were no further significant interactions in the analysis of RTs for the leftward-shifting prism group ($ps>0.05$).

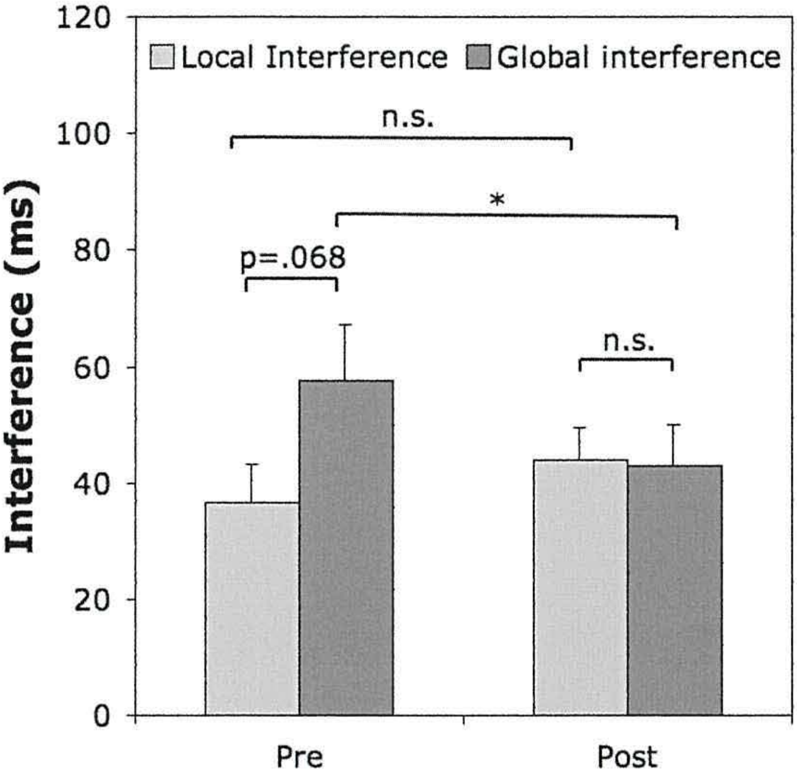

Figure 5.3. Interference effects before and after prism adaptation for the leftward-shifting prism group. Error bars represent +1 *SEM*; * indicates $p<0.05$; n.s. indicates *ps*>0.05.

Rightward-shifting prism group

There were significant main effects of Session ($F(1,18)=10.77$, $p<0.005$), Level ($F(1,18)=19.10$, $p<0.001$) and Congruency ($F(1,18)=65.92$, $p<0.001$). These reflected faster responses in the post-adaptation session ($M=572.38$, $SEM=21.39$) compared to the pre-adaptation session ($M=605.54$, $SEM=26.39$), to global targets ($M=563.12$, $SEM=22.20$) compared to local targets ($M=614.80$, $SEM=26.07$), and to congruent stimuli ($M=566.96$, $SEM=23.17$) compared to incongruent stimuli ($M=610.96$, $SEM=24.09$).

There was also a significant Level x Congruency interaction ($F(1,18)=13.83$, $p<0.005$). Significant RT costs for incongruent compared to congruent stimuli were found for both global targets ($M=28$ms, $t(18)=4.45$, $p<0.001$) and local targets ($M=60$ms; $t(18)=8.08$, $p<0.001$), and global interference was significantly larger than local interference ($t(18)=3.72$, $p<0.005$).

Although the interaction of Session x Level x Congruency was not statistically significant (*F*(1,18)=1.28, *p*=0.27), the global and local interference effects before and after prism adaptation are plotted in Figure 5.4 to enable comparison with the changes in interference effects that were observed for the leftward-shifting prism group (Figure 5.3). Before prism adaptation, global interference (*M*=62.40, *SEM*=10.06) was significantly larger than local interference (*M*=24.37, *SEM*=8.38; *t*(18)=3.29, *p*<0.005), as was found for the leftward-shifting prism group. Unlike the leftward-shifting prism group, however, the post-adaptation performance also reflected greater global interference (*M*=57.27, *SEM*=7.08) than local interference (*M*=32.00, *SEM*=6.39), *t*(18)=25.29, *p*<0.01. That is, adaptation to rightward-shifting prisms had no influence on global and local interference.

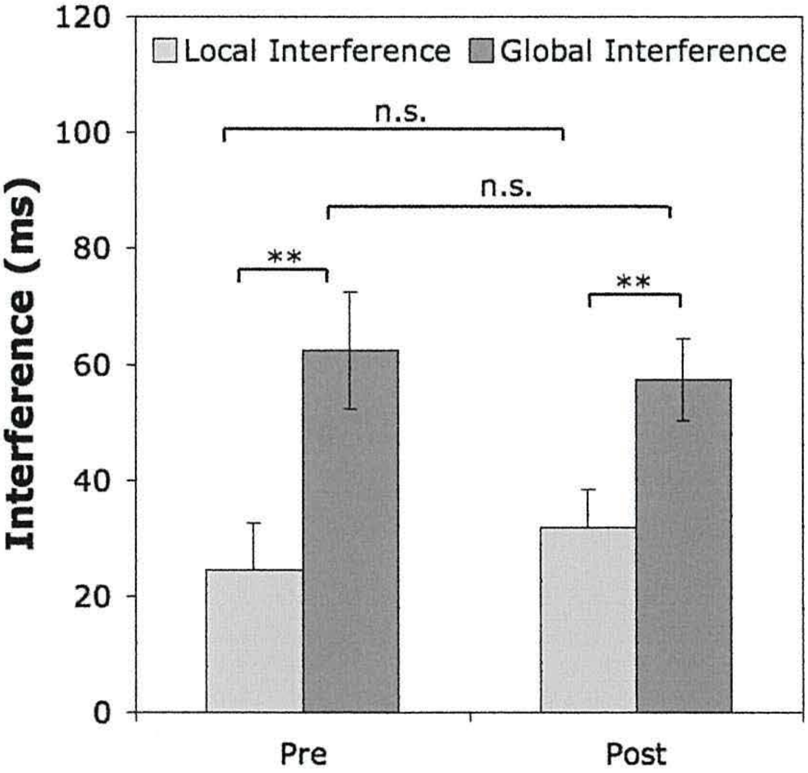

Figure 5.4. Interference effect before and after prism adaptation for the rightward-shifting prism group. Error bars represent +1 *SEM*; ** indicates *p*<0.01; n.s. indicates *ps*>0.05.

Discussion

Healthy participants demonstrated a global processing bias on a directed attention test of hierarchical processing before prism adaptation. Faster responses were made to global than local targets, and the interference of irrelevant global level information on local target identification was larger than that of irrelevant local level information on global target identification. Participants who adapted to leftward-shifting prisms showed a significant decrease in global interference and a reciprocal trend for increased local interference. In contrast, no change in interference effects was observed in participants who adapted to rightward-shifting prisms. These results suggest that adaptation to leftward-shifting prisms can decrease processing of global level information relative to the local level, similar to the local processing bias demonstrated by patients with right TPJ lesions.

This conclusion is based on a non-significant trend for an interaction of Session x Level x Congruency in the responses of the leftward-shifting prism group. However, it is further supported by four additional circumstances: 1) the reciprocal changes in local and global interference that this interaction reflected; 2) their consistency with the experimental hypothesis; 3) the absence of any changes for the rightward-shifting prism group; and 4) the resemblance between these results and the reduction in local interference shown by patients with right TPJ lesions after adaptation to rightward-shifting prisms (Experiment 4.1, Chapter 4).

The differential effect of prism adaptation on global and local interference was not the only difference between the leftward- and rightward-shifting prism groups. The rightward-shifting prism group showed an overall RT advantage for the global blocks as well as significantly larger global interference. In the leftward-shifting prism group these effects differed between visual fields in a manner consistent with the left and right hemisphere specialisation for local and global processing. Visual field differences in the processing of lateralised hierarchical stimuli by healthy participants have been reported by some studies (e.g., Hübner, 1998; M. Martin, 1979a; Sergent, 1982; Van Kleeck, 1989; but see Alivisatos & Wilding, 1982; Boles, 1984), and may be due as much to inter-individual differences as to variations in tasks and stimuli. It is possible that a larger baseline disparity between interference effects may have made it more likely that this difference would reduce in the post-adaptation session due to extraneous factors such as regression to the mean. However as it was the rightward-shifting prism group who showed a larger difference between local and global interference, it is unlikely that the differences between baseline interference levels shown by the two groups can explain the changes observed following adaptation to leftward-shifting prisms.

In summary, adaptation to leftward-shifting prisms improved healthy participants' ability to ignore global information while identifying the local level of hierarchical stimuli in a directed attention task. Experiment 5.2 examined whether adaptation to leftward-shifting prisms can also influence hierarchical processing in healthy participants performing a divided attention task that requires both levels to be monitored simultaneously.

EXPERIMENT 5.2: THE EFFECT OF PRISM ADAPTATION ON HIERARCHICAL PROCESSING IN HEALTHY PARTICIPANTS PERFORMING A DIVIDED ATTENTION TASK.

Forty new healthy participants completed a divided attention test of hierarchical processing before and after adaptation to leftward- or rightward-shifting prisms. The divided attention task was similar to that which was presented to patients with right TPJ lesions in Experiment 4.2 of Chapter 4. Participants identified targets that appeared randomly, but equiprobably at the local or global level of hierarchical stimuli within the same block. In Chapter 4 prism adaptation resulted in no change in patients' performance on the divided attention task, however, this may have been because the patients did not show an overall local RT bias at baseline. It was expected that before prism adaptation healthy participants would show faster responses for targets appearing at the global level compared to targets appearing at the local level. This pattern may be more apparent for left visual field stimuli than right visual field stimuli, consistent with the specialisation of the right hemisphere for global processing. If adaptation to leftward-shifting prisms increases the efficiency of local processing relative to global processing then this would be reflected by a decrease or reversal of the global RT advantage for the experimental group, while no change would be expected for the rightward-shifting prism (control) group.

Methods

Participants

Forty new neurologically healthy undergraduates were recruited (12 males, mean age=23 years, *SEM*=0.60). All participants were right-handed (mean handedness score =-0.86, *SEM*=0.02) and had normal or corrected-to-normal vision.

Procedure

An identical procedure was used as for Experiment 5.1 with the exception that hierarchical processing was measured using a divided attention task rather than a directed attention task.

Divided attention task. Stimuli for the divided attention task were smaller versions of those that were presented to patients with right TPJ lesions (Experiment 4.2, Chapter 4). Eight hierarchical figures were made by arranging eleven 3mm wide x 4mm high letters to form one 20mm wide x 28mm high letter. Stimuli were presented in the left or right visual fields such that there was a 28mm gap between the inner edge of the stimulus and the edge of the fixation cross. The time course for each trial was identical to that used in Experiment 5.1 of this chapter, except that targets were presented for 200ms instead of 100ms. Participants indicated their response by pressing one of two keys on a standard keyboard with their index or middle finger of their right hand, and key assignment was counterbalanced between participants.

Results

Prism Adaptation

A Prism (left and right) x Session (pre, post and late) ANOVA of mean pointing errors revealed a significant Prism x Session interaction ($F(2, 76) = 168.3, p < 0.001$). This reflected significant adaptation after-effects in both the leftward- and rightward-shifting prism groups, which were still present in the late-test (Tables 5.3 and 5.4)

Table 5.3: Summary of the pointing errors for the leftward-shifting prism group in Experiment 5.2.

Session	M	SEM	t (compared to baseline)	p
Pre	0.12	0.33	-	-
Post	4.36	0.35	10.91	<0.001
Late	1.94	0.40	5.4	<0.001

Table 5.4: Summary of the pointing errors for the rightward-shifting prism group in Experiment 5.2.

Session	M	SEM	t (compared to baseline)	p
Pre	-0.51	0.43	-	-
Post	-4.72	0.38	11.4	<0.001
Late	-3.13	0.34	7.2	<0.001

Divided Attention Task

Mean accuracy was at 91%, precluding meaningful analysis. Incorrect trials and trials with reaction times lower than 200ms were excluded from the analysis of RTs (<10% of trials). Individual participant data were inspected for cells in which accuracy was below 60%. The RTs for these cells were replaced with the group mean for that condition (less than 3% of cells).

An omnibus 5-way mixed ANOVA was performed on mean RTs with Prism (left, right) as the between-subjects factor and Session (pre, post), Visual Field (left, right), Level (global, local) and Target (A, S) as within-subjects factors. Among the significant main effects and interactions was a 4-way interaction of Session x Visual Field x Level x Target ($F(1,38)$, $p<0.05$), therefore the data were divided by session and further analysed with two 4-way repeated measures ANOVAS of Visual Field x Level x Target, as well as Prism as an *a priori* factor of interest.

Pre-adaptation

The analysis of pre-adaptation RTs revealed significant main effects of Level (*F*(1,38)=18.23, *p*<0.001) and Target (*F*(1,38)=46.44, *p*<0.001), with significantly faster RTs for global (*M*=813.18, *SEM*=23.48) than local targets (*M*=904.11, *SEM*=27.59), and for S's (*M*=814.28, *SEM*=23.36) compared to A's (*M*=903.01, *SEM*=25.00).

There was a significant Visual Field x Target interaction (*F*(1,38)=6.21, *p*<0.05) and a trend for a Visual Field x Level interaction (*F*(1,38)=3.80, *p*=0.06), which are plotted in Figure 5.5. T-tests comparing mean RTs for S's and A's in the left and right visual fields revealed that responses to the target S were significantly faster than to the target A in both visual fields (*p*<0.001), however there were trends for faster RTs for A's in the left visual field compared to the right visual field (*t*(39)=1.74, *p*=0.09), and faster RTs for S's in the right visual field compared to the left visual field (*t*(39)=1.74, *p*=0.09).

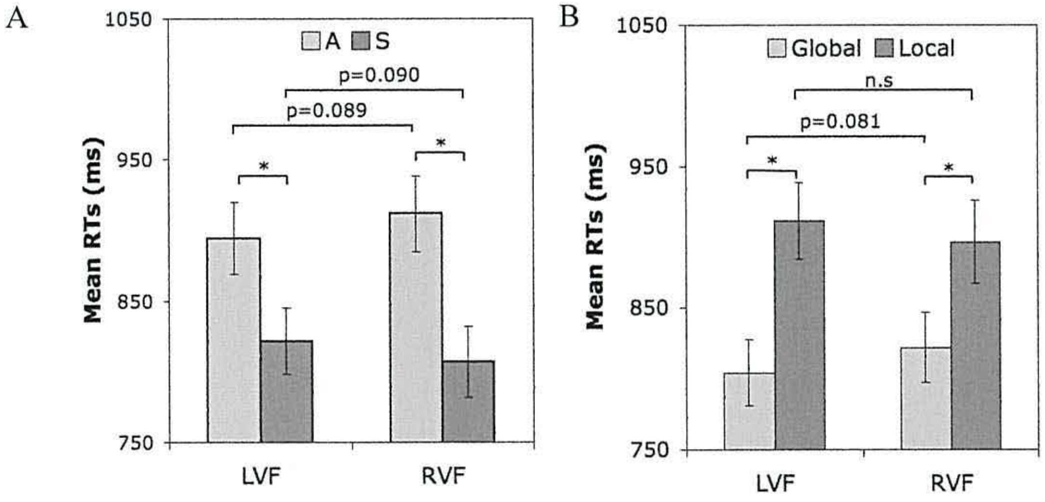

Figure 5.5. Mean RTs for the A) Visual Field x Target, and B) Visual Fields x Level interactions in the analysis of pre-adaptation performance on the divided attention task. Error bars represent ±1 *SEM*; * indicates *p*<0.05; n.s. indicates *ps*>0.05.

Follow-up analysis of the trend for a Visual Field x Level interaction revealed significantly faster responses to global than to local targets in both visual fields

($p<0.05$). However, comparisons between the two visual fields showed a trend for faster responses to global stimuli in the left visual field (*M*=804.33, *SEM*=23.31) than in the right visual field (*M*=822.04, *SEM*=24.87; $t(39)=1.79$, $p=0.08$), consistent with right-hemisphere specialisation for global processing. Responses to local stimuli were faster in the right visual field (*M*=896.64, *SEM*=30.01) than in the left visual field (*M*=911.57, *SEM*=28.04), consistent with left-hemisphere specialisation for local processing, however this difference was not significant ($t(39)=1.32$, $p=0.19$).

The analysis also revealed a significant Level x Target interaction ($F(1,38)=5.92$, $p<0.05$), which was driven by a 3-way interaction of Prism x Level x Target ($F(1,38)=4.89$, $p<0.05$). Mean RTs for these interactions are plotted in Figure 5.6. Follow-up t-tests comparing RTs to global and local stimuli for each condition showed that, for unknown reasons, the leftward-shifting prism group showed no global advantage when the target was an A (*ps*>0.05). Significant global advantages were shown by the leftward-shifting prism group for the target S, and by the rightward-shifting prism group for both S's and A's (*ps*<0.05).

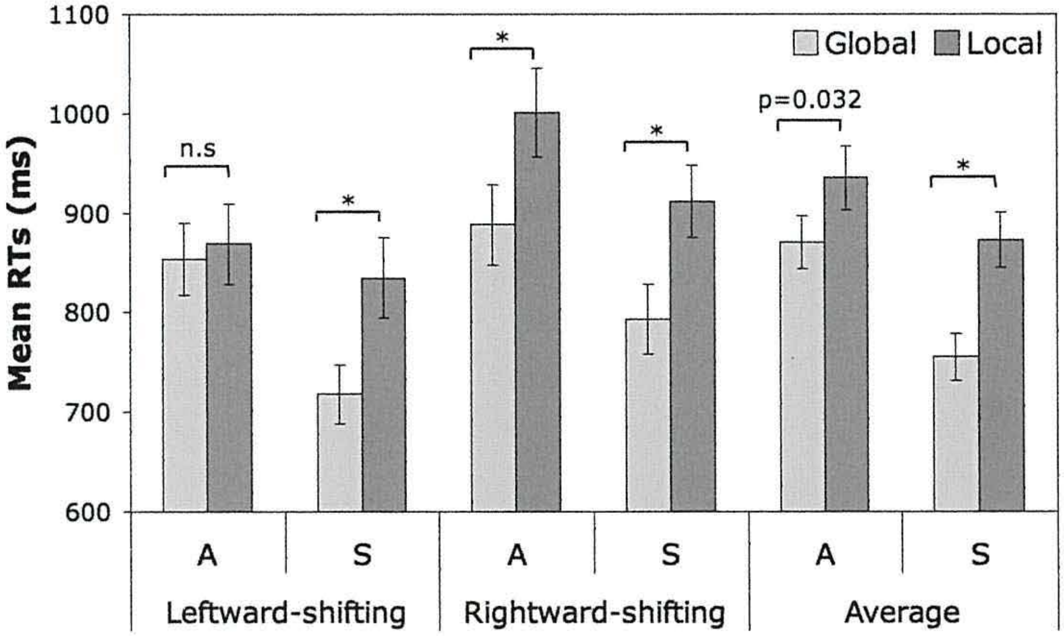

Figure 5.6. Mean RTs for the Prism x Level x Target and Level x Target interactions in the analysis of pre-adaptation performance on the divided attention task. Error bars represent ±1 *SEM*; * indicates $p<0.05$; n.s. indicates *ps*>0.05.

There were no further significant interactions in the analysis of pre-adaptation RTs ($p<0.05$).

Post-adaptation

The analysis of post-adaptation RTs revealed significant main effects of Level ($F(1,38)=6.45$, $p<0.05$) and Target ($F(1,38)=44.76$, $p<0.001$). As in the analysis of pre-adaptation RTs, these reflected faster responses to global ($M=742.48$ $SEM=18.63$) than local targets ($M=783.6$, $SEM=22.61$), and to S's ($M=722.75$, $SEM=18.76$) than to A's ($M=803.34$, $SEM=21.16$).

Three significant two-way interactions were found: Visual Field x Level ($F(1,38)=6.19$, $p<0.05$), Visual Field x Target ($F(1,38)=5.21$, $p<0.05$), and Level x Target ($F(1,38)=5.22$, $p<0.05$). These were driven by a trend for a three-way Visual Field x Level x Target interaction ($F(1,38)=3.20$, $p=0.09$), plotted in Figure 5.7. When the target was an S there was a significant global RT advantage in both visual fields. In contrast, when the target was an A the global RT advantage was present only as a trend in the left visual field and not at all in the right visual field. When RTs were averaged across target types, the global RT advantage was only significant in the left visual field, consistent with the right-hemisphere dominance for global processing.

Discussion

As with the results of Experiment 5.1, the healthy participants showed an overall RT advantage for global-level targets compared to local-level targets. In both the pre- and post-adaptation testing sessions, this advantage was larger in the left visual field, consistent with right-hemisphere dominance for global processing.

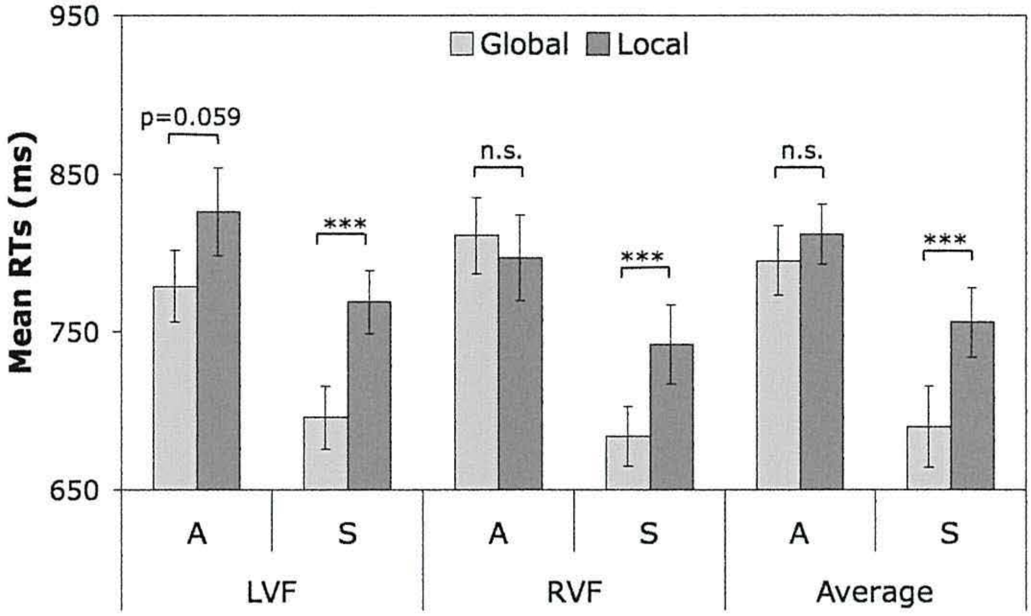

Figure 5.7. Mean RTs for the Visual Field x Level x Target and Visual Field x Level interactions in the analysis of post-adaptation performance on the divided attention task. Error bars represent ±1 *SEM*; *** indicates $p<0.001$; n.s. indicates $ps>0.05$.

Although there was a minor difference between the pre-adaptation RTs for the leftward and rightward prism groups when the target was an A (Figure 5.6), there were no group differences in post-adaptation RTs, and no evidence that adaptation to leftward-shifting prisms influenced hierarchical processing. These results are similar to those of Experiment 4.2, which showed that prism adaptation did not influence the performance of patients with right TPJ lesions on a directed attention test of hierarchical processing.

GENERAL DISCUSSION

In Experiment 5.1, adaptation to leftward-shifting prisms reduced the amount of global interference shown by healthy participants on a directed attention test of hierarchical processing, while there was no change in performance in participants who adapted to rightward-shifting prisms. In contrast, in both Experiments 5.1 and 5.2 there was no change in the relative RTs to global compared to local stimuli for either the leftward- or rightward-shifting prism group. Adaptation to leftward-shifting prisms therefore improved participants' ability to ignore irrelevant global information when identifying local targets, but had no effect on the relative speed of identifying the global and local levels.

These results complement those of Chapter 4 showing that adaptation to rightward-shifting prisms improved the ability of patients with right TPJ lesions to ignore irrelevant local level information during global target identification. The reduction of global interference in healthy participants, which was accompanied by a trend for an increase in local interference, suggests that adaptation to leftward-shifting prisms induced a neglect-like reduction in global processing (i.e., a relative local processing bias). Previous research has reported that prism adaptation can induce neglect-like rightward biases on tests of lateralised spatial attention such as line bisection (Colent et al., 2000; Michel, Pisella et al., 2003), the Landmark Test (Berberovic et al., 2004; Michel, Pisella et al., 2003) and the Greyscales Task (Loftus et al., 2009). The present results show that prism adaptation can also induce a neglect-like change in a non-lateralised component of spatial attention: hierarchical processing.

Another similarity between the results of this chapter and those of Chapter 4 is that relative RTs to global and local levels were unchanged by prism adaptation. In patients this may have been simply because they exhibited no baseline RT bias, however the participants in this chapter had a significant global RT advantage before prism adaptation. The results from both this chapter and Chapter 4 therefore show that prism adaptation can change the ability of healthy participants and patients with TPJ lesions to ignore one level while attending to the other, but, at least in healthy participants, does not influence the relative speeds with which each level is processed.

The contrasting effects of prism adaptation on the global RT advantage and global interference effect in healthy participants may be due to different cognitive and neurological mechanisms underlying these biases. The speed with which global and local level targets are identified can vary independently to the amount of interference from irrelevant global and local level information. Navon and Norman (1983) showed that global interference reduced with increasing visual angle, while there was no change in global RT advantage. Lamb and Robertson (1988, 1989) found the complementary pattern, of large differences in RT advantage for hierarchical stimuli presented under different conditions of spatial certainty, which were not accompanied by differences in interference levels. These studies suggest that separate mechanisms are involved in the relative level advantage and interference. The global RT advantage and interference effects are also differentially impaired by brain lesions: lesions centred on the left and right posterior STG resulted in increased global and local RT advantages respectively, but lesions to either site eradicated interference effects altogether (Lamb, Robertson and Knight, 1989; 1990). While individual studies have found abnormal interference effects in patients with brain lesions without concurrent abnormality in global compared to local RTs (Doyon & Milner, 1991; Lux et al., 2008), no specific locus within temporo-parietal cortex has been associated with increasing the interference of one level.

The influence of prism adaptation on one component of hierarchical processing but not another is similar to the findings that prism adaptation improved neglect patients' processing of chimeric objects, but not of chimeric faces (Ferber et al., 2003; Sarri, Kalra, Greenwood, & Driver, 2006). In both cases there is extensive literature supporting separate cognitive and neurological processes for what may at first seem to be comparable tasks, and experimental evidence shows that only one is influenced by prism adaptation.

Different patterns of responses were recorded depending on whether the target was an A or an S. Specifically, responses were faster for S's than A's for both the directed and divided attention tests, an S at the irrelevant level in the directed attention task interfered with the identification of the target A more than an A interfered with the target S, and in the divided attention task the RT advantage for global compared to local targets was greater when the target was an S than when it was an A. Different patterns of results for different target letters have been found previously (e.g., Lamb and Robertson, 1988), and probably stem from differences in the discriminability of the targets used. Importantly, there were no interactions of Target with Prism and Session, indicating no differential effects of prism adaptation for A or S targets.

In summary, the results show that the global interference effect shown by neurologically healthy participants is overcome by adaptation to leftward-shifting prisms. This adds to the evidence of Chapter 3 that adaptation to leftward-shifting prisms can induce performance resembling non-lateralised spatial deficits associated with neglect. The influence of prism adaptation on behaviour therefore extends beyond that of low-level visuo-motor changes and spatial reorientation.

Chapter 6

Derangement of somatomotor representations in Complex Regional Pain Syndrome: Report of a case treated with mirror feedback and prism adaptation

ABSTRACT

Complex Regional Pain Syndrome (CRPS) is a disabling and enigmatic condition that can follow relatively minor trauma to a limb. It manifests as severe sympathetically maintained pain that is disproportionate to the precipitating injury, accompanied by motor, autonomic and sensory abnormalities. Some symptoms of CRPS suggest that there is distortion of body representation on the cortex. These symptoms are referred to as 'neglect-like' because they resemble those seen in patients with hemispatial neglect due to parietal lobe damage. For some patients, stiffness and pain can be reduced using mirror box therapy, which was originally devised to treat phantom limb pain in amputees. Recently, Sumitani and colleagues (2007) demonstrated that two weeks of daily adaptation to 20° prismatic shifts, that induced an after-effect towards the affected limb, relieved the pain and autonomic dysfunction in five patients with CRPS. This chapter reports the case of SM, a woman suffering from CRPS for whom mirror box therapy provided momentary relief of stiffness but no reduction in pain. Over fifteen weeks SM underwent periods of daily prism adaptation, and adaptation-free periods. Prism adaptation provided pain relief and reduced disability, and this was contingent upon adapting with the affected limb. However, prism treatment was less effective in increasing range of movement. These observations have implications for understanding the mechanisms that maintain pain and rigidity in CPRS, and for treating other disorders of neurogenically maintained pain.

Some patients who have suffered trauma to a limb go on to experience chronic, disabling pain accompanied by autonomic and trophic changes, sensory disturbances, ‘neglect-like’ symptoms and motor dysfunction due to Complex Regional Pain Syndrome (CRPS; Wong & Wilson, 1997). First described by Mitchell in American civil war soldiers after peripheral nerve injury ('causalgia' Koehler & Lanska, 2004), and later by Sudeck (1900) after limb fracture (‘Sudeck’s atrophy’), CRPS has subsequently been observed after sprains, frostbite, burns and other soft tissue trauma (Choi et al., 2008; de Mos et al., 2008; Dijkstra, Groothoff, ten Duis, & Geertzen, 2003). The disorder can be triggered by nerve injury (Type II), or can occur after tissue injury without any nerve damage (Type I). Symptoms can emerge weeks after the limb has healed and are disproportionate to the inciting event. In fact, in some cases no obvious precipitating insult could be recalled by the patient.

The primary symptoms of CRPS – pain – can be experienced as dull aching, sharp stabbing, throbbing, or burning by different patients; or by the same patient on different days. Pain often increases upon movement, is elicited by normally innocuous stimuli (‘allodynia’), and there is heightened sensitivity to painful stimuli such as a pin prick (‘hyperalgesia’). Swelling and stiffness are common, and tremor can also be present. Sensory, autonomic and trophic changes vary remarkably between patients. There may be an increase or a decrease in hair and nail growth. The limb may be hotter or colder, and the skin may be sweaty or dry.

Treatment of CRPS is a challenge. Corticosteroids, amitriptylene and gabapentin provide some relief in some patients and approximately 85% of patients receive some symptomatic relief from sympathetic blockade if instituted early (AbuRahma, Robinson, Powell, Bastug, & Boland, 1994); but even then the benefits are often transient (Wasner, Schattschneider, Binder, & Baron, 2003). Without aggressive physiotherapy and adequate pain control, the limb can become withered and assume dystonic postures rendering it permanently useless and an enduring misery. Muscle and bone loss is common in chronic sufferers (>1 year; Gibbons & Wilson, 1992; Otake, Ieshima, Ishida, Ushigome, & Saito, 1998).

Identifying the pathophysiology of the disorder has been elusive, to the point where historically cases have been attributed to malingering or catastrophic psychological reactions to the trauma. However, CRPS has been clearly established as a biological disorder, with the discovery of disease mechanisms such as local nerve degeneration (Oaklander, 2008; van der Laan, Veldman, & Goris, 1998) and elevated levels of inflammatory mediators in cerebrospinal fluid (Alexander, van Rijn, van Hilten, Perreault, & Schwartzman, 2005) and in the affected limb (Huygen et al., 2002). CRPS is now recognised as a disorder of sympathetically maintained pain, along with phantom limb pain in amputees and post-stroke hand-shoulder pain.

Some symptoms of CRPS suggest that the disorder is not limited to the peripheral and autonomic nervous systems, but also reflects a reorganisation of cortical function. These symptoms are referred to as 'neglect-like' because they resemble those seen in patients with hemispatial neglect due to parietal lobe damage. There is a distortion of body image. Half of interviewed patients reported feeling that the affected limb seemed foreign or did not seem to belong to them; and half had difficulty identifying which finger was touched (Forderreuther, Sailer, & Straube, 2004). When patients chose the 'accurate' picture from a selection of photographs of their forearms and hands in which the width of the affected limb had been compressed or expanded, their choices reflected an overestimation of limb size (Moseley, 2005). When seated in a darkened room and asked to position a light in front of their body midline, judgements of visual straight ahead were deviated towards the side of the affected limb, suggesting a pathologically altered representation of body midline (Sumitani et al., 2007). Indeed, motor neglect – a dearth of spontaneous movement of the limb resulting in disuse that aggravates the problem – is often present. Patients report difficulty moving their fingers unless they look at them. Bimanual movements performed while viewing the unaffected limb in a mirror, which result in the illusion of a normally functioning damaged limb, can increase the range of motion of the affected hand (McCabe, Haigh, Ring et al., 2003). Pain can be precipitated by viewing an approaching object, and the pain increases as the object gets closer (McCabe & Blake, 2008). It has recently been shown that movement-induced pain is aggravated by viewing the limb through lenses that make the limb look bigger, and reduced by viewing it through a minimising lens (Moseley, Parsons, & Spence, 2008).

These observations suggest that the brain has been pathologically reorganised such that there is an extension of the neural representation of peripersonal space (the space within grasp). Touch to the affected limb can induce referred sensation in body areas with neighbouring cortical representations (McCabe, Haigh, Halligan, & Blake, 2003). Recent imaging studies in patients with CRPS have shown that the size of its representation in the motor cortex is enlarged (Pleger et al., 2005), while the size of its representation in the primary sensory cortex is reduced (Maihöfner, Handwerker, Neundorfer, & Birklein, 2003). This reorganisation appears to be both reversible and directly related to pain symptoms: the degree of pain reduction following rehabilitation correlated with normalisation of the primary sensory cortex (Maihofner, Handwerker, Neundorfer, & Birklein, 2004).

Recently, two therapeutic interventions for CRPS have been introduced that are based on perturbing or manipulating body image: ‘mirror box’ therapy and prism adaptation. Mirror box therapy was initially introduced to treat phantom limb pain (Ramachandran, Rogers-Ramachandran, & Cobb, 1995). For patients with CRPS, the treatment can enhance range of motion, and may also be effective in reducing pain in some patients. The patient executes synchronous bimanual movements while viewing the reflection of the unaffected hand in a mirror placed in the sagittal midline. The patient ‘sees’ their affected limb executing the full range of movement and, indeed, the affected hand does execute deft movements with the injured hand in synchrony with the unaffected hand.

The prevalence of ‘neglect-like’ symptoms in CRPS, and their observation that CRPS patients exhibited deviations away from the affected hand when pointing straight ahead with the eyes closed, led Sumitani and colleagues (2007) to undertake a trial of prism adaptation therapy in a small number of patients.

When patients with neglect undergo adaptation to rightward-shifting prisms, resulting in a leftward visuo-motor after-effect, improvements are observed in neglect symptoms. This improvement has been confirmed for many aspects of neglect, including perception of body midline (Pisella et al., 2002; Sarri et al., 2008), tactile sensation (Maravita et al., 2003), haptic exploration (McIntosh et al., 2002), and finger position sense (Dijkerman et al., 2004).

Sumitani and colleagues (2007) demonstrated that two weeks of daily adaptation to 20° prismatic shifts that induced an after-effect towards the affected limb relieved the pain and autonomic dysfunction in five patients with CRPS and shifted their pathological perceptions of body midline. In a further longitudinal study of a single patient they found that adaptation to neutral or 5° refracting lenses did not produce any effects, and adaptation towards the affected side exacerbated pain.

This chapter reports observations on the benefits of both mirror therapy and prism adaptation in a woman with CRPS Type I over fifteen weeks in which she underwent periods of daily prism adaptation, and adaptation-free periods.

CASE REPORT

SM is a 53-year-old right-handed woman who we first examined 5 months after she suffered fractures of the hand. On the day of injury the hammock she was lying in collapsed. A piece of wood struck her right hand, resulting in spiral fractures of the third and fourth metacarpals. The hand was splinted for three weeks, and was discarded then because the orthopaedic surgeon observed that 'she is stiffening up considerably'. A week later her physiotherapist noted reduced range of motion, swelling of the hand and tenderness to light touch. Subsequent X-ray confirmed complete healing of the fracture in the fourth and near complete healing of the third metacarpal.

She had been fit prior to this injury. However at the age of seventeen, SM sustained a traumatic amputation of the entire index finger and half of the middle finger of her left (unaffected) hand. This had been followed by the occasional sensation of phantom pain in the missing index finger, which decreased in frequency with time and which SM described as having been only a mild annoyance.

During the time that she was wearing the splint, she noted that there were times when she did not 'know where my hand was'. SM reported being unable to sense what her hand was doing, and had difficulty visualising its position when she was not directly looking at it. The pain was much improved by the time the splint was removed. However, shortly thereafter, she began to experience a different kind of pain in the hand. Initially there were intermittent paroxysms of sharp burning pain in the palm, but eventually the pain became continuous and affected her fingers, hand and forearm.

When we first examined SM, she had been experiencing months of constant pain in her right forearm and hand that she described as being dull and 'like a toothache you can just about bear most of the time'. Several times a day she would experience a sharp increase in pain that was burning in quality, with the focal point varying from day to day. This could occur spontaneously; however opening and closing her hand also caused a sharp pain. Amitriptylene had provided no relief and she required narcotic analgesic mediation at least once a day. She had been treated with mirror therapy (see below) for several months without any improvement in pain.

The right hand and wrist were swollen. The right hand was warmer than the left and the palm was sweaty. No discolouration or trophic changes were observed, although SM reported that at times her right hand appeared 'almost blue' compared to the left. Movements were slow and clumsy, with particular impairment of fine finger movements, and she was unable to fully open or close the hand. The restriction in range of motion was greater for hand closure than opening. Light touch sensation was intact and there was no tactile extinction. Atypically for CRPS, allodynia was not conspicuous (although had been noted by a physiotherapist during the first few weeks of symptoms): light touch did not produce much discomfort. There was, however, hyperalgesia: mild pin prick discomfort was experienced as painful. Position sense and two-point discrimination were less acute in the injured right hand compared to the left hand. An ulstrasound confirmed mild degenerative changes and subcutaneous swelling consistent with CRPS.

Mirror Therapy Observations

Full range of movement was restored when SM made synchronous movements of her hands while viewing the reflected image of her unaffected left hand. This was unaccompanied by the pain that she usually experienced with movement. She was able to fully close the right hand while using the mirror. However, this ability was lost as soon as the mirror was removed. Indeed, if she closed her right hand while using the mirror, she was unable to open it after the mirror was removed – even though this would only have required that she be able to relax her hand. Mirror therapy did not facilitate movement of the affected hand when attempted while viewing the reflection of the examiner's moving hand in the mirror, nor if she attempted bimanual synchronous movements without the mirror. However, it was effective when viewing the reflection of the examiner's moving hand, if she simultaneously executed the movements with her unaffected hand while it was out of view under the table. Thus, the efficacy of mirror therapy was not dependent upon the hand viewed in the mirror being in the homologous position to the injured hand, or looking like her own injured hand. Indeed, mirror therapy was effective despite the obvious visual differences between the affected and unaffected hand due to the missing digits on the left (unaffected) hand. Rather, efficacy was dependent upon the execution of bimanual, synchronous movements while simultaneously perceiving the visual illusion of normal movement in the injured hand.

Mirror therapy also provided momentary relief of pain and stiffness, which unfortunately resumed almost immediately after the mirror was removed. However, SM did find it helpful to perform mirror therapy 2-3 times a day to relieve the stiffness in her hand.

Prism Adaptation

Design and Procedure

CRPS symptoms were formally assessed in nine sessions spanning 15 weeks (Figure 6.1A), during which the following conditions were applied: Treatment (3 weeks), washout (13 days), treatment using the unaffected hand ('left-hand treatment', 1 week), treatment (9 weeks). In addition to the formal assessments SM recorded daily ratings from 0 to 10 of the average level of pain and range of movement (ROM) she had experienced in the last 24 hours (Figure 6.1B). She continued normal use of mirror therapy (2-3 short sessions per day) and medical pain relief (as required).

For prism adaptation SM wore welding goggles that were fitted with 25-diopter (~17°) leftward-shifting Fresnel lenses. She made 50 alternate pointing movements to targets located at arm's length and shoulder height at approximately 10° to the left and right of her mid-sagittal plane. She pointed as fast as possible with the index finger of her right hand, returning her hand to her torso in between each pointing movement. The first adaptation session was performed under experimenter guidance immediately after the baseline assessment (B) to ensure SM understood the procedure. Comparison of errors for ten open-loop pointing movements performed immediately before and prism adaptation confirmed a significant 7.25-degree rightward visuo-motor after-effect ($t(9)=9.3$, $p<0.001$). SM continued daily prism adaptation at home at approximately the same time each evening.

Results

The outcomes of the formal assessment sessions are outlined in Table 6.1. SM first underwent three weeks of adaptation to leftward-shifting prisms using her right hand. There was a progressive decrease in pain, swelling and temperature difference, as well as an increase in range of movement (T1 and T2). Within nine days the patient was pain-free, requiring no pain relief medication. For the remainder of this treatment period pain remained absent (NRS=0), or was experienced only as minor pain ('like a shoe that is a little too tight'), lasting for a few minutes and no longer than an hour (NRS=1). ROM increased although SM was still not able to completely close her hand outside mirror therapy (NRS=9).

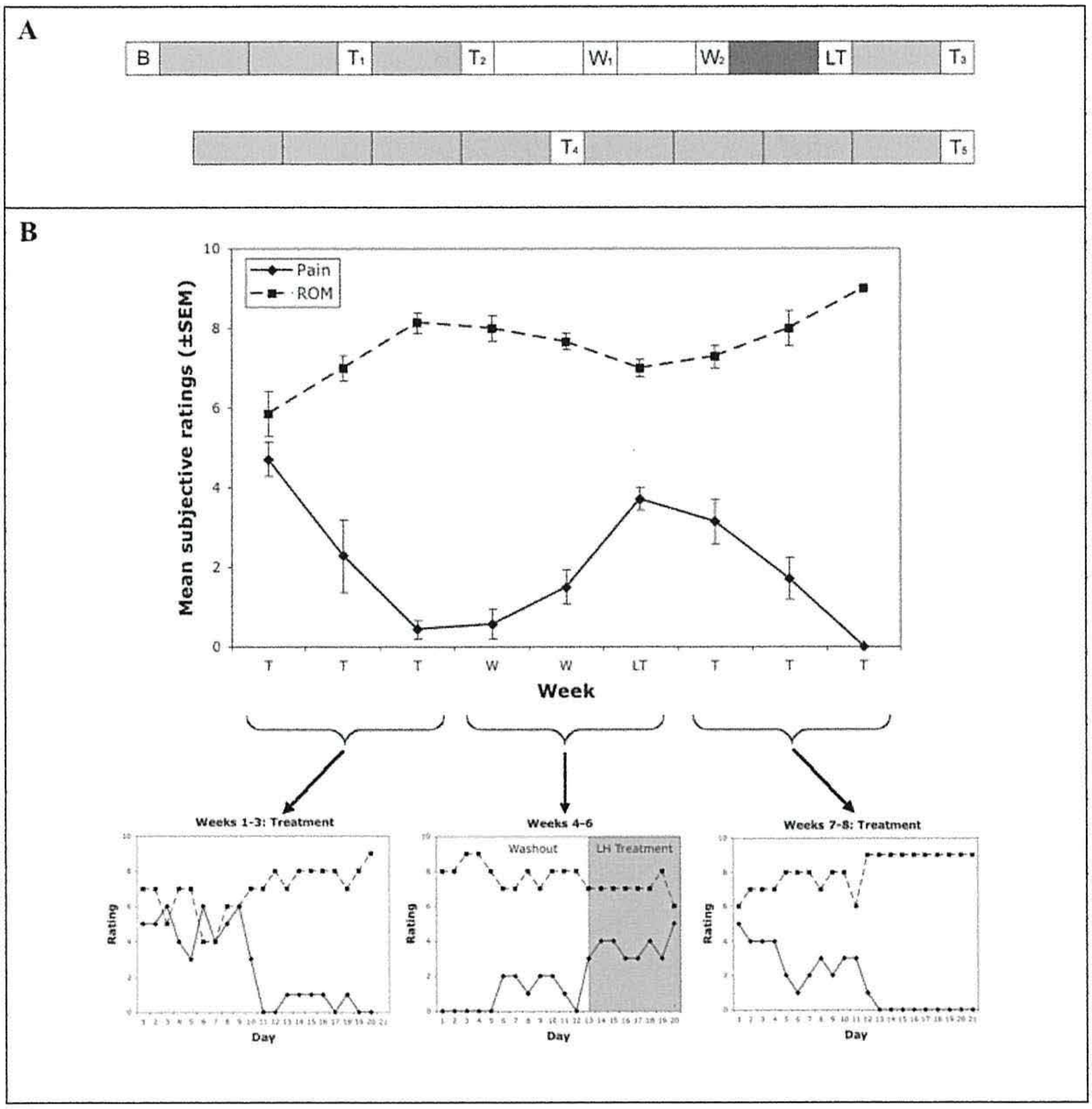

Figure 6.1. A) Treatment schedule. In one-week blocks SM underwent daily sessions of adaptation to leftward shifting prisms with her affected hand ('treatment', light grey, 6 days only in the second block), with her unaffected hand ('left-hand treatment', dark grey), or no prism adaptation ('washout', white). Formal assessment sessions are indicated by white squares: B=baseline; T1-T5=post treatment; W1-W2=post washout; LT=post left-hand treatment. B) SM's ratings of average pain and range of movement for each day for the first nine weeks. Ratings were made immediately prior to daily treatment sessions on two eleven-point Numerical Rating Scales (NRS) ranging from 0 ('no pain at all'/'no range of movement at all') to 10 ('pain as bad as it could be'/ 'full range of movement'). Error bars indicate ±1 SEM.

Table 6.1. Details of formal CRPS assessment sessions. Symptoms were assessed by direct comparison of the affected and unaffected hand.

Description	B	T1	T2	W1	W2	LT	T3	T4	T5
Oedema[*]	+++	+	-	+	+	++	+	+	+
Discolouration[*]	-	-	-	+	+	+	+	+	-
Decreased ROM[*]	++	+	+	+	+	++	+	Not tested	+
Temperature increase[*]	+	-	-	-	+	hyperhydrosis	+	+	-, but hyperhydrosis
Straight ahead pointing (M, ±*SEM*)[†]	Pre: +1.25, ±0.44 Post: +8.5, ±0.64	+5.5, ±0.28	+0.35, ±0.44	+2.6, ±0.47	-0.4, ±0.55 (left hand: +4.55, ±0.31)	+0.95, ±0.56 (left hand: +2.35, ± 0.51)	+3.75, ±0.30	+5.95, ±0.57	Not tested
Pain at time of assessment[§]	4	1	0	3	4	4	3	2	1
Additional information	Pain is ‘like a toothache you can just about bear most of the time’	Pain is intermittent, and is ‘like a shoe that is a little too tight’		Hand is stiff ‘like I have a really tight glove on’	Wanted to cut her hand off. Right hand feels bigger than left from just below the elbow. Forearm feels longer compared to left arm.			No difference in sensation of hand size	Tips of fingers felt bigger on right compared to left hand.

---

[*] ‘-‘ indicates no difference to the unaffected hand; ‘+’, ‘++’ and ‘+++’ indicate differences of increasing severity.

[†] Averaged over ten pointing trials; ‘-‘ indicates leftward errors; ‘+’ indicates rightward errors

[§] Rating by SM on a scale from 0 (‘no pain at all’) to 10 (’pain as bad as it could be’)

Pain returned five days after prism adaptation was discontinued ('washout' 13 days). This was at first intermittent, but continued to increase in frequency and severity until on day 13 SM once again had the need for medical pain relief. This was mirrored by a decrease in ROM. A gradual return of symptoms was also noted in formal assessments (W1 and W2). Interestingly, in the final two days of the washout period the patient experienced occasional sharp jabbing pains in her *left* hand, which resembled the pain that she had first felt in her right hand at the onset of CRPS.

Symptoms continued to worsen over one week of adaptation to leftward-shifting prisms using the unaffected hand ('left-hand treatment'). Assessment (LT) revealed a stiff and swollen limb with hyperhydrosis. SM reported loss of function to pre-treatment levels, with greatly diminished power and pain that was not relieved by medication. This frustrated her a great deal and she spontaneously described wanting to cut her hand off. When SM closed her eyes her right arm from the elbow to the fingertips felt larger and the forearm longer compared to the left.

After returning to prism adaptation with the right hand, swelling and temperature difference once again decreased after one week (T3) and SM was completely pain-free after 13 days. Pain remained completely absent or mild and infrequent over a further two months of treatment (T4 and T5), with one notable exception: SM missed prism treatment for two days while on holiday and this was followed by a sharp rise in pain two days later (NRS=5), even though she had recommenced prism treatment. The pain subsided after four days. Sensory disturbance also decreased in the second treatment period, with little or no difference between the felt size of the right hand relative to the left.

SM is continuing daily adaptation sessions, with a view to gradually decrease the frequency of treatments in the future if pain control is sustained. In both treatment periods the improvement in symptoms were accompanied by improvement in range of motion and function in everyday activities. She has recovered the ability to perform tasks requiring fine motor control or accurately applied pressure such as using a needle and thread, picking up a cup by its handle, bending wire with pliers or ironing a garment.

Although pain free for several weeks, she is still not able to fully close her hand, except when using a mirror; and when she closes her hand in the mirror, she is still unable to unclench the closed fist when the mirror is removed. When asked why she cannot open her hand, she seems bemused and can only respond that 'I don't know how'. She is unable to pick up a teapot or carry heavy bags. Thus, there is a continuing impairment of motor function that is not simply a limitation due to pain.

DISCUSSION

SM's history of both phantom digit pain and CRPS supports the suggestion that these syndromes have similar causes and some individuals may be more susceptible to sympathetically maintained pain (Swart, Stins, & Beek, 2008). Her symptoms of CRPS included some that resembled aspects of neglect: distorted sense of limb size, lack of knowledge of limb location, and hostility towards the limb. In two treatment periods pain, stiffness and other CRPS signs decreased in less than two weeks (~10 days), replicating the results of Sumitani and colleagues (2007). In addition, the results showed that the benefits of prism adaptation were maintained with continued treatment, symptoms worsened when treatment was discontinued, and that adaptation to leftward shifting prisms using the left hand was ineffective.

It has recently been suggested that CRPS arises from incongruencies between the true sensory consequences of motor commands and the anticipated sensory consequences – or efference copy – of those commands to sensory cortex (McCabe & Blake, 2008; Swart et al., 2008). The mismatch between the efference copy and sensory input may initiate protective and defensive sympathetic mechanisms through the autonomic nervous system. Several observations suggest that patients with CRPS have pathologically reorganised neural representations of peripersonal space that normalise with recovery. Repeatedly experiencing the sensory-motor discordance that is induced by prism lenses may have reduced the distorted sensory-motor representations.

Both the above observations of SM and the results of Sumitani and colleagues (2007) suggest that this realignment requires at least several days of treatment. This contrasts with the clinical effects of prism adaptation on neglect, which can be observed after only a single session. There is also a difference in the longevity of the treatment effects of prism adaptation on CRPS in SM and those in neglect patients. For neglect patients, a two-week treatment period benefits symptoms for weeks, months and even a year following the end of treatment (Frassinetti et al., 2002; Serino et al., 2005; Serino et al., 2009; Serino et al., 2007); but for SM symptoms gradually returned.

Sensory feedback of the affected hand during prism adaptation seems essential for therapeutic benefit, as SM's symptoms were not improved by adaptation with the left hand but continued to return to baseline. It would be interesting to combine prism adaptation and mirror therapy to test the effectiveness of adaptation of the *unaffected* limb while the patient views its reflected image in a mirror. If the illusory visual feedback of the affected limb is sufficient to produce improvements then prism adaptation may also hold promise as a treatment for neurogenic pain in phantom or hemiplegic limbs.

When treatment was discontinued pain returned to the affected hand and also began to emerge in the left hand. Emergence of CRPS symptoms in equivalent contralateral locations, or 'mirror-image' spread, has been reported and is a further argument against purely local inflammatory causes (Maleki, LeBel, Bennett, & Schwartzman, 2000). However SM's history of amputation of the first and second digits of the left hand leads me to speculate that as the prism-induced realignment faded there may have been a reawakening of phantom pain caused by the re-detection of sensory-motor mismatch.

Finally, although prism adaptation resulted in substantial relief of symptoms and return of function, it was not completely curative. At the most recent assessment there remained some swelling in the knuckles of the first and second finger, sweatiness of the palm and sensory disturbance. All of these symptoms were very mild and detected only on close comparison to the left hand. Pin pricks were experienced as blunt, non-painful brushing of the skin. The residual restriction of movement was, however, more apparent. Alleviation of pain with prism adaptation, accompanied by mirror treatment that may have prevented atrophy and motor deterioration by enabling her full hand movements periodically, did achieve a sustained improvement range of motion and functionality of the hand. However, SM is still not able to fully close her fingers, and it is therefore clear that there is a deficit in somatomotor function in this syndrome that is independent from sympathetically mediated pain. It remains to be seen whether continued daily sessions can completely restore normal function in limbs affected by CRPS.

Chapter 7

General Discussion

This thesis examined the effects of prism adaptation on higher-level cognitive processing in healthy participants and neurological patients, focusing particularly on elements of visuospatial performance associated with hemispatial neglect. This chapter summarizes the main findings, their implications, and directions for future research.

SINGLE SESSIONS OF PRISM ADAPTATION DO NOT REDUCE THE CLINICAL SIGNS OF NEGLECT FOR ALL PATIENTS

Twelve patients with spatial neglect who underwent a single session of prism adaptation showed no improvement on standard clinical tests (Chapter 2). Furthermore, there was little evidence of improvement in three patients who underwent repeated sessions of prism adaptation either on consecutive days or spaced over several weeks. This is in contrast with multiple findings of neglect improvement after a single prism adaptation session (Rossetti et al.; 1998; Pisella et al., 2002) but is in agreement with Rosseaux and colleagues (2006), and Nys and colleagues (2007). The same adaptation procedure reversed the local processing bias of five patients with chronic TPJ lesions (Chapter 4). Therefore it is unlikely that the lack of clinical improvement reported in Chapter 2 is due to errors in the administration of prism adaptation.

Instead, comparisons of the results of Chapter 2 and other studies reporting no change in symptoms to those that found neglect improvement suggest that neglect chronicity may have a role in whether a patient will derive significant benefit from prism treatment. The performance deficits that are evident in the period immediately following brain injury are due not only to loss of function at the lesion site, but also to swelling causing dysfunction in intact tissue neighbouring the lesion, and changed activity in more remote areas that are connected to the same functional network as the lesioned location. Over time swelling subsides and there is rebalancing of activity in the neural network disrupted by the lesion (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Sapir, d'Avossa, McAvoy, Shulman, & Corbetta, 2005). The extent of this rebalancing probably relates to the degree of recovery between the acute and chronic stages. A re-establishment of equilibrium may be required before prism adaptation can influence higher-level performance, in which case prism adaptation would not be effective for acute neglect patients. Another possibility is simply that for a significant benefit to be obtained, acute neglect patients may require more sessions than has yet been tested (i.e., >4 sessions). This suggests a future course of research to 1) directly compare the effects of single sessions of prism adaptation on neglect signs in patients with acute and chronic neglect, and 2) examine whether two weeks of daily treatment improves neglect symptoms in acute sufferers. A large-scale clinical study involving acute and chronic patients may also identify anatomical correlates of neglect improvement following prism adaptation, and determine if early responsiveness (i.e., improvement following a single treatment) is predictive of ultimate treatment outcome (i.e., long-lasting improvement following multiple sessions).

PRISM ADAPTATION IMPROVES RIGHT SPATIAL NEGLECT

Chapter 2 also included the case of a woman with mild right spatial neglect following left hemisphere damage who showed reduced leftward bisection errors after adaptation to leftward-shifting prisms. To the best of my knowledge this is the first report of prism adaptation ameliorating right spatial neglect (Bultitude & Rafal, accepted article).

Neglect following left hemisphere damage is less frequent, severe and persistent than its right hemisphere counterpart (Beis et al., 2004; Bowen, McKenna, & Tallis, 1999; Ogden, 1985). However for those patients in whom right spatial neglect proves persistent the disorder can be a barrier to rehabilitation, especially when associated with other left-hemisphere syndromes such as aphasia and apraxia. Prism adaptation is a simple treatment that may be easily administered to patients whose treatment is also complicated by aphasia.

DS suffered from only mild neglect and as a result there was only one measure upon which she did not perform at ceiling: line bisection. Further testing of prism treatment in larger samples of right neglect patients with more pronounced symptoms would be useful, but perhaps not realistic due to the relative infrequency of right neglect, and the barriers to systematic testing posed by associated left-hemisphere deficits. One possible method would be to examine spontaneous eye movements in patients with right spatial neglect before and after prism adaptation as a more sensitive test.

The results suggest that prism adaptation can improve right spatial neglect through similar, but mirror-reversed, mechanisms as those occurring in left neglect patients during adaptation to rightward-shifting prisms. This is perhaps not surprising, although there is evidence that left and right spatial neglect have different neurological correlates (Ogden, 1985; but see Beis et al., 2009) and symptom profiles (Beis et al., 2004; Kleinman et al., 2007). Striemer and colleagues hypothesised that the SPL of the lesioned hemisphere is important for the clinical benefits of prism adaptation. However, as DS's lesion included the left SPL, her improvement after prism adaptation does not support this suggestion, at least for patients with right spatial neglect.

PRISM ADAPTATION INFLUENCES NON-LATERALISED SPATIAL PERFORMANCE IN BOTH RIGHT-HEMISPHERE LESIONED PATIENTS AND HEALTHY PARTICIPANTS

Prism adaptation reversed the local processing bias in patients with right TPJ lesions (Chapter 4; Bultitude, Rafal, & List, 2009); and reduced global interference (Chapter 5) and induced a neglect-like withdrawal bias (Chapter 3) in healthy participants. This demonstrates that prism adaptation can change aspects of higher-level spatial performance that are not defined on the horizontal axis of space (that is, non-lateralised spatial components of behaviour), a finding that had only previously been shown in three individual cases of neglect (Beis et al., 2004; Kleinman et al., 2007; Rode, Klos et al., 2006; Rode, Pisella et al., 2006), and not heretofore in healthy participants. A clear direction for future research is to examine whether prism adaptation can influence other aspects of non-lateralised spatial performance (e.g., object-based attention) or non-spatial functions that are frequently impaired in neglect patients (e.g., sustained attention). This could improve understanding of the mechanisms of the clinical effects of prism adaptation on neglect, and support the use of prism adaptation to treat patients in whom the primary deficit is not spatial neglect but an associated disorder of right hemisphere dysfunction.

Changes in non-lateralised spatial functions after prism adaptation imply that prism adaptation does not merely result in long-term adjustments of spatial representations, but influences cortical processing involved in many aspects of spatial performance. Two proposed mechanisms for neglect improvement following prism adaptation are that there is a resetting of the ocular-motor system; and that prism adaptation directly influences the spatial attention deficit that is core to the disorder. It is difficult to conceive of how increased leftward ocular exploration or attentional orienting could bring about improvements in non-lateralised spatial symptoms. Furthermore, in Chapter 4 prism adaptation was followed by a reduction in the local processing bias of five patients with right TPJ lesions, without a concomitant shift in lateralised spatial attention (probably because most of the patients showed no consistent spatial attention bias at baseline). Finally, patient AC showed a marked reduction in local interference following prism adaptation (Chapter 4), but improved on only one of three tests for neglect in the same experiment, and not at all when treated with prism adaptation during the weeks immediately following his stroke (Chapter 2). Overall, this suggests that prism-induced changes in non-lateralised spatial functions occur in parallel to, rather than as a consequence of, changes to lateralised spatial functions. This may occur through a general recruitment of left hemisphere areas for lateralised and non-lateralised right hemisphere functions, or a bolstering of function in residual right hemisphere areas.

This proposed mechanism, combined with the prism-induced reduction in right spatial neglect shown by patient DS, suggests a further avenue for future research: To examine whether prism adaptation can change functions that are lateralised to the left hemisphere. For example, adaptation to leftward-shifting prisms may reduce the pathologically large global processing bias of patients with left TPJ lesions (i.e., improve local processing). If evidence arises for improvements in non-spatial right hemisphere functions following adaptation to rightward-shifting prisms, there may even be grounds for examining the effects of prism adaptation on non-spatial functions of the left parietal lobe such as aphasia.

PRISM ADAPTATION INFLUENCES MOTOR-INTENTIONAL PERFORMANCE IN HEALTHY PARTICIPANTS

The results of Chapter 3 showed that adaptation to leftward-shifting prisms induced a withdrawal bias in healthy participants performing a lever task (Experiment 3.1), and that there may have been a larger reduction in RTs for approach stepping in the leftward-shifting prism group compared to the rightward-shifting prism group (Experiment 3.2). This indicates that prism adaptation can influence motor-intentional performance in healthy participants. Further research is required to: 1) replicate this effect in healthy participants, 2) compare approach and withdrawal responses - and how they are changed by prism adaptation - in patients with frontal and parietal lesions; and 3) examine the relationship, if any, between the purely motor-intentional mode of approach and withdrawal examined in this thesis and those described in emotion-motivation literature, for which an evaluative response or emotional elicitor is key.

Chapter 3 also showed that adaptation to leftward-shifting prisms did not induce directional hypokinesia in healthy participants. The significant change in one type of behaviour (approach-withdrawal) and not another (lateralised movements) may be due to the different neural mechanisms underlying the two. The withdrawal bias is associated with parietal damage, whereas directional hypokinesia is associated with subcortical damage, especially to the putamen. As discussed in Chapter 1, converging evidence implicates the parietal lobe in prism adaptation. Changes in higher-level function after prism adaptation may be restricted to those that are also mediated by parietal areas, in which case future research examining the effect of prism adaptation on non-lateralised spatial deficits would be expected to find changes only in those deficits that result from parietal lobe dysfunction.

Nonetheless, prism adaptation did reverse directional hypokinesia in neglect patients (Rossetti et al., 2005, as cited in Pisella et al., 2006), and prism-induced changes in healthy participants tend to be of a smaller magnitude than in neglect patients. A more sensitive measure of movement initiation may yet reveal changes in RTs for leftward compared to rightward movements in healthy participants who have adapted to leftward-shifting prisms.

This leads to a broader question regarding the influence of prism adaptation: Do the same cognitive and neural mechanisms underlie the higher-level effects of prism adaptation in brain-lesioned patients and healthy participants? Although the longevity of the higher-level effects in healthy participants has not been formally tested, they are assumed to be short-lived, lasting for as long as the visuo-motor after-effect. Performance improvements in neglect patients are not only long-lasting, but can increase over the first two hours post-treatment. Also, higher-level prism effects have been demonstrated for a broader range of tests in patients than in healthy participants (See Tables 1.1 and 1.2 in Chapter 1).

Two possibilities are suggested by these differences: That the higher-level effects of prism adaptation occur through a slightly different mechanism in healthy participants as in neglect patients; or that it is the same mechanism, but the normal equilibrium or 'default' state of the intact brain is not as readily perturbed as the altered neural environment of patients. An argument that seems to support the latter suggestion is that many of the aspects of performance which changed after prism adaptation in healthy participants are ones for which 'normal' behaviour is biased: line bisection, mental number and alphabet bisection, haptic circle centring and judgements on the greyscales task. Rather than inducing a neglect-like bias on these tasks, prism adaptation could be considered to 'treat' or reduce the pseudoneglect of healthy participants following prism adaptation, in the same way that prism adaptation reduces neglect in patients.

The prism-induced changes are numerically smaller in healthy participants than neglect patients. For example, rightward-shifts in line bisection errors of healthy participants following adaptation to leftward-shifting prisms are in the order of around one degree of visual angle on lines of 200mm in length or more (Colent et al., 2000; Michelle et al., 2003; Berberovic and Mattingley, 2003), whereas after adaptation to rightward-shifting prisms the bisection errors of neglect patients shift by as much as 20-40% on the Shenkenberg line bisection test, depending on the line location (Rossetti et al., 1998; Pisella et al., 2002). Similarly, results from Chapters 4 and 5 of this thesis show that hierarchical processing, for which both patients with right TPJ lesions and healthy participants show a baseline bias, was influenced by prism adaptation in both populations. Where prism adaptation reversed the local processing bias of brain-lesioned patients, the global processing bias of the healthy participants in Chapter 5 was merely reduced. Overall, with some exceptions (e.g., Chapter 3 of this thesis; Striemer et al., 2006), the effects of prism adaptation on healthy participants form an emerging pattern: 1) prism adaptation is more likely to perturb higher-level functions for which the baseline performance is already biased, and 2) this perturbation is more readily achieved in patients in whom the balance of neural networks has been disrupted due to brain lesion.

DAILY SESSIONS OF PRISM ADAPTATION IMPROVES PAIN AND RELATED SYMPTOMS IN COMPLEX REGIONAL PAIN SYNDROME, A DISORDER OF BODY REPRESENTATION

Chapter 6 reports the case of a woman with CRPS in the right hand and forearm for whom daily sessions of prism adaptation decreased autonomic symptoms and provided total pain relief. This application of prism adaptation has only been described in one published study, but holds considerable promise for improving the lives of thousands of people suffering from chronic pain and disability of the limb.

Recently, CRPS has been attributed to a distorted neural representation of the limb. Both left and right parietal lobes are implicated in body schema, and, when lesioned, can result in disorders of the representation of spatial organization of body parts (e.g. somatoagnosia, finger agnosia, and left-right agnosia following left parietal lesions), or dysfunction in the sense of body ownership (e.g., personal neglect, anosognosia, and asomatagnosia following right parietal lesions). Heightened motor cortex excitability and structural changes in the neural representations of the affected limb on sensory and motor cortex have been reported in patients with CRPS. Unusual symptoms such as pain experienced upon viewing an approaching object (McCabe and Blake, 2008), hostility toward the limb, and the need to look directly at the limb to perform a simple movement (Bradley and Jensen; 1999), suggest distorted neural representations of peripersonal space and body schema consistent with functional changes in parietal cortex. Longitudinal repeated measures studies could use fMRI to examine whether reduction of CRPS symptoms after prism adaptation corresponds with normalisation of sensory and motor representations of the affected limb as well as changes in parietal lobe activity.

SUMMARY AND CONCLUSIONS

A decade of research demonstrates that the influence of prism adaptation is not limited to low-level sensory-motor function, but extends to affect higher cognitive aspects of spatial performance. The experiments described in this thesis further explored this higher-level spatial influence in both healthy participants and neurological populations, with a particular focus on hemispatial neglect.

Previous findings that a single session of adaptation to rightward-shifting prisms improved the performance of neglect patients on standard pen-and-paper tests were not replicated in twelve patients with acute neglect. This suggests a need to further examine the usefulness of prism adaptation in early neglect rehabilitation. In contrast, results from patients with chronic lesions extended on previous clinical findings to demonstrate, for the first time, that 1) right spatial neglect is reduced by adaptation to leftward-shifting prisms; and 2) adaptation to rightward-shifting prisms reverses the local processing bias in patients with right TPJ lesions. Furthermore, prism adaptation induced a neglect-like withdrawal bias and reduced the global processing bias in healthy participants. A major outcome of this thesis was that the higher-level spatial influence of prism adaptation on the performance of both brain-lesioned and healthy participants is not limited to lateralised aspects of performance, but also extends to non-lateralised functions. Finally, this thesis replicated evidence that prism adaptation can reduce pain and other symptoms of CRPS, a disorder of body representation that does not stem from damage to the central or peripheral nervous system. I extended previous results to demonstrate, in a single case study, that reduction of symptoms depended on proprioception from the affected limb, and that prism adaptation and mirror feedback had different effects on symptoms. In summary, this thesis provides evidence that prism adaptation can perturb aspects of performance that are mediated by the parietal lobe, including spatially lateralised attention, hierarchical processing, approach and withdrawal, and body schema. With such a broad influence on behaviour, prism adaptation represents a promising treatment for chronic pathologies of parietal dysfunction.

References

AbuRahma, A. F., Robinson, P. A., Powell, M., Bastug, D., & Boland, J. P. (1994). Sympathectomy for reflex sympathetic dystrophy: factors affecting outcome. *Ann Vasc Surg, 8*(4), 372-379.

Alexander, G. M., van Rijn, M. A., van Hilten, J. J., Perreault, M. J., & Schwartzman, R. J. (2005). Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain, 116*(3), 213-219.

Alivisatos, B., & Wilding, J. (1982). Hemispheric differences in matching. Stroop-type letter stimuli. *Cortex, 18*, 5-22.

Amirkhiabani, G., & Lovegrove, W. J. (1996). Role of eccentricity and size in the globel precedence effect. *Journal of Experimental Psychology: Human Perception and Performance, 22*, 1434-1447.

Anderson, S. W., & Tranel, D. (1989). Awareness of disease states following cerebral infarction, dementia and head trauma: Standardized assessment. *The Clinical Neuropsychologist, 3*(4), 327-339.

Andre, J. M., Beis, J. M., Morin, N., & Paysant, J. (2000). Buccal hemineglect. *Arch Neurol, 57*(12), 1734-1741.

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

Angeli, V., Meneghello, F., Mattioli, F., & Làdavas, E. (2004). Mechanisms underlying visuo-spatial amelioration of neglect after prism adaptation. *Cortex, 40*, 155-156.

Arend, I., Rafal, R., & Ward, R. (2008). Spatial and temporal deficits are regionally dissociable in patients with pulvinar lesions. *Brain, 131*(Pt 8), 2140-2152.

Arene, N. U., & Hillis, A. E. (2007). Rehabilitation of unilateral spatial neglect and neuroimaging. *Eura Medicophys, 43*(2), 255-269.

Bacchini, M., Frassinetti, F., Farnè, A., Affanni, P., & Rossi, M. (2006). Effects of prism adaptation on motor deficit in neglect: A single-case study with gait analysis. *Gait & Posture, 24*, S40-S41.

Bailey, M. J., Riddoch, M. J., & Crome, P. (2002). Treatment of visual neglect in elderly patients with stroke: a single-subject series using either a scanning and cueing strategy or a left-limb activation strategy. *Phys Ther, 82*(8), 782-797.

Baizer, J. S., Kralj-Hans, I., & Glickstein, M. (1999). Cerebellar lesions and prism adaptation in macaque monkeys. *Journal of Neurophysiology, 81*(4), 1960-1965.

Bartolomeo, P., & Chokron, S. (1999). Egocentric frame of reference: its role in spatial bias after right hemisphere lesions. *Neuropsychologia, 37*(8), 881-894.

Beckett, P. A., & Melamed, L. E. (1980). Further evidence for dissociating decay and readaptation in prism adaptation. *Bulletin of the Psychonomic Society, 16*(1), 73-75.

Beis, J.-M., Keller, C., Morin, N., Bartolomeo, P., Bernati, T., Chokron, S., et al. (2004). Right spatial neglect after left hemisphere stroke: Qualitative and quantitative study. *Neurology, 63*(9), 1600-1605.

Bellas, D. N., Novelly, R. A., Eskenazi, B., & Wasserstein, J. (1988a). The nature of unilateral neglect in the olfactory sensory system. *Neuropsychologia, 26*(1), 45-52.

Bellas, D. N., Novelly, R. A., Eskenazi, B., & Wasserstein, J. (1988b). Unilateral displacement in the olfactory sense: a manifestation of the unilateral neglect syndrome. *Cortex, 24*(2), 267-275.

Berberovic, N., & Mattingley, J. B. (2003). Effects of prismatic adaptation on judgements of spatial extent in peripersonal and extrapersonal space. *Neuropsychologia, 41*(4), 493-503.

Berberovic, N., Pisella, L., Morris, A. P., & Mattingley, J. B. (2004). Prismatic adaptation reduces biased temporal order judgements in spatial neglect. *NeuroReport, 15*(7), 1199-1204.

Bergan, J. F., Ro, P., Ro, D., & Knudsen, E. I. (2005). Hunting increases adaptive auditory map plasticity in adult barn owls. *J Neurosci, 25*(42), 9816-9820.

Berti, A., Bottini, G., Gandola, M., Pia, L., Smania, N., Stracciari, A., et al. (2005). Shared cortical anatomy for motor awareness and motor control. *Science, 309*(5733), 488-491.

Bird, C. M., Malhotra, P., Parton, A., Coulthard, E., Rushworth, M. F., & Husain, M. (2006). Visual neglect after right posterior cerebral artery infarction. *J Neurol Neurosurg Psychiatry, 77*(9), 1008-1012.

Bisiach, E., Geminiani, G., Berti, A., & Rusconi, M. L. (1990). Perceptual and premotor factors of unilateral neglect. *Neurology, 40*(8), 1278-1281.

Bisiach, E., & Luzzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*(1), 129-133.

Bisiach, E., Vallar, G., Perani, D., Papagno, C., & Berti, A. (1986). Unawareness of disease following lesions of the right hemisphere: Anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia, 24*(4), 471-482.

Boles, D. B. (1984). Global versus local processing: Is there a hemispheric dichotomy? *Neuropsychologia, 22*(4), 445-455.

Bowen, A., Lincoln, N. B., & Dewey, M. (2002a). Cognitive rehabilitation for spatial neglect following stroke. *Cochrane Database Syst Rev*(2), CD003586.

Bowen, A., Lincoln, N. B., & Dewey, M. E. (2002b). Spatial neglect: is rehabilitation effective? *Stroke, 33*(11), 2728-2729.

Bowen, A., McKenna, K., & Tallis, R. C. (1999). Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. *Stroke, 39*(6), 1196-1202.

Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: effects of hemispace on a tactile line bisection task. *Neuropsychologia, 18*(4-5), 491-498.

Brainard, M. S., & Knudsen, E. I. (1998). Sensitive periods for visual calibration of the auditory space map in the barn owl optic tectum. *J Neurosci, 18*(10), 3929-3942.

Bultitude, J. H., & Aimola Davies, A. M. (2006). Putting attention on the line: investigating the activation-orientation hypothesis of pseudoneglect. *Neuropsychologia, 44*(10), 1849-1858.

Bultitude, J. H., & Rafal, R. (accepted article). Amelioration of right spatial neglect after visuo-motor adaptation to leftward-shifting prisms. *Cortex.*

Bultitude, J. H., Rafal, R. D., & List, A. (2009). Prism adaptation reverses the local processing bias in patients with right temporo-parietal junction lesions. *Brain, 132*(Pt 6), 1669-1677.

Cacioppo, J. T., Priester, J. R., & Berntson, G. G. (1993). Rudimentary determinants of attitudes. II: Arm flexion and extension have differential effects on attitudes. *J Pers Soc Psychol, 65*(1), 5-17.

Cambier, J., Masson, M., Graveleau, P., & Elghozi, D. (1982). [Symptomatology of neglect in ischemic lesions of the territory of the right posterior cerebral artery. Role of thalamic lesions]. *Rev Neurol (Paris), 138*(8-9), 631-648.

Campbell, D. C., & Oxbury, J. M. (1976). Recovery from unilateral visuo-spatial neglect? *Cortex, 12*(4), 303-312.

Cappelletti, M., Freeman, E. D., & Cipolotti, L. (2007). The middle house or the middle floor: bisecting horizontal and vertical mental number lines in neglect. *Neuropsychologia, 45*(13), 2989-3000.

Chen, M., & Bargh, J. A. (1999). Consequences of automatic evaluation: Immediate behavioural predispositions to approach or avoid the stimlus. *Personality and Social Psychology Bulletin, 25*, 215-225.

Choe, C. S., & Welch, R. B. (1974). Variables affecting the intermanual transfer and decay of prism adaptation. *J Exp Psychol, 102*(6), 1076-1084.

Choi, Y. S., Lee, M. G., Lee, H. M., Lee, C. J., Jo, J. Y., Jeon, S. Y., et al. (2008). Epidemiology of complex regional pain syndrome: a retrospective chart review of 150 Korean patients. *J Korean Med Sci, 23*(5), 772-775.

Chokron, S., & Bartolomeo, P. (2000). Correlation between the position of the egocentric reference and right neglect signs in left-brain-damaged patients. *Brain Cogn, 43*(1-3), 99-104.

Clower, D. M., Hoffman, J. M., Votaw, J. R., Faber, T. L., Woods, R. P., & Alexander, G. E. (1996). Role of posterior parietal cortex in the recalibration of visually guided reaching. *Nature, 383*(6601), 618-621.

Cohen, M. M. (1967). Continuous versus terminal visual feedback in prism aftereffects. *Percept Mot Skills, 24*(3), 1295-1302.

Colent, C., Pisella, L., Bernieri, C., Rode, G., & Rossetti, Y. (2000). Cognitive bias induced by visuo-motor adaptation to prisms: A simulation of unilateral neglect in normal individuals? *Cognitive Neuroscience, 11*(9), 1899-1902.

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat Neurosci, 8*(11), 1603-1610.

Courtois-Jacquin, S., Rossetti, Y., Rode, G., Fischer, C., Michel, C., & Boisson, D. (2002). Clinical and Neurophysiological evaluation of effect of prism adaptation on auditory extinction: An attentional effect? *Neurorehabilitation and Neural Repair, 16*(2), 136-137.

Cubelli, R., Nichelli, P., Bonito, V., De Tanti, A., & Inzaghi, M. G. (1991). Different patterns of dissociation in unilateral spatial neglect. *Brain Cogn, 15*(2), 139-159.

Cui, Q. N., Bachus, L., Knoth, E., O'Neill, W. E., & Paige, G. D. (2008). Eye position and cross-sensory learning both contribute to prism adaptation of auditory space. *Prog Brain Res, 171*, 265-270.

Da Gloria, J., Pahlavan, F., Duda, D., & Bonnet, P. (1994). Evidence for a motor mechanism of pain-induced aggression instigation in humans. *Aggressive Behaviour, 20*(1), 1-7.

Damasio, A. R., Damasio, H., & Chui, H. C. (1980). Neglect following damage to frontal lobe or basal ganglia. *Neuropsychologia, 18*(2), 123-132.

Danckert, J., & Ferber, S. (2006). Revisiting unilateral neglect. *Neuropsychologia, 44*(6), 987-1006.

Danckert, J., Ferber, S., & Goodale, M. A. (2008). Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study. *Eur J Neurosci, 28*(8), 1696-1704.

Datie, A. M., Paysant, J., Destainville, S., Sagez, A., Beis, J. M., & Andre, J. M. (2006). Eye movements and visuoverbal descriptions exhibit heterogeneous and dissociated patterns before and after prismatic adaptation in unilateral spatial neglect. *Eur J Neurol, 13*(7), 772-779.

de Mos, M., Huygen, F. J., Dieleman, J. P., Koopman, J. S., Stricker, B. H., & Sturkenboom, M. C. (2008). Medical history and the onset of complex regional pain syndrome (CRPS). *Pain, 139*(2), 458-466.

Delis, D. C., Robertson, L. C., & Efron, R. (1986). Hemispheric specialization of memory for visual hierarchical stimuli. *Neuropsychologia, 24*(2), 205-214.

Denny-Brown, D. (1956). Positive and negative aspects of cerebral cortical functions. *North Carolina medical journal, 17*(7), 295-303.

Denny-Brown, D. (1958). The nature of apraxia. *Journal of Nervous and Mental Disease, 126*(1), 9-32.

Denny-Brown, D., & Chambers, R. A. (1958). The parietal lobe and behavior. *Association for research in nervous and mental diseases proceedings., 36*, 35-117.

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nat Neurosci, 2*(6), 563-567.

di Pellegrino, G. (1995). Clock-drawing in a case of left visuo-spatial neglect: A deficit of disengagement? *Neuropsychologia, 33*(33), 3.

di Pellegrino, G., Rafal, R. D., & Tipper, S. P. (2005). Implicitly evoked actions modulate visual selection: Evidence from parietal extinction. *Current Biology, 15*(16), 1469-1472.

Dijkerman, H. C., McIntosh, R. D., Milner, A. D., Rossetti, Y., Tilikete, C., & Roberts, R. C. (2003). Ocular scanning and perceptual size distortion in hemispatial neglect: Effects of prism adaptation and sequential stimulus presentation. *Experimental Brain Research, 153*(2), 220-230.

Dijkerman, H. C., Webeling, M., ter Wal, J. M., Groet, E., & van Zandvoort, M. J. E. (2004). A long-lasting improvement of somatosensory function after prism adaptation, a case study. *Neuropsychologia, 42*(12), 1697-1702.

Dijkstra, P. U., Groothoff, J. W., ten Duis, H. J., & Geertzen, J. H. (2003). Incidence of complex regional pain syndrome type I after fractures of the distal radius. *Eur J Pain, 7*(5), 457-462.

Doricchi, F., & Galati, G. (2000). Implicit semantic evaluation of object symmetry and contralesional visual denial in a case of left unilateral neglect with damage of the dorsal paraventricular white matter. *Cortex, 36*(3), 337-350.

Doricchi, F., Guariglia, C., Paolucci, S., & Pizzamiglio, L. (1991). Disappearance of leftward rapid eye movements during sleep in left visual hemi-inattention. *Neuroreport, 2*(5), 285-288.

Doricchi, F., Guariglia, C., Paolucci, S., & Pizzamiglio, L. (1996). Asymmetry of rapid eye movements in chronic unilateral neglect does not change with behavioral improvement induced by rehabilitation treatment. *Electroencephalogr Clin Neurophysiol, 98*(1), 51-58.

Doyon, J., & Milner, B. (1991). Right temporal-lobe contribution to global visual processing. *Neuropsychologia, 29*(5), 343-360.

Duckworth, K. L., Bargh, J. A., Garcia, M., & Chaiken, S. (2002). The automatic evaluation of novel stimuli. *Psychol Sci, 13*(6), 513-519.

Eder, A. B., & Rothermund, K. (2008). When do motor behaviors (mis)match affective stimuli? An evaluative coding view of approach and avoidance reactions. *J Exp Psychol Gen, 137*(2), 262-281.

Edgeworth, J. A., Robertson, I. H., & McMillan, T. M. (1998). *The Balloons Test*. Bury St Edmunds, England: Thames Valley Test Company.

Efstathiou, E. (1969). Effects of exposure time and magnitude of prism transform on eye-hand coordination. *J Exp Psychol, 81*(2), 235-240.

Egly, R., Driver, J., & Rafal, R. D. (1994). Shifting visual attention between objects and locations: Evidence from normal and parietal lesion subjects. *Journal of Experimental Psychology: General, 123*(2), 161-177.

Ergun-Marterer, A., Ergun, E., Mentes, M., & Oder, W. (2001). Altitudinal neglect in a patient with occipital infarction. *Brain Inj, 15*(4), 363-370.

Farnè, A., Buxbaum, L. J., Ferraro, M., Frassinetti, F., Whyte, J., Veramonti, T., et al. (2004). Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *J Neurol Neurosurg Psychiatry, 75*(10), 1401-1410.

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

Ferber, S., Danckert, J., Joanisse, M., Goltz, H. C., & Goodale, M. A. (2003). Eye movements tell only half the story. *Neurology, 60*(11), 1826-1829.

Ferber, S., & Murray, L. J. (2005). Are perceptual judgments dissociated from motor processes?--A prism adaptation study. *Brain Res Cogn Brain Res, 23*(2-3), 453-456.

Fernandez-Ruiz, J., Diaz, R., Hall-Haro, C., Vergara, P., Mischner, J., Nuñez, L., et al. (2003). Normal prism adaptation but reduced after-effect in basal ganglia disorders using a throwing task. *European Journal of Neuroscience, 18*(3), 689-694.

Fierro, B., Brighina, F., & Bisiach, E. (2006). Improving neglect by TMS. *Behavioural Neurology, 17*(3-4), 169-176.

Fink, G. R., Halligan, P. W., Marshall, J. C., Frith, C.D., Frackowiak, R. S. J., & R.J., D. (1996). Where in the brain does visual attention select the forest and the trees? *Nature, 392*(6592), 626-628.

Fink, G. R., Marshall, J. C., Halligan, P. W., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1997). Hemispheric specialization for global and local processing: The effect of stimulus category. *Proceedings: Biological Sciences, 264*(1381), 487-494.

Folegatti, A., Spinazzola, L., Neppi-Mòdona, M., Ricci, R., Rabffetti, M., Ferrarin, M., et al. (2008). *Long lasting improvement of walking trajectory after prism adaptation in neglect.* Paper presented at the 26th European Workshop on Cognitive Neuropsychology, Brixen (Italy).

Forderreuther, S., Sailer, U., & Straube, A. (2004). Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain, 110*(3), 756-761.

Frassinetti, F., Angeli, V., Meneghello, F., Avanzi, S., & Làdavas, E. (2002). Long-lasting amelioration of visuospatial neglect by prism adaptation. *Brain, 125*(3), 608-623.

Friedrich, F. J., Egly, R., Rafal, R. D., & Beck, D. (1998). Spatial attention deficits in humans: A comparison of superior parietal and temporal-parietal junction lesions. *Neuropsychology, 12*(2), 193-207.

Gainotti, G., D'Erme, P., Monteleone, D., & Silberi, M. C. (1986). Mechanisms of unilateral spatial neglect in relation to laterality of cerebral lesions. *Brain, 109*(4), 599-612.

Gainotti, G., Messerli, P., & Tissot, R. (1972). Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions. *J Neurol Neurosurg Psychiatry, 35*(4), 545-550.

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

Gibbons, J. J., & Wilson, P. R. (1992). RSD score: criteria for the diagnosis of reflex sympathetic dystrophy and causalgia. *Clin J Pain, 8*(3), 260-263.

Girardi, M., McIntosh, R. D., Michel, C., Vallar, G., & Rossetti, Y. (2004). Sensorimotor effects on central space representation: Prism adaptation influences haptic and visual representations in normal subjects. *Neuropsychologia, 42*(11), 1477-1487.

Gold, M., Shuren, J., & Heilman, K. M. (1994). Proximal intentional neglect: a case study. *J Neurol Neurosurg Psychiatry, 57*(11), 1395-1400.

Graveleau, P., Viader, F., & Cambier, J. (1986). Subcortical neglect. *Ital J Neurol Sci, 7*(6), 573-580.

Grea, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., et al. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia, 40*(13), 2471-2480.

Guariglia, C., & Antonucci, G. (1992). Personal and extrapersonal space: a case of neglect dissociation. *Neuropsychologia, 30*(11), 1001-1009.

Halligan, P. W., Manning, L., & Marshall, J. C. (1991). Hemispheric activation vs spatio-motor cueing in visual neglect: A case study. *Neuropsychologia, 29*(2), 165-176.

Halligan, P. W., & Marshall, J. C. (1989). Is neglect (only) lateral? A quadrant analysis of line cancellation. *Journal of Clinical and Experimental Neuropsychology, 11*(6), 793-798.

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

Halligan, P. W., & Marshall, J. C. (1993). The bisection of horizontal and radial lines: a case study of normal controls and ten patients with left visuospatial neglect. *Int J Neurosci, 70*(3-4), 149-167.

Halligan, P. W., & Marshall, J. C. (1994). Focal and global attention modulate the expression of visuo-spatial neglect: A case study. *Neuropsychologia, 32*(1), 13-21.

Halligan, P. W., & Marshall, J. C. (1998a). Neglect of awareness. *Conscious Cogn, 7*(3), 356-380.

Halligan, P. W., & Marshall, J. C. (1998b). Visuospatial neglect: the ultimate deconstruction? *Brain Cogn, 37*(3), 419-438.

Halligan, P. W., Marshall, J. C., & Wade, D. T. (1992). Left on the right: allochiria in a case of left visuo-spatial neglect. *J Neurol Neurosurg Psychiatry, 55*(8), 717-719.

Han, S., Weaver, J. A., Murray, S. O., Kang, X., Yund, E. W., & Woods, D. L. (2002). Hemispheric asymmetry in global/local processing: effects of stimulus position and spatial frequency. *Neuroimage, 17*(3), 1290-1299.

Hanlin, P. (2008). Prism thinning and progressive addition lenses. *20/20,* Retrieved March 30, 2009, from www.2020mag.com.

Harris, C. S. (1965). Perceptual adaptation to inverted, reversed, and displaced vision. *Psychol Rev, 72*(6), 419-444.

Hatada, Y., Miall, R. C., & Rossetti, Y. (2006). Two waves of a long-lasting aftereffect of prism adaptation measured over 7 days. *Exp Brain Res, 169*(3), 417-426.

Heilman, K. M. (2004). Intentional neglect. *Front Biosci, 9*, 694-705.

Heilman, K. M., Bowers, D., Coslett, H. B., Whelan, H., & Watson, R. T. (1985). Directional hypokinesia: Prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect. *Neurology, 35*(6), 855-859.

Heilman, K. M., Bowers, D., & Watson, R. T. (1983). Performance on hemispatial pointing task by patients with neglect syndrome. *Neurology, 33*(5), 661-664.

Heilman, K. M., & Valenstein, E. (1972a). Auditory neglect in man. *Arch Neurol, 26*(1), 32-35.

Heilman, K. M., & Valenstein, E. (1972b). Frontal lobe neglect in man. *Neurology, 22*(6), 660-664.

Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Ann Neurol, 5*(2), 166-170.

Heinze, H. J., & Munte, T. F. (1993). Electrophysiological correlates of hierarchical stimulus processing: dissociation between onset and later stages of global and local target processing. *Neuropsychologia, 31*(8), 841-852.

Held, R., & Bossom, J. (1961). Neonatal deprivation and adult rearrangement: complementary techniques for analyzing plastic sensory-motor coordinations. *J Comp Physiol Psychol, 54*, 33-37.

Hillis, A. E. (2006). Neurobiology of unilateral spatial neglect. *Neuroscientist, 12*(2), 153-163.

Hillis, A. E., Newhart, M., Heidler, J., Barker, P. B., Herskovits, E. H., & Degaonkar, M. (2005). Anatomy of spatial attention: insights from perfusion imaging and hemispatial neglect in acute stroke. *J Neurosci, 25*(12), 3161-3167.

Hübner, R. (1998). Hemispheric differences in global/local processing revealed by same-different judgements. *Visual Cognition, 5*(4), 457-478.

Humphreys, G. W., Watelet, A., & Riddoch, M. J. (2006). Long-term effects of prism adaptation in chronic visual neglect: A single case study. *Cognitive Neuropsychology, 23*, 463-478.

Husain, M., & Kennard, C. (1996). Visual neglect associated with frontal lobe infarction. *J Neurol, 243*(9), 652-657.

Husain, M., Mannan, S., Hodgson, T., Wojciulik, E., Driver, J., & Kennard, C. (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. *Brain, 124*(Pt 5), 941-952.

Husain, M., Mattingley, J. B., Rorden, C., Kennard, C., & Driver, J. (2000). Distinguishing sensory and motor biases in parietal and frontal neglect. *Brain, 123 (Pt 8)*, 1643-1659.

Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience, 4*(1), 26-36.

Husain, M., Shapiro, K., Martin, J., & Kennard, C. (1997). Abnormal temporal dynamics of visual attention in spatial neglect patients. *Nature, 385*(6612), 154-156.

Huygen, F. J., De Bruijn, A. G., De Bruin, M. T., Groeneweg, J. G., Klein, J., & Zijlstra, F. J. (2002). Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm, 11*(1), 47-51.

Ishai, S., Seki, K., Koyama, Y., & Yokata, T. (1996). Mechanisms of unilateral spatial neglect in copying a single object. *Neuropsychologia, 34*(10), 965-971.

Jackson, S. R., & Newport, R. (2001). Prism adaptation produces neglect-like patterns of hand path curvature in healthy adults. *Neuropsychologia, 39*(8), 810-814.

Jackson, S. R., Newport, R., Husain, M., Harvey, M., & Hindle, J. V. (2000). Reaching movements may reveal the distorted topography of spatial representations after neglect. *Neuropsychologia, 38*(4), 500-507.

Jacquin-Courtois, S., Rode, G., Pisella, L., Boisson, D., & Rossetti, Y. (2008). Wheel-chair driving improvement following visuo-manual prism adaptation. *Cortex, 44*(1), 90-96.

Jeannerod, M., & Rossetti, Y. (1993). Visuomotor coordination as a dissociable visual function: experimental and clinical evidence. *Baillieres Clin Neurol, 2*(2), 439-460.

Jehkonen, M., Laihosalo, M., & Kettunen, J. E. (2006). Impact of neglect on functional outcome after stroke - a review of methodological issues and recent research findings. *Restorative Neurology and Neurocience, 24*, 209-215.

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia, 38*(1), 93-110.

Johannsen, L., Ackermann, H., & Karnath, H. O. (2003). Lasting amelioration of spatial neglect by treatment with neck muscle vibration even without concurrent training. *J Rehabil Med, 35*(6), 249-253.

Karnath, H.-O. (1994). Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation. *Brain, 117 (Pt 5)*, 1001-1012.

Karnath, H.-O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature, 411*(6840), 950-953.

Karnath, H.-O., Fruhmann Berger, M., Kuker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cereb Cortex, 14*(10), 1164-1172.

Karnath, H.-O., Himmelbach, M., & Rorden, C. (2002). The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar. *Brain, 125*(Pt 2), 350-360.

Karnath, H.-O., Huimmelback, M., & Küker, W. (2003). The cortical substrate of visual extinction. *NeuroReport, 14*(3), 437-442.

Keane, S., Turner, C., Sherrington, C., & Beard, J. R. (2006). Use of fresnel prism glasses to treat stroke patients with hemispatial neglect. *Arch Phys Med Rehabil, 87*(12), 1668-1672.

Kerkhoff, G. (2001). Spatial hemineglect in humans. *Prog Neurobiol, 63*(1), 1-27.

Kinchla, R. A., Solis-Macias, V., & Hoffman, J. (1983). Attending to different levels of structure in a visual image. *Percept Psychophys, 33*(1), 1-10.

Kinchla, R. A., & Wolfe, J. M. (1979). The order of visual processing: "Top-down," "bottom-up", or "middle-out". *Percept Psychophys, 25*(3), 225-231.

Kinsbourne, M. (1970). The cerebral basis of lateral asymmetries in attention. *Acta Psychologica, 33*(193-201).

Kinsbourne, M. (1993). Orientational bias model of unilateral neglect: Evidence from attentional gradients within hemispace. In I. H. Robertson & J. C. Marshall (Eds.), *Unilateral neglect: Clinical and experimental studies.* (pp. 63-86). Hillsdale, NJ: Erlbaum.

Kleinman, J. T., Newhart, M., Davis, C., Heidler-Gary, J., Gottesman, R. F., & Hillis, A. E. (2007). Right hemispatial neglect: frequency and characterization following acute left hemisphere stroke. *Brain Cogn, 64*(1), 50-59.

Knudsen, E. I., & Knudsen, P. F. (1989a). Vision calibrates sound localization in developing barn owls. *J Neurosci, 9*(9), 3306-3313.

Knudsen, E. I., & Knudsen, P. F. (1989b). Visuomotor adaptation to displacing prisms by adult and baby barn owls. *J Neurosci, 9*(9), 3297-3305.

Kodsi, M. H., & Heilman, K. M. (2002). The contribution of an avoidance response to contralateral neglect. *Neurology, 58*(1111), 1692-1694.

Koehler, P. J., & Lanska, D. J. (2004). Mitchell's influence on European studies of peripheral nerve injuries during World War I. *J Hist Neurosci, 13*(4), 326-335.

Kori, A., & Geldmacher, D. S. (1999). Three-dimensional neglect phenomena following right anterior choroidal artery infarction. *J Int Neuropsychol Soc, 5*(6), 567-571.

Kornheiser, A. S. (1976). Adaptation to laterally displaced vision: A review. *Psychological Bulletin, 83*(5), 783-816.

Kurata, K., & Hoshi, E. (1999). Reacquisition deficits in prism adaptation after muscimol microinjection into the ventral premotor cortex of monkeys. *Journal of Neurophysiology, 81*(4), 1927-1938.

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

Ladavas, E., Petronio, A., & Umilta, C. (1990). The deployment of visual attention in the intact field of hemineglect patients. *Cortex, 26*(3), 307-317.

Lamb, M. R., & Robertson, L. C. (1988). The processing of hierarchical stimuli: Effects of retinal locus, locational uncertainty, and stimulus identity. *Perception and Psychophysics, 44*(2), 172-181.

Lamb, M. R., Robertson, L. C., & Knight, R. T. (1989). Attention and interference in the processing of global and local information: Effects of unilateral temporal-parietal junction lesions. *Neuropsychologia, 27*(4), 471-483.

Lamb, M. R., Robertson, L. C., & Knight, R. T. (1990). Component mechanisms underlying the processing of hierarchically organized patterns: Inferences from patients with unilateral cortical lesions. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16*(3), 471-483.

Lavender, A. P., & Nosaka, K. (2008). A light load eccentric exercise confers protection against a subsequent bout of more demanding eccentric exercise. *J Sci Med Sport, 11*(3), 291-298.

Lee, J.-H., & van Donkelaar, P. (2006). The human dorsal premotor cortex generates on-line error corrections during sensorimotor adaptation. *The Journal of Neuroscience, 26*(12), 3330-3334.

Loftus, A. M., Nicholls, M. E., Mattingley, J. B., & Bradshaw, J. L. (2008). Left to right: representational biases for numbers and the effect of visuomotor adaptation. *Cognition, 107*(3), 1048-1058.

Loftus, A. M., Vijayakumar, N., & Nicholls, M. E. (2009). Prism adaptation overcomes pseudoneglect for the greyscales task. *Cortex, 45*(4), 537-543.

Luauté, J., Halligan, P., Rode, G., Jacquin-Courtois, S., & Boisson, D. (2006). Prism adaptation first among equals in alleviating left neglect: a review. *Restor Neurol Neurosci, 24*(4-6), 409-418.

Luauté, J., Halligan, P. W., Rode, G., Rossetti, Y., & Boisson, D. (2006). Visuo-spatial neglect: A systematic review of current interventions and their effectiveness. *Neuroscience and Biobehavioral Reviews, 30*(7), 961-982.

Luauté, J., Michel, C., Rode, G., Pisella, L., Jacquin-Courtois, S., Costes, N., et al. (2006). Functional anatomy of the therapeutic effects of prism adaptation on left neglect. *Neurology, 66*(12), 1859-1867.

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., et al. (2009). Dynamic changes in brain activity during prism adaptation. *J Neurosci, 29*(1), 169-178.

Lux, S., Marcshall, J. C., Thimm, M., & Fink, G. R. (2008). Differential processing of hierarchical visual stimuli in young and older healthy adults: Implications for pathology. *Cortex, 44*(1), 21-28.

Maihofner, C., Handwerker, H. O., Neundorfer, B., & Birklein, F. (2004). Cortical reorganization during recovery from complex regional pain syndrome. *Neurology, 63*(4), 693-701.

Maihöfner, C., Handwerker, H. O., Neundorfer, B., & Birklein, F. (2003). Patterns of cortical reorganization in complex regional pain syndrome. *Neurology, 61*(12), 1707-1715.

Maleki, J., LeBel, A. A., Bennett, G. J., & Schwartzman, R. J. (2000). Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). *Pain, 88*(3), 259-266.

Malhotra, P., Jager, H. R., Parton, A., Greenwood, R., Playford, E. D., Brown, M. M., et al. (2005). Spatial working memory capacity in unilateral neglect. *Brain, 128*(Pt 2), 424-435.

Malhotra, P., Mannan, S., Driver, J., & Husain, M. (2004). Impaired spatial working memory: one component of the visual neglect syndrome? *Cortex, 40*(4-5), 667-676.

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

Mark, V. W., Kooistra, C. A., & Heilman, K. M. (1988). Hemispatial neglect affected by non-neglected stimuli. *Neurology, 38*(7), 1207-1211.

Markman, A. B., & Brendl, C. M. (2005). Constraining theories of embodied cognition. *Psychol Sci, 16*(1), 6-10.

Marshall, J. C., & Halligan, P. W. (1988). Blindsight and insight in visuo-spatial neglect. *Nature, 336*(6201), 766-767.

Marshall, J. C., & Halligan, P. W. (1990). The psychophysics of visuospatial neglect: A new orientation. *Medical Science Research, 18*, 429-430.

Marshall, J. C., & Halligan, P. W. (1993). Visuo-spatial neglect: a new copying test to assess perceptual parsing. *J Neurol, 240*(1), 37-40.

Marshall, J. C., & Halligan, P. W. (1995). Seeing the forest but only half the trees? *Nature, 373*(6514), 521-523.

Martin, M. (1979a). Hemispheric specialization for local and global processing. *Neuropsychologia, 17*(1), 33-40.

Martin, M. (1979b). Local and global processing: The role of sparsity. *Memory and Cognition, 7*(6), 476-484.

Martin, T. A., Keating, J. G., Goodkin, H. P., Bastian, A. J., & Thach, W. T. (1996). Throwing while looking through prisms. I. Focal olivocerebellar lesions impair adaptation. *Brain, 119 (Pt 4)*, 1183-1198.

Mattingley, J. B., Bradshaw, J. L., & Phillips, J. G. (1992). Impairments of movement initiation and execution in unilateral neglect. Directional hypokinesia and bradykinesia. *Brain, 115 (Pt 6)*, 1849-1874.

Mattingley, J. B., Husain, M., Rorden, C., Kennard, C., & Driver, J. (1998). Motor role of human inferior parietal lobe revealed in unilateral neglect patients. *Nature, 392*(6672), 179-182.

Maxwell, J. S., & Davidson, R. J. (2007). Emotion as motion: asymmetries in approach and avoidant actions. *Psychol Sci, 18*(12), 1113-1119.

Mazzoni, P., & Krakauer, J. W. (2006). An implicit plan overrides an explicit strategy during visuomotor adaptation. *J Neurosci, 26*(14), 3642-3645.

McCabe, C. S., & Blake, D. R. (2008). An embarrassment of pain perceptions? Towards an understanding of and explanation for the clinical presentation of CRPS type 1. *Rheumatology (Oxford), 47*(11), 1612-1616.

McCabe, C. S., Haigh, R. C., Halligan, P. W., & Blake, D. R. (2003). Referred sensations in patients with complex regional pain syndrome type 1. *Rheumatology (Oxford), 42*(9), 1067-1073.

McCabe, C. S., Haigh, R. C., Ring, E. F., Halligan, P. W., Wall, P. D., & Blake, D. R. (2003). A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology (Oxford), 42*(1), 97-101.

McIntosh, R. D., Rossetti, Y., & Milner, A. D. (2002). Prism adaptation improves chronic visual and haptic neglect: A single case study. *Cortex, 38*(3), 309-320.

Mesulam, M.-M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology, 10*(4), 309-325.

Mesulam, M.-M. (1999). Spatial attention and neglect: Parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philisophical Transactions of the Royal Society of London. Series B, Biological Sciences, 354*(1387), 1325-1346.

Michel, C. (2006). Simulating unilateral neglect in normals: myth or reality? *Restor Neurol Neurosci, 24*(4-6), 419-430.

Michel, C., Pisella, L., Halligan, P. W., Luauté, J., Rode, G., Boisson, D., et al. (2003). Simulating unilateral neglect in normals using prism adaptation: Implications for theory. *Neuropsychologia, 41*(1), 25-39.

Michel, C., Pisella, L., Prablanc, C., Rode, G., & Rossetti, Y. (2007). Enhancing visuomotor adaptation by reducing error signals: single-step (aware) versus multiple-step (unaware) exposure to wedge prisms. *J Cogn Neurosci, 19*(2), 341-350.

Michel, C., Rossetti, Y., Rode, G., & Tilikete, C. (2003). After-effects of visuo-manual adaptation to prisms on body posture in normal subjects. *Experimental Brain Research, 148*(2), 219-226.

Morris, A. P., Kritikos, A., Berberovic, N., Pisella, L., Chambers, C. D., & Mattingley, J. B. (2005). Prism adaptation and spatial attention: A study of visual search in normals and patients with unilateral neglect. *Cortex, 40*(4-5), 703-721.

Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain, 126*(Pt 9), 1986-1997.

Morton, S. M., & Bastian, A. J. (2004). Prism adaptation during walking generalizes to reaching and requires the cerebellum. *Journal of Neurophysiology, 92*(4), 2497-2509.

Moseley, G. L. (2005). Distorted body image in complex regional pain syndrome. *Neurology, 65*(5), 773.

Moseley, G. L., Parsons, T. J., & Spence, C. (2008). Visual distortion of a limb modulates the pain and swelling evoked by movement. *Curr Biol, 18*(22), R1047-1048.

Na, D. L., Adair, J. C., Williamson, D. J., Schwartz, R. L., Haws, B., & Heilman, K. M. (1998). Dissociation of sensory-attentional from motor-intentional neglect. *J Neurol Neurosurg Psychiatry, 64*(3), 331-338.

Navon, D. (1977). Forest before trees: The precedence of global features in visual perception. *Cognitive Psychology, 9*, 353-383.

Navon, D., & Norman, J. (1983). Does global precedence really depend on visual angle? *J Exp Psychol Hum Percept Perform, 9*(6), 955-965.

Newport, R., Brown, L., Mort, D., & Jackson, S. R. (2006). The role of the posterior parietal lobe in prism adaptation: Failure to adapt to optical prisms in a patient with bilateral damage to posterior parietal cortex. *Cortex, 42*(5), 720-729.

Newport, R., & Jackson, S. R. (2006). Posterior parietal cortex and the dissociable components of prism adaptation. *Neuropsychologia, 44*(13), 2757-2765.

Nicholls, M. E., Kamer, A., & Loftus, A. M. (2008). Pseudoneglect for mental alphabet lines is affected by prismatic adaptation. *Exp Brain Res, 191*(1), 109-115.

Nijboer, T. C., McIntosh, R. D., Nys, G. M., Dijkerman, H. C., & Milner, A. D. (2008). Prism adaptation improves voluntary but not automatic orienting in neglect. *Neuroreport, 19*(3), 293-298.

Nys, G. M., de Haan, E. H., Kunneman, A., de Kort, P. L., & Dijkerman, H. C. (2008). Acute neglect rehabilitation using repetitive prism adaptation: a randomized placebo-controlled trial. *Restor Neurol Neurosci, 26*(1), 1-12.

Oaklander, A. L. (2008). RSD/CRPS: the end of the beginning. *Pain, 139*(2), 239-240.

Ogden, J. A. (1985). Anterior-posterior interhemispheric differences in the loci of lesions producing visual hemineglect. *Brain and Cognition, 4*(1), 59-75.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Otake, T., Ieshima, H., Ishida, H., Ushigome, Y., & Saito, S. (1998). Bone atrophy in complex regional pain syndrome patients measured by microdensitometry. *Can J Anaesth, 45*(9), 831-838.

Parton, A., Malhotra, P., & Husain, M. (2004). Hemispatial neglect. *J Neurol Neurosurg Psychiatry, 75*(1), 13-21.

Pisella, L., & Mattingley, J. B. (2004). The contribution of spatial remapping impairments to unilateral visual neglect. *Neurosci Biobehav Rev, 28*(2), 181-200.

Pisella, L., Michel, C., Gréa, H., Tilikete, C., Vighetto, A., & Rossetti, Y. (2004). Preserved prism adaptation in bilateral optic ataxia: Strategic versus adaptive reaction to prisms. *Experimental Brain Research, 156*(4), 399-408.

Pisella, L., Rode, G., Farnè, A., Boisson, D., & Rossetti, Y. (2002). Dissociated long lasting improvements of straight-ahead pointing and line bisection tasks in two hemineglect patients. *Neuropsychologia, 40*(3), 327-334.

Pisella, L., Rode, G., Farne, A., Tilikete, C., & Rossetti, Y. (2006). Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders. *Curr Opin Neurol, 19*(6), 534-542.

Pisella, L., Rossetti, Y., Michel, C., Rode, G., Boisson, D., Pélisson, D., et al. (2005). Ipsidirectional impairment of prism adaptation after unilateral lesion of anterior cerebellum. *Neurology, 65*(1), 150-152.

Pitzalis, S., Spinelli, D., & Zoccolotti, P. (1997). Vertical neglect: behavioral and electrophysiological data. *Cortex, 33*(4), 679-688.

Pizzamiglio, L., Guariglia, C., Antonucci, G., & Zoccolotti, P. (2006). Development of a rehabilitative program for unilateral neglect. *Restor Neurol Neurosci, 24*(4-6), 337-345.

Pleger, B., Tegenthoff, M., Ragert, P., Forster, A. F., Dinse, H. R., Schwenkreis, P., et al. (2005). Sensorimotor retuning in complex regional pain syndrome parallels pain reduction. *Ann Neurol, 57*(3), 425-429.

Pomerantz, J. R. (1983). Global and local precedence: selective attention in form and motion perception. *J Exp Psychol Gen, 112*(4), 516-540.

Posner, M. I., Cohen, Y., & Rafal, R. D. (1982). Neural systems control of spatial orienting. *Philos Trans R Soc Lond B Biol Sci, 298*(1089), 187-198.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annu Rev Neurosci, 13*, 25-42.

Proverbio, A. M., Minniti, A., & Zani, A. (1998). Electrophysiological evidence of a perceptual precedence of global vs. local visual information. *Brain Res Cogn Brain Res, 6*(4), 321-334.

Rafal, R. D., & Posner, M. I. (1987). Deficits in human visual spatial attention following thalamic lesions. *Proc Natl Acad Sci U S A, 84*(20), 7349-7353.

Rafal, R. D., & Robertson, L. C. (1995). The neurology of visual attention. In M. Gazzaniga (Ed.), *Handbook of cognitive neuroscience.* (pp. p. 625-648). Cambridge, MA: MIT Press.

Ramachandran, V. S., Rogers-Ramachandran, D., & Cobb, S. (1995). Touching the phantom limb. *Nature, 377*(6549), 489-490.

Redding, G. M., Rader, S. D., & Lucas, D. R. (1992). Cognitive load and prism adaptation. *Journal of Motor Behavior, 24*(3), 238-246.

Redding, G. M., & Wallace, B. (1992). Effects of Pointing Rate and Availability of Visual Feedback on Visual and Proprioceptive Components of Prism Adaptation. *J Mot Behav, 24*(3), 226-237.

Redding, G. M., & Wallace, B. (1997). *Adaptive Spatial Alignment*. Mahwah, New Jersey: Lawrence Erlbaum Associates.

Rizzolatti, G., Riggio, L., Dascola, I., & Umilta, C. (1987). Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia, 25*(1A), 31-40.

Robertson, I. H., Hogg, K., & MacMillan, T. M. (1998). Rehabilitation of unilateral neglect: Improving function by contralesional limb activation. *Neuropsychological Rehabilitation, 8*(1), 19-29.

Robertson, I. H., Manly, T., Beschin, N., Haeske-Dewick, H., Hömberg, V., Jehkonen, M., et al. (1997). Auditory sustained attention is a marker of unilateral spatial neglect. *Neuropsychologia, 35*(12), 1527-1532.

Robertson, I. H., & North, N. (1992). Spatio-motor cueing in unilateral left neglect: The role of hemispace, hand and motor activation. *Neuropsychologia, 30*(6), 553-563.

Robertson, I. H., & North, N. T. (1994). One hand is better than two: Motor extinction of left hand advantage in unilateral neglect. *Neuropsychologia, 32*(1), 1-11.

Robertson, I. H., Tegnér, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: Theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology, 17*(3), 416-430.

Robertson, L. C., & Lamb, M. R. (1991). Neuropsychological contributions to theories of part/whole organization. *Cognitive Psychology, 23*(2), 299-330.

Robertson, L. C., Lamb, M. R., & Knight, R. T. (1988). Effects of lesions of temporal-parietal junction on perceptual and attentional processing in humans. *The Journal of Neuroscience, 8*(10), 3757-3769.

Rode, G., Klos, T., Courtois-Jacquin, S., Rossetti, Y., & Pisella, L. (2006). Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders. *Restor Neurol Neurosci, 24*(4-6), 347-356.

Rode, G., Pisella, L., Marsal, L., Mercier, S., Rossetti, Y., & Boisson, D. (2006). Prism adaptation improves spatial dysgraphia following right brain damage. *Neuropsychologia, 44*(12), 2487-2493.

Rode, G., Rossetti, Y., & Biosson, D. (2001). Prism adaptation improves representational neglect. *Neuropsychologia, 39*(11), 1250-1254.

Rode, G., Rossetti, Y., & Boisson, D. (2001). Prism adaptation improves representational neglect. *Neuropsychologia, 39*(11), 1250-1254.

Rorden, C., Fruhmann Berger, M., & Karnath, H. O. (2006). Disturbed line bisection is associated with posterior brain lesions. *Brain Res, 1080*(1), 17-25.

Rossetti, Y., Rode, G., Pisella, L., Farnè, A., Li, L., Boisson, D., et al. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 395*(6698), 166-169.

Rossi, P. J. (1968). Adaptation and negative aftereffect to lateral optical displacement in newly hatched chicks. *Science, 160*(826), 430-432.

Rossi, P. J. (1969). Primacy of the negative aftereffect over positive adaptation in prism adaptation with newly hatched chicks. *Dev Psychobiol, 2*(1), 45-53.

Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., Birschel, P., et al. (2009). The neural basis of visuomotor deficits in hemispatial neglect. *Neuropsychologia, 47*(10), 2149-2153.

Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., Livingstone, K., et al. (2009). No neglect-specific deficits in reaching tasks. *Cereb Cortex.*

Rotteveel, M., & Phaf, R. H. (2004). Automatic affective evaluation does not automatically predispose for arm flexion and extension. *Emotion, 4*(2), 156-172.

Rousseaux, M., Bernati, T., Saj, A., & Kozlowski, O. (2006). Ineffectiveness of prism adaptation on spatial neglect signs. *Stroke, 37*(2), 542-543.

Saevarsson, S., Kristjansson, A., Hildebrandt, H., & Halsband, U. (2009). Prism adaptation improves visual search in hemispatial neglect. *Neuropsychologia, 47*(3), 717-725.

Samuelsson, H., Hjelmquist, E. K., Jensen, C., Ekholm, S., & Blomstrand, C. (1998). Nonlateralized attentional deficits: An important component behind persisting visuospatial neglect? *Journal of Clinical Neuropsychology, 20*(1), 73-88.

Sapir, A., d'Avossa, G., McAvoy, M., Shulman, G. L., & Corbetta, M. (2005). Brain signals for spatial attention predict performance in a motion discrimination task. *Proc Natl Acad Sci U S A, 102*(49), 17810-17815.

Sapir, A., Kaplan, J. B., He, B. J., & Corbetta, M. (2007). Anatomical correlates of directional hypokinesia in patients with hemispatial neglect. *The Journal of Neuroscience, 27*(15), 4045-4051.

Sarri, M., Greenwood, R., Kalra, L., Papps, B., Husain, M., & Driver, J. (2008). Prism adaptation aftereffects in stroke patients with spatial neglect: pathological effects on subjective straight ahead but not visual open-loop pointing. *Neuropsychologia, 46*(4), 1069-1080.

Sarri, M., Kalra, L., Greenwood, R., & Driver, J. (2006). Prism adaptation changes perceptual awareness for chimeric visual objects but not for chimeric faces in spatial neglect after right-hemisphere stroke. *Neurocase, 12*(3), 127-135.

Schenkenberg, T., Bradford, D. C., & Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*(5), 509-517.

Schindler, I., McIntosh, R. D., Cassidy, T. P., Birchall, D., Benson, V., Ietswaart, M., et al. (2009). The disengage deficit in hemispatial neglect is restricted to between-object shifts and is abolished by prism adaptation. *Exp Brain Res, 192*(3), 499-510.

Schubert, F., & Spatt, J. (2001). Double dissociations between neglect tests: possible relation to lesion site. *Eur Neurol, 45*(3), 160-164.

Sergent, J. (1982). The cerebral balance of power: confrontation or cooperation? *J Exp Psychol Hum Percept Perform, 8*(2), 253-272.

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2005). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia, 44*(7), 1068-1078.

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2006). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia, 44*(7), 1068-1078.

Serino, A., Barbiani, M., Rinaldesi, M. L., & Ladavas, E. (2009). Effectiveness of prism adaptation in neglect rehabilitation: a controlled trial study. *Stroke, 40*(4), 1392-1398.

Serino, A., Bonifazi, S., Pierfederici, L., & Làdavas, E. (2007). Neglect treatment by prism adaptation: What recovers and for how long. *Neuropsychological Rehabilitation, 23*(2), 137-151.

Shindo, K., Sugiyama, K., NHuabao, L., Nishijima, K., Kondo, T., & Izumi, S. (2006). Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. *Journal of Rehabilitation Medicine, 38*(1), 65-67.

Shiraishi, H., Yamakawa, Y., Itou, A., Muraki, T., & Asada, T. (2008). Long-term effects of prism adaptation on chronic neglect after stroke. *NeuroRehabilitation, 23*(2), 137-151.

Shulman, G. L., & Wilson, J. (1987). Spatial frequency and selective attention to local and global information. *Perception, 16*(1), 89-101.

Stein, J. F., & Glickstein, M. (1992). Role of the cerebellum in visual guidance of movement. *Physiol Rev, 72*(4), 967-1017.

Striemer, C., Blangero, A., Rossetti, Y., Boisson, D., Rode, G., Salemme, R., et al. (2008). Bilateral parietal lesions disrupt the beneficial effects of prism adaptation: evidence from a patient with optic ataxia. *Experimental Brain Research, 187*(2), 295-302.

Striemer, C., Sablatnig, J., & Danckert, J. (2006). Differential influences of prism adaptation on reflexive and voluntary covert attention. *J Int Neuropsychol Soc, 12*(3), 337-349.

Sudeck, P. (1900). Ueber die acute entzundliche knochenatrophie. *Arch Klin Chir, 62*, 147.

Sumitani, M., Rossetti, Y., Shibata, M., Matsuda, Y., Sakaue, G., Inoue, T., et al. (2007). Prism adaptation to optical deviation alleviates pathologic pain. *Neurology, 68*(2), 128-133.

Swart, C. M., Stins, J. F., & Beek, P. J. (2008). Cortical changes in complex regional pain syndrome (CRPS). *Eur J Pain.*

Tegner, R., & Levander, M. (1991). Through a looking glass. A new technique to demonstrate directional hypokinesia in unilateral neglect. *Brain, 114 (Pt 4)*, 1943-1951.

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

Turton, A., O'Leary, K., Gabb, J., & Gilchrist, I. (2007). *An exploratory randomized control trial of prism aaptation treatment for improving self-care in unilateral neglect.* Paper presented at the British Psychological Society Spring Meeting, Nottingham.

Vallar, G. (2001). Extrapersonal visual unilateral spatial neglect and its neuroanatomy. *Neuroimage, 14*(1 Pt 2), S52-58.

Vallar, G., Bottini, G., Rusconi, M. L., & Sterzi, R. (1993). Exploring somatosensory hemineglect by vestibular stimulation. *Brain, 116 (Pt 1)*, 71-86.

Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right hemisphere stroke lesions: A clinical/CT-scan correlation study in man. *Neuropsychologia, 24*(5), 609-622.

Vallar, G., Zilli, T., Gandola, M., & Bottini, G. (2006). Productive and defective impairments in the neglect syndrome: graphic perseveration, drawing productions and optic prism exposure. *Cortex, 42*(6), 911-920.

van der Laan, L., Veldman, P. H., & Goris, R. J. (1998). Severe complications of reflex sympathetic dystrophy: infection, ulcers, chronic edema, dystonia, and myoclonus. *Arch Phys Med Rehabil, 79*(4), 424-429.

Van Kleeck, M. H. (1989). Hemispheric differences in global versus local processing of hierarchical visual stimuli by normal subjects: New data and a meta-analysis of previous studies. *Neuropsychologia, 27*(9), 1165-1178.

Van Vleet, T. M., & Robertson, L. C. (2006). Cross-modal interactions in time and space: auditory influence on visual attention in hemispatial neglect. *Journal of Cognitive Neuroscience, 18*, 1368-1379.

von Helmholz, H. (1925). *Treatise on physiological optics*. Rochester, NY: Optical Society of America.

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

Ward, L. M. (1982). Determinants of attention to local and global features of visual forms. *J Exp Psychol Hum Percept Perform, 8*(4), 562-581.

Wasner, G., Schattschneider, J., Binder, A., & Baron, R. (2003). Complex regional pain syndrome--diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord, 41*(2), 61-75.

Watson, R. T., Miller, B. D., & Heilman, K. M. (1978). Nonsensory neglect. *Ann Neurol, 3*(6), 505-508.

Weiner, M. J., Hallet, M., & Funkenstein, H. H. (1983). Adaptation to a lateral displacement of vision in patients with lesions of the central nervous system. *Neurology, 33*(6), 766-772.

Weissman, D. H., & Woldorff, M. G. (2005). Hemispheric asymmetries for different components of global/local attention occur in distinct temporo-parietal loci. *Cereb Cortex, 15*(6), 870-876.

Wells, P. L., & Reusch, J. (1945). *Mental examiner's handbook. Revised edition.* New York: The Psychological Corporation.

Wentura, D., Rothermund, K., & Bak, P. (2000). Automatic vigilance: the attention-grabbing power of approach- and avoidance-related social information. *J Pers Soc Psychol, 78*(6), 1024-1037.

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). Behavioural Inattention Test. Suffolk, UK: Thames Valley Test Company.

Wong, G. Y., & Wilson, P. R. (1997). Classification of complex regional pain syndromes. New concepts. *Hand Clin, 13*(3), 319-325.

Yamaguchi, S., Yamagata, S., & Kobayashi, S. (2000). Cerebral asymmetry of the "top-down" allocation of attention to global and local features. *J Neurosci, 20*(9), RC72.

Yin, P. B., & Kitazawa, S. (2001). Long-lasting aftereffects of prism adaptation in the monkey. *Exp Brain Res, 141*(2), 250-253.