ATTENTION AND THE PARIETAL CORTEX:

INVESTIGATIONS OF SPATIAL NEGLECT, OPTIC ATAXIA, AND THE INFLUENCE OF PRISM ADAPTATION ON ATTENTION

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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ABSTRACT

Some authors have argued that the primary function of the posterior parietal cortex is to control visual attention and awareness, whereas others have argued that the posterior parietal cortex is specialized for controlling actions. The purpose of the present thesis was to examine the influence of prism adaptation – a visuomotor adaptation technique – on visual attention deficits in patients with lesions of parietal cortex. Lesions to dorsal regions of the posterior parietal cortex lead to optic ataxia – a disorder in which visually guided reaching is disrupted. In contrast lesions to ventral (i.e. inferior) regions of the posterior parietal cortex of the right hemisphere lead to spatial neglect – a disorder in which patients are unaware of people or objects in contralesional (left) space. Chapter 1 presents an overview of the organization of the posterior parietal cortex, as well as an introduction to the disorders of spatial neglect and optic ataxia and the use of prism adaptation as a treatment for spatial neglect. Chapter 2 examined the influence of prism adaptation on attentional deficits in patients with right brain damage. Results demonstrated that prism adaptation reduced both the disengage deficit and the rightward attentional bias, two of the classic attentional deficits in neglect. Chapter 3 investigated the role of the dorsal posterior parietal cortex in controlling both reflexive and voluntary attention in two patients with optic ataxia. Lesions to the dorsal posterior parietal cortex led to both a disengage deficit and a rightward attentional bias, similar to patients with neglect, even though neither of the patients had any clinical symptoms of neglect. Contrary to previous work these results indicated that dorsal portions of the posterior parietal cortex – a region not commonly damaged in neglect – are important for controlling the orienting and reorienting of both reflexive and voluntary attention. Furthermore, these results indicated that optic ataxia is not purely a visuomotor disorder that is independent of any perceptual or attentional deficits as was previously assumed. Based on the results of Chapters 2 and 3 it was hypothesized that the beneficial effects of prism adaptation on attention may operate via the superior parietal lobe, a region which is typically undamaged in neglect, and is known to be important for controlling attention and action. Chapter 4 provided support for this hypothesis by demonstrating that a patient with lesions to the superior parietal lobe, who had the same attentional deficits as the right brain damaged patients tested in Chapter 2, failed to demonstrate any beneficial effects of prism adaptation on his attentional performance. Specifically, prism adaptation had no influence on his disengage deficit or his rightward attentional bias. Therefore, these data provide direct evidence that the beneficial effects of prisms on attention rely, at least in part, on the superior parietal lobe. Finally, Chapter 5 concludes with a summary of the research findings from the present thesis, and puts forward a new theory to conceptualize the mechanisms underlying the beneficial effects of prisms in patients with neglect.

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DEDICATION

In memory of my loving grandparents John (1919-2003) and Mary Striemer (1934-2005), and Jacob Giesbrecht (1917-2008). I would also like to dedicate this thesis to my son William Marc Striemer, born August 18, 2007.

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LIST OF ABBREVIATIONS

AIP=anterior intraparietal sulcus

CES=cue effect size

COVAT=covert orienting of visual attention task

CS=central sulcus

IPL=inferior parietal lobe

IPS=intraparietal sulcus

LIP=lateral intraparietal sulcus

MIP=medial intraparietal sulcus

POJ=parietal-occipital junction

PPC=posterior parietal cortex

RBD=right brain damage

RT=response time

SOA=stimulus onset asynchrony

SPL=superior parietal lobe

STG=superior temporal gyrus

TPJ=temporo-parietal junction

VIP=ventral intraparietal sulcus

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Chapter 1: General Introduction

Macdonald Critchley (1953) published his treatise on the parietal cortex over 50 years ago, and although we have learned a great deal about the cognitive functions of the parietal cortex since that time through patient studies, neurophysiological recordings in primates, and functional neuroimaging, many important questions remain unanswered. Perhaps most importantly, there is no clear consensus on the exact role the posterior parietal cortex (PPC) plays in controlling behaviour. Some authors emphasize the important role of the PPC in attention and visual awareness (e.g. Colby & Goldberg, 1999; Corbetta & Shulman, 2002; Driver & Mattingley, 1998), whereas others contend that the primary role of the PPC is to serve as a sensorimotor interface for the control of visually guided actions (e.g. Andersen & Buneo, 2002; Buneo & Andersen, 2006; Goodale & Milner, 1992; Milner & Goodale, 2006; Snyder, Batista, & Andersen, 1997). Finally, other researchers suggest that attention itself may be linked to motor programming such that shifts of attention represent motor movements that are planned but not executed (the so called 'premotor' theory of attention; Rizzolatti, Riggio, Dascola, & Umilta, 1987; Rizzolatti, Riggio, & Sheliga, 1994; Sheliga, Craighero, Riggio, & Rizzolatti, 1997). Consistent with these themes, the present thesis will examine the effects of prismatic adaptation – a visuomotor adaptation procedure – on visual attention in patients who have suffered damage to the parietal cortex. More specifically, Chapter 2 will examine the influence of prismatic adaptation on leftward reorienting and the rightward attentional bias in patients with right brain damage (RBD), Chapter 3 will investigate the effects of lesions to the superior parietal lobe (SPL) and intraparietal sulcus (IPS) on visual attention in patients with optic ataxia, and Chapter 4 examines the influence

of prism adaptation on attentional deficits in a patient with optic ataxia. Finally, Chapter 5 presents a summary of the findings before proposing a new theory to explain the effects of prisms in neglect, and suggesting directions for future research.

1.1 Organization of the human posterior parietal cortex (PPC).

The PPC can be divided into two major sections: the inferior parietal lobe (IPL) and SPL which are separated by the IPS. Deep within the IPS further functional subdivisions are made between the medial (MIP), lateral (LIP) and anterior (AIP) portions of the IPS (Figure 1). The IPL consists of the angular and supramarginal gryri. Superior to the IPS is the SPL which has traditionally been considered part of the dorsal 'vision-for-action' stream (extending from the primary visual cortex to the SPL and the IPS) which is thought to be important for the control of visually guided actions (Connolly, Andersen, & Goodale, 2003; Culham, Cavina-Pratesi, & Singhal, 2006; Culham et al., 2003; Goodale & Milner, 1992; Milner & Goodale 2006). Importantly, primate neurophysiology and human neuroimaging work has demonstrated distinct roles for specific regions of the IPS involved in the control of eye movements (LIP), reaching movements (MIP and AIP), attention (LIP), and representing the salience or behavioural relevance of stimuli in contralateral space (LIP; Andersen & Buneo, 2002; Astafiev et al., 2003; Bisley & Goldberg, 2003; Buneo & Andersen, 2006; Buneo, Jarvis, Batista, & Andersen, 2002; Colby, Duhamel, & Goldberg, 1996; Colby & Goldberg, 1999; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta & Shulman, 2002; Gottlieb, Kusunoki, & Goldberg, 1998; Murata, Gallese, Luppino, Kaseda, & Sakata, 2000; Sakata, 2003; Silver, Ress, & Heeger, 2005). Finally, the IPL plays an important role in attention and visual awareness (Driver & Mattingley, 1998) by

incorporating incoming visual information from the ventral ‘vision-for-perception’ stream (extending from primary visual cortex to inferior temporal cortex) subserving conscious vision, with attentional and motor control signals from the dorsal vision-for-action stream in the SPL and the IPS (Husain & Nachev, 2007; Milner & Goodale, 2006).

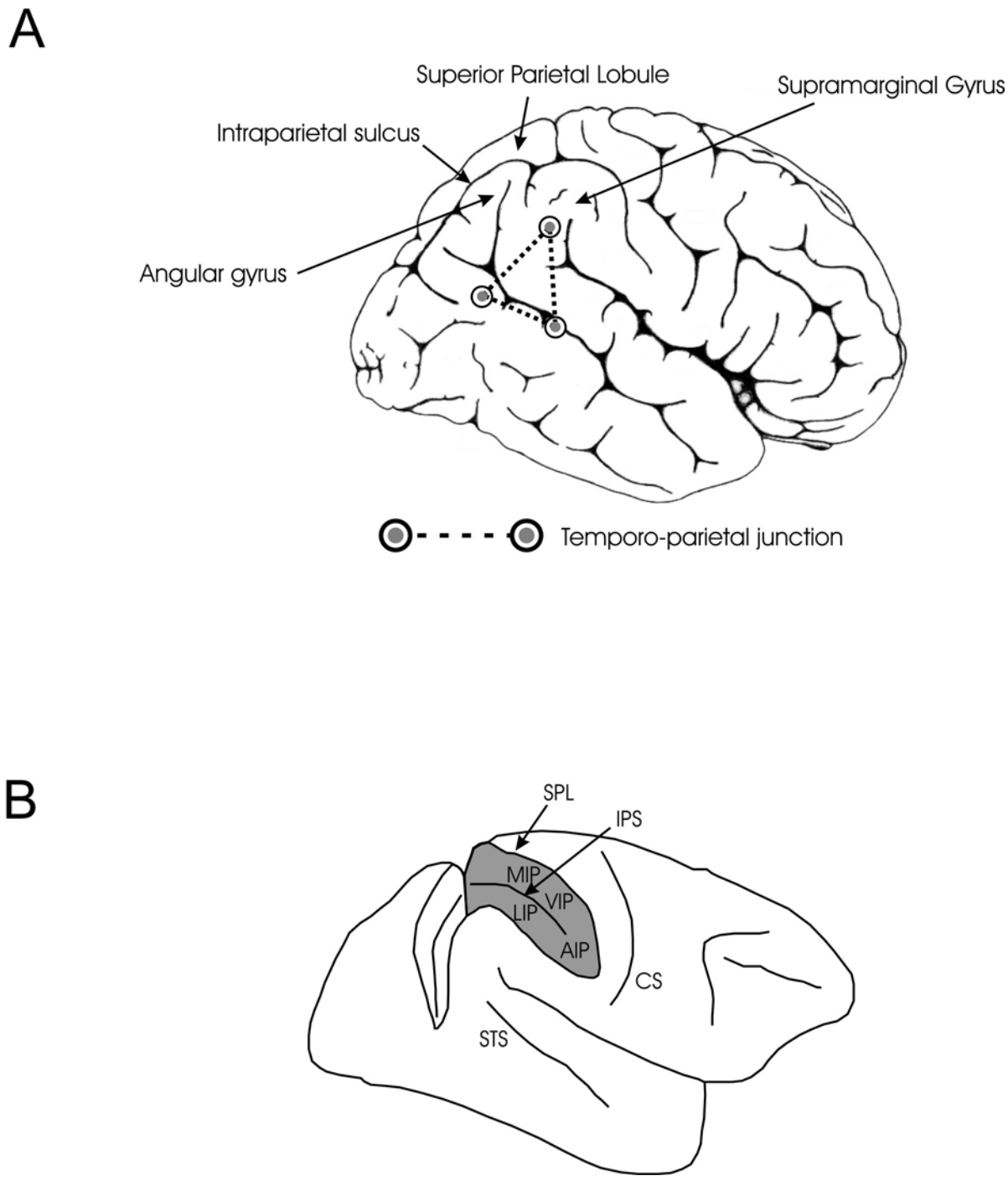


Figure 1: Organization of the human (A) and primate (B) posterior parietal cortex (PPC). This figure depicts sagittal right hemisphere views of the human (A) and primate (B) parietal cortex. Superior parietal lobule=SPL, inferior parietal lobule=IPL, temporo-parietal junction=TPJ, central sulcus=CS, intraparietal sulcus=IPS, medial intraparietal region=MIP, ventral intraparietal region=VIP, lateral intraparietal region=LIP, anterior intraparietal region=AIP.

1.1.2 Parietal control of visual attention

A wealth of research from brain lesioned patients and functional neuroimaging suggests that the PPC plays a pivotal role in directing visual attention. One cognitive paradigm that has had a substantial (and continuing) impact on our understanding of how the parietal cortex controls visual attention is the covert orienting of visual attention task (COVAT) developed by Posner and colleagues (Figure 2; Posner, 1978, 1980; Posner, Snyder, & Davidson, 1980). The COVAT examines response time (RT) differences for cued and uncued target locations across the visual field. While maintaining central fixation, participants must respond to the appearance of targets in the periphery that can be preceded by a cue at the same location (termed a 'valid' trial), or can appear at a location that was not previously cued (termed an 'invalid' trial). In general, RTs are faster for validly cued targets when compared with RTs to invalidly cued targets. Faster RTs on valid trials results from the fact that attention has already been drawn to the location where the target subsequently appears. In contrast, for invalidly cued targets, the participant must first *disengage* attention from the cued location, and the *move*, and *engage* attention at the uncued location (Posner, Walker, Friedrich, & Rafal, 1984). This results in an increase in RT that is typically referred to as the 'validity effect' or 'cue-effect size (CES).'

Covert orienting can operate either reflexively (exogenously) or voluntarily (endogenously; Figure 2). Reflexive orienting is considered to be largely 'automatic' and is examined using abrupt onset peripheral cues that are non-informative concerning the impending target location. That is, targets can appear at the cued or uncued locations with equal probability (sometimes referred to as a 50% cue-target probability COVAT) such that participants cannot use the cues to accurately predict where the target will appear. In this task

there is an early facilitation for validly cued targets (i.e. faster RTs) when the time between the onset of the cue and the onset of the target is short (i.e. <200ms; Maruff, Yucel, Danckert, Stuart, & Currie, 1999).

Voluntary (endogenous) orienting refers to the ability to direct attention to a particular location based on prior goals or intentions. In the COVAT, voluntary orienting is typically measured using a central symbolic cue (e.g. an arrow or word cue) that necessitates some level of semantic processing of the cue in order to voluntarily allocate attention to the appropriate location. Importantly, for endogenous orienting to be successful the cues must be predictive (i.e., 80% of trials are validly cued) such that participants are able to use the cues to accurately predict the impending location of the target. This mode of orienting results in an RT advantage for validly cued trials that normally begins at cue target intervals greater than 200ms and remains at even longer cue-target intervals (Muller & Rabbitt, 1989). This has led some researchers to postulate that these two modes of orienting (reflexive and voluntary) may be carried out by separate, but interacting cognitive and neural systems (Corbetta & Shulman, 2002; Muller & Rabbitt, 1989).

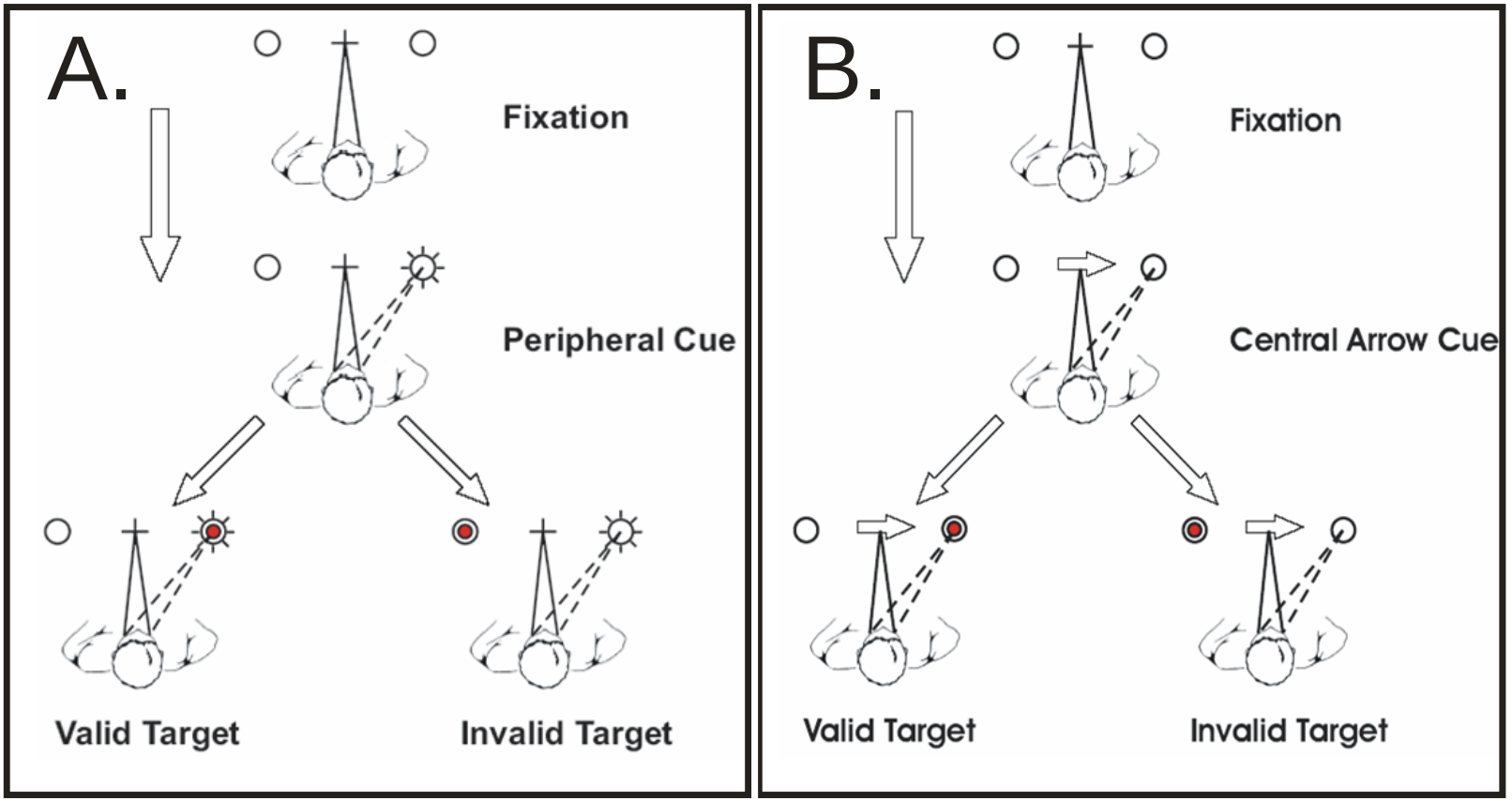


Figure 2: The covert orienting of visual attention task (COVAT). Panel A depicts the reflexive covert attention task which utilizes non-predictive (i.e. 50% valid) peripheral cues. The solid lines indicate where the participant is fixating, the dotted line indicates the location to which covert attention is allocated. The participant fixates centrally while attending to marked locations on the left and right of center (fixation). At the beginning of a trial one of the peripheral landmarks brightens which reflexively attracts the participants' attention to that location (peripheral cue). Following a specified stimulus onset asynchrony (SOA) a target (in this case a red circle) appears at either the cued location (i.e. a valid target), or the uncued location (i.e. an invalid target). Panel B depicts the voluntary covert attention task where the peripheral cue is replaced by a predictive (e.g. 80% valid) central arrow cue.

1.1.3 Covert attention and the 'disengage deficit' following parietal injury.

The first systematic investigation of the role of the parietal cortex in covert attention was carried out by Posner and colleagues (1984). In this classic study, Posner and colleagues examined the influence of parietal lesions on covert visual attention in a group of left (N=7) and right (N=6) parietal lesioned patients. The most important finding from this study was that parietal lesions disrupted the ability to disengage attention from ipsilesional stimuli. More specifically, patients were abnormally slow to respond to targets on invalidly cued trials when they were first cued to attend to the ipsilesional field, and the target subsequently appeared in the contralesional field. Interestingly, this 'disengage deficit' was larger in patients with right than left parietal lesions, and was positively correlated with the amount of damage to the SPL, suggesting that SPL involvement was critical.

In a subsequent study, Friedrich and colleagues (Friedrich, Egly, Rafal, & Beck, 1998) examined the neural correlates of the disengage deficit more directly by comparing the effects of lesions in the SPL and the temporo-parietal junction (TPJ) on reflexive and voluntary covert attention. Their results suggested that the SPL lesions had no influence on reflexive attention or the disengage deficit but did influence some aspects of voluntary attention. Thus, Friedrich and colleagues (1998) concluded that the TPJ, and not the SPL, was the critical lesion site associated with the disengage deficit. It is important to note that the Friedrich and colleagues study (1998) did not use a purely voluntary orienting paradigm. Specifically, to examine voluntary orienting they used predictive (i.e. 80% valid), peripheral cues. Thus, the combination of peripheral cues with probability information creates a covert attention task that is neither purely reflexive nor purely voluntary. While there is still some uncertainty then as to the different roles played by the SPL and IPL in orienting and

reorienting attention in either a reflexive or voluntary mode, these data do strongly suggest that the parietal cortex is crucial for disengaging or reorienting attention (for a review see Losier & Klein, 2001).

1.1.4 'Dorsal' and 'ventral' attention networks in the parietal cortex.

Based on their own work, as well as a review of human neuroimaging and non-human primate neurophysiology literature, Corbetta and Shulman (2002) recently put forward a model to explain the contribution of distinct regions of parietal cortex to the control of visual attention. They argue for two distinct but interacting attention systems within parietal cortex. The 'dorsal attention network', which is bilaterally represented in the SPL/IPS is thought to be important for *allocating* attention to a specific region in space (i.e. voluntary attention). However, the 'ventral attention network' which is lateralized to the right IPL/TPJ, is thought to be important for detecting salient events in the environment, acting as a 'circuit breaker' which serves to interrupt the current focus of attention, in order to signal the dorsal network to reorient attention towards meaningful stimuli or events.

Lesions to these two different networks result in very different clinical syndromes. Specifically, lesions to the ventral attention network in the right IPL/TPJ commonly lead to spatial neglect – a disorder in which patients are unable to attend to people or objects in left space (Danckert & Ferber, 2006; Heilman, Watson, & Valenstein, 1993; Husain & Rorden, 2003). In contrast, lesions to the dorsal attention network in the SPL/IPS commonly lead to optic ataxia – a disorder characterized by misreaching to objects in peripheral vision (Karnath & Perenin, 2005; Perenin & Vighetto, 1988). The next two sections will examine

spatial neglect (Section 1.2) and optic ataxia (Section 1.3) to outline what each syndrome can tell us about the organization of the parietal cortex.

1.2 Spatial neglect and the 'ventral attention network'.

Damage to the IPL or the superior temporal gyrus (STG; i.e. Corbetta's ventral attention network) of the right hemisphere commonly leads to spatial neglect (Karnath, Ferber, & Himmelbach, 2001; Mort et al., 2003; Vallar & Perani, 1986). Patients with neglect are unable to attend to or acknowledge people or objects that appear in left (neglected) space (Danckert & Ferber, 2006; Heilman, Watson, & Valenstein, 1993; Husain & Rorden, 2003; Mesulam, 1999). In severe cases patients with neglect may only dress the right side of their body, groom the right side of their face, and eat food from only the right half of their plate (Robertson & Halligan, 1999). Put simply, the patient behaves as if the left half of their world has ceased to exist (Mesulam, 1981, 1999).

Neglect is a complex disorder in which the clinical presentation of patients can vary greatly in regards to both the presence and severity of symptoms. Neglect is typically assessed at the patients' bedside using a number of simple paper and pencil tasks that assess the ability to process information on the left versus the right half of space. Three common tasks that are used to assess neglect are line bisection, in which the patient is asked to mark the center of a horizontal line placed at their body midline, cancellation tests, in which the patient has to place a mark through target objects presented on a sheet of paper, and figure copying tasks in which the patient must reproduce line drawings (Robertson & Halligan, 1999). In these tasks a typical neglect patient would bisect a line to the right of true center, will fail to cancel targets on the left of the page, and will omit or distort details from the left

half of figures they were asked to reproduce. Although many theories have been put forward to account for the behavioural deficits observed in patients with neglect, it has traditionally been explained in terms of a disorder of attention.

1.2.1 Neglect as an attentional disorder.

Traditionally neglect has been explained in relation to two separate but interacting attentional deficits. Specifically, neglect patients are thought to have a strong rightward attentional bias, in combination with an inability to disengage attention from ipsilesional stimuli in order to reorient attention towards left, neglected space (for a review see Bartolomeo & Chokron, 2002; but see also Pisella & Mattingley, 2004 for an alternate account of neglect involving spatial remapping deficits). In combination, these deficits are thought to underlie the loss of awareness for left visual field stimuli in spatial neglect.

Evidence in support of a rightward attentional bias in patients with neglect is readily obtainable by simply observing the behaviour of a patient with severe neglect. Many of these patients not only fail to attend to stimuli on the left side of space, but typically are seated with their head, body, and eyes, deviated rightwards (Fruhmann-Berger & Karnath, 2005). Even though they are *capable* of making leftward eye and head movements they may fail to explore the left half of space unless prompted to do so. In other words, many patients with neglect seem to be magnetically attracted to stimuli on the right. For example, when performing a cancellation task healthy individuals will typically scan from left to right, consistent with a reading bias. However, patients with neglect will almost invariably start at the right side of the page and scan leftward.

One of the earliest theories put forward to explain the rightward attentional bias in neglect was the orientation bias model developed by Kinsbourne (Kinsbourne, 1987, 1993). Kinsbourne suggested that each cerebral hemisphere orients attention to the contralateral side of space, with the left hemisphere orienting attention to right space and the right hemisphere orienting attention to left space. The two hemispheres are considered to be mutually inhibitory such that the left hemisphere inhibits the right and vice versa. However, if the right hemisphere is damaged, as is the case in neglect, then the left hemisphere becomes dis-inhibited and subsequently biases attention towards the ipsilesional (right) side of space. Interestingly, this theory predicts that patients with neglect should not only fail to attend to items in contralesional (left) space, but should also display a 'hyper-attention' to the rightmost items in ipsilesional (right) space, an hypothesis that remains controversial. Although some studies have found evidence for hyper-attention to the right when comparing neglect patients to healthy controls (e.g. Ladavas, Petronio, & Umilta, 1990), others have found an overall slowing of RTs in both visual fields in patients with neglect relative to healthy controls, with RTs for stimuli in left space being slower overall in neglect patients (e.g. Bartolomeo & Chokron, 1999b).

In contrast, alternative theories of neglect have posited that the left hemisphere directs attention to right space, whereas the right hemisphere directs attention to both left *and* right space (Heilman & Valenstein, 1979; Mesulam, 1981 , 1999). The notion that the right hemisphere (specifically the right parietal cortex) is important for attending to both left and right space is well supported by imaging studies which have demonstrated increased right parietal activation when attending to the left or right visual field (e.g. Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta, Miezin, Shulman, & Petersen, 1993;

Corbetta & Shulman, 2002; Kim et al., 1999; Yantis et al., 2002). In addition, the fact that neglect is much more common following right hemisphere lesions can be easily explained by virtue of the right hemisphere dominance for attention. That is, patients with RBD would be unable to attend to left space, while the undamaged left hemisphere would bias attention towards right space. However, if the left hemisphere were damaged, the undamaged right hemisphere would still be able to direct attention to both hemi-spaces, thereby decreasing the probability that the patient will demonstrate neglect for right space. Interestingly, given that the right parietal lobe is thought to control attention in both left and right space, this theory predicts that patients with neglect should also demonstrate deficits, albeit less severe in nature, for attention within ipsilesional (right) space. Consistent with this theory, Bartolomeo and colleagues (Bartolomeo & Chokron, 1999b) demonstrated that patients with neglect have an overall increase in RT for both visual fields with RTs in the left visual field being slowest overall. Importantly, this overall increase in RT was larger in patients with more severe neglect. This is inconsistent with Kinsbourne's orientation bias model (1987, 1993) which would predict that RTs for right visual field stimuli should *decrease* with increasing neglect severity. This suggests that although patients with neglect are *biased* to attend to items in right space, their ability to attend to this information is impaired, not enhanced (Bartolomeo & Chokron, 1999b).

1.2.2 Neglect and the 'disengage deficit'.

In addition to a rightward attentional bias, patients with neglect are also thought to have difficulty in disengaging attention from ipsilesional stimuli in order to reorient attention back towards left, neglected space. In a seminal study (described previously in Section 1.1.3),

Posner and colleagues (Posner, et al., 1984) found that patients with parietal lesions were abnormally slow to detect targets in contralesional space if attention had first been drawn to a cue in ipsilesional space – the so-called 'disengage deficit.' Interestingly, this disengage deficit was larger in patients with right versus left parietal lesions. Although Posner and colleagues (Posner et al., 1984, 1987) did not explicitly examine neglect patients, subsequent studies have observed a disengage deficit in patients with neglect (Bartolomeo, Sieroff, Decaix, & Chokron, 2001; Morrow & Ratcliff, 1988; Sieroff, Decaix, Chokron, & Bartolomeo, 2007). In addition, the magnitude of the disengage deficit is thought to be positively correlated with neglect severity (Morrow & Ratcliff, 1988). Finally, in a recent review of the evidence for a disengage deficit following parietal injury Losier and Klein (2001) noted that the disengage deficit is larger in right than left parietal patients, larger in patients with neglect, and tended to be largest when utilizing tasks with non-predictive peripheral cues and short (i.e. <100ms) SOAs. This has led some researchers to suggest that neglect is primarily a disorder *reflexive* attention (Bartolomeo & Chokron, 2002; Bartolomeo, Sieroff, Decaix, & Chokron, 2001).

As mentioned previously, the lesion locations that most commonly lead to neglect include the IPL (Mort et al., 2003; Vallar & Perani, 1986) and the STG (Karnath, Ferber, & Himmelbach, 2001), which together form the core of Corbetta and Shulman's (2002) ventral attention network. Importantly, according to this model damage to the right IPL/TPJ has two separate but interacting effects. First, damage to this region will disrupt the circuit breaker function which impairs the ability to detect salient events in the environment. Second, damage to the right IPL/TPJ disrupts communication *between* the circuit breaker and the dorsal attention network in the right SPL/IPS, making it difficult for the dorsal attention

network to orient and reorient attention towards salient stimuli in contralesional (left) space (i.e. the disengage deficit). In addition, because the right SPL/IPS no longer receives inputs from the IPL/TPJ to reorient attention towards left space, the intact left SPL/IPS subsequently biases attention towards ipsilesional (right) space (i.e. the rightward attentional bias).

1.3 Optic ataxia and the 'dorsal attention network'.

As mentioned previously, the dorsal attention network in the SPL/IPS is thought to be important for orienting attention towards a specific location in contralateral space (Corbetta & Shulman, 2002). In addition, imaging studies in humans and single unit recording studies in non-human primates indicate that these areas play an important role in programming eye movements and reaching movements (Andersen & Buneo, 2002; Astafiev et al., 2003; Buneo, Jarvis, Batista, & Andersen, 2002; Colby, Duhamel, & Goldberg, 1996; Colby & Goldberg, 1999; Connolly, Andersen, & Goodale, 2003; Culham et al., 2003; Duhamel, Colby, & Goldberg, 1992; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975; Snyder, Batista, & Andersen, 1997). Although many imaging studies have demonstrated that the SPL and IPS in humans is important for directing visual attention (Astafiev et al., 2003; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta, Miezin, Shulman, & Petersen, 1993; Corbetta & Shulman, 2002; Corbetta, Shulman, Miezin, & Petersen, 1995; Giesbrecht, Woldorff, Song, & Mangun, 2003; Hopfinger, Buonocore, & Mangun, 2000; Silver, Ress, & Heeger, 2005; Yantis et al., 2002), very few studies have investigated the effects of SPL/IPS lesions on attention in humans. In fact, in the only previous study to examine the effect of SPL/IPS lesions on covert attention in humans, Friedrich and

colleagues (1998) suggested that the SPL/IPS played very little role in either reflexive attention or the disengage deficit. However, these authors suggested that the SPL/IPS might play some role in voluntary attention. Thus, the effects of SPL/IPS lesions on attention are not well known.

Whereas lesions to the ventral attention network in the IPL/TPJ commonly lead to spatial neglect (Karnath, Ferber, & Himmelbach, 2001; Mort et al., 2003; Vallar & Perani, 1986), SPL/IPS lesions are not frequently associated with neglect (Coulthard, Parton, & Husain, 2006; Perenin & Vighetto, 1988). Instead, lesions to the dorsal SPL/IPS attention system and the parietal-occipital junction (POJ) commonly lead to optic ataxia – a disorder in which patients have difficulty reaching and grasping objects in peripheral vision (Karnath & Perenin, 2005; Perenin & Vighetto, 1988; Rossetti, Pisella, & Vighetto, 2003). Importantly, recent research suggests that these patients are most impaired when there is a need to correct their movements 'online' whereas movement planning is less affected (Glover, 2003; Grea et al., 2002; Pisella et al., 2000). This is consistent with the notion that the dorsal vision-for-action stream is specialized for visuomotor control (Goodale & Milner, 1992; Milner & Goodale, 2006).

Optic ataxia is tested clinically using a simple reaching task in which the examiner stands behind the patient and places an object (e.g. a pencil) in central vision, or in the patients' ipsilesional or contralesional visual field. The patients' task is to fixate a location straight-ahead of their body's midline (typically a second experimenters' nose) while grasping for the target with either their ipsilesional or contralesional hand. Typically the patient makes the largest reaching errors when reaching for the object with the contralesional hand in contralesional space.

Interestingly, very little is known about the attentional abilities of patients with optic ataxia. According to the theory put forward by Corbetta and Shulman (2002), if the SPL/IPS is important for directing attention towards contralateral space, and the spatial attention deficits in neglect patients are a consequence of the disconnection between the ventral (IPL/TPJ) and dorsal (SPL/IPS) attention systems, then one would predict that patients with optic ataxia should also present with attention deficits similar to patients with neglect, albeit without the characteristic loss of awareness for contralesional stimuli (Chapter 3).

1.4 Prism adaptation as a treatment for spatial neglect.

The previous sections highlight the fact that damage to different regions of the parietal cortex lead to distinct clinical disorders. In particular, damage to the ventral attention network in the right IPL/TPJ results in spatial neglect, whereas damage to the dorsal attention network in the SPL/IPS of either hemisphere, results in optic ataxia. In general, neglect is a more debilitating disorder than optic ataxia. Accordingly, many attempts have been made to rehabilitate neglect using a variety of techniques (for reviews see Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Luaute, Halligan, Rode, Rossetti, & Boisson, 2006). Importantly, attempts at rehabilitating spatial cognitive disorders following parietal damage have the potential of informing our understanding of the distinct roles played by different regions of the PPC.

In a seminal study, Rossetti and colleagues (Rossetti et al., 1998) examined the influence of prism adaptation on symptoms of neglect. Prior to exposure to prisms, neglect patients were blindfolded and asked to point straight-ahead of their body midline. Many, neglect patients pointed to the right of an objective midpoint, reflecting a shift of the

egocentric reference frame to ipsilesional space (however, not all patients will demonstrate this effect; see Bartolomeo & Chokron, 1999a; Chokron & Bartolomeo, 1997). Patients were then asked to wear prismatic lenses that shifted vision 10° to the right. They then pointed to targets located to the left and right of their body midline for five minutes. In order to accurately point to the targets, patients must adjust their pointing movements *leftward* to compensate for the rightward shift in vision. When the prisms are removed and the patients must again point straight-ahead while blindfolded, they now point further *leftward*, much closer to true center (Figure 3). That is, adaptation to prisms successfully realigns neglect patients' egocentric reference frame to be closer to true center.

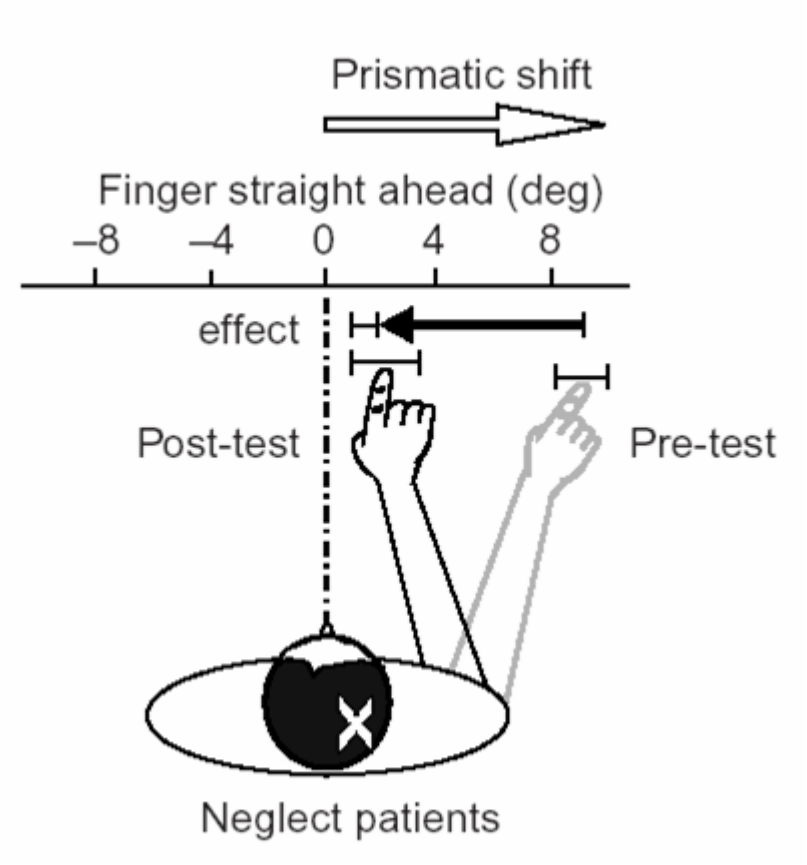


Figure 3: Schematic representation of the prism adaptation procedure. Prior to adaptation the patient is blindfolded and asked to point straight ahead (grey hand). Many neglect patients will point to the right of true center due to a shift in their egocentric reference frame towards ipsilesional (right) space. During the adaptation phase, the patient wears rightward shifting prismatic lenses while they are asked to point to targets to the left and right of their body midline. Following adaptation, the patient is blindfolded again and asked to point straight ahead (black hand). Now the patient points much closer to true center as their egocentric reference frame has been shifted leftward by the adaptation process (adapted from Rossetti et al., 1998).

More interesting than the direct visuomotor consequences of adaptation in this study, and certainly more relevant to this thesis, were the observed influence of prisms on clinical tests of neglect. Specifically, following rightward prism adaptation patients with neglect now bisected lines closer to true center, cancelled more targets on the left side of an array in cancellation tests, and included more details from the left half of drawings made in the figure copying task. In short, these findings indicated that adaptation to rightward shifting prisms could be used to rehabilitate some of the symptoms of neglect. Furthermore, they indicated that directional prism adaptation could influence higher order spatial representations. Rossetti and colleagues (Rossetti et al., 1998) suggested that the beneficial effects of prisms may arise as a consequence of processing within the undamaged (left) parietal cortex.

Subsequent studies have demonstrated that prisms can also influence postural balance, visual imagery, tactile extinction, neglect dyslexia, oculomotor biases, and wheelchair navigation in patients with neglect (Angeli, Benassi, & Ladavas, 2004; Dijkerman et al., 2003; Farné, Rossetti, Toniolo, & Ladavas, 2002; Jacquin-Courtois, Rode, Boisson, & Rossetti, in press; Maravita et al., 2003; McIntosh, Rossetti, & Milner, 2002; Rode, Rossetti, & Boisson, 2001; Serino, Angeli, Frassinetti, & Ladavas, 2006; Tilikete et al., 2001). Furthermore, recent studies have demonstrated that adaptation can have long-lasting effects. Farné and colleagues (Farné, Rossetti, Toniolo, & Ladavas, 2002) demonstrated that the beneficial after-effects of a single adaptation session can last for up to 24 hours. In addition, Frassinetti and colleagues (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002) found that patients who were adapted two times a day for a period of two weeks demonstrated beneficial effects for up to five weeks following the final exposure period. In short, prism

adaptation has been shown to evoke a long-lasting amelioration of some symptoms of spatial neglect.

In addition to examining the effects of prisms on neglect, several studies have also demonstrated that it is possible to induce neglect-like patterns of behaviour in healthy individuals using leftward shifting prisms. Specifically, proprioceptive judgements of straight-ahead in healthy individuals tend to be very close to true center. Once adapted to leftward shifting prisms that require a *rightward* visuomotor transformation, participants will now point to the *right* of center, similar to the behaviour of neglect patients *prior* to exposure to prisms. Furthermore, following adaptation to leftward shifting prisms healthy individuals will demonstrate neglect-like patterns of performance on line bisection, postural balance, and tactile exploration (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004; Michel et al., 2003; Michel, Rossetti, Rode, & Tilikete, 2003). That is, healthy individuals will start to bisect lines further to right, shift their center of mass to the right, and demonstrate a rightward shift in tactile exploration. Thus, prisms influence a broad-range of higher level visuospatial and visuomotor behaviours in patients with neglect and induce some neglect-like behaviours in healthy individuals (for reviews see Michel, 2006; Pisella, Rode, Farné, Tilikete, & Rossetti, 2006; Redding & Wallace, 2006).

1.4.1 Prism adaptation and visual attention.

Although prisms have been shown to alleviate some symptoms of neglect, and have been shown to create neglect-like patterns of behaviour in healthy individuals, the mechanisms underlying these effects remain largely unknown. One of the ways in which prism adaptation may ameliorate symptoms of neglect is by altering damaged attentional

orienting mechanisms. To date, the few studies that have directly examined visual attention prior to and following adaptation have provided somewhat contradictory results.

The first study to examine the influence of prisms on attention was conducted by Berberovic and colleagues (Berberovic, Pisella, Morris, & Mattingley, 2004). In this study healthy individuals and patients with neglect made temporal order judgments prior to and following a period of adaptation. In the temporal order judgment task two stimuli are presented in succession at varying SOAs with the left or the right stimulus leading. In addition, on a number of trials, both items are presented simultaneously (although the participant is told that one stimulus *always* leads the other). The participant is asked to make a forced choice judgment as to which of the two stimuli appeared first (i.e. left or right). In healthy individuals the subjective point of simultaneity (i.e. when the person is equally likely to choose the left or right target as appearing first) closely matches the point of objective simultaneity (i.e. when the two stimuli actually were presented simultaneously). However, in patients with neglect, the left stimulus must lead the right stimulus by at least 200ms before the patient will respond that the left stimulus appeared first, implying a strong bias towards attending to stimuli on the right (Berberovic et al., 2004; Robertson, Mattingley, Rorden, & Driver, 1998; for similar work in patients with extinction see Rorden, Mattingley, Karnath, & Driver, 1997).

Prior to adaptation Berberovic and colleagues (2004) observed that neglect patients demonstrated a typical rightward attentional bias such that a left target had to precede the right target by more than 400ms before it would accurately be reported as having appeared first. Following adaptation this rightward attentional bias was reduced by approximately 50%. In contrast, neither leftward nor rightward shifting prisms had any influence on

temporal order judgments made by healthy individuals. In short, these results suggest that prisms can reduce the rightward attentional bias in neglect.

In contrast to the temporal order judgement results in healthy individuals discussed above (Berbevoric et al., 2004), a more recent study by Striemer and colleagues (Striemer, Sablatnig, & Danckert, 2006), showed that prism adaptation facilitated attentional reorienting in a reflexive COVAT in healthy individuals. Specifically, following adaptation healthy individuals were *faster* to reorient attention away from cues appearing on the side of space opposite the prismatic shift. That is, following adaptation to leftward shifting prisms participants were faster to reorient attention away from a cue on the right towards a target on the left, whereas adaptation to rightward shifting prisms induced faster reorienting away from a cue on the left towards a target on right. Interestingly, these directional effects were only present in participants who demonstrated a large cuing effect prior to adaptation (i.e., those who were slower to reorient attention overall prior to exposure to prisms). These data are similar to the pattern of performance that Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984) observed in patients with left or right parietal damage albeit with the opposite effects on RT. Specifically, following right parietal lesions patients were slower to reorient from a cue on the right to a target on the left (vice versa for left parietal patients). Given the similar patterns of performance (with opposite effects on RT) these data suggest that leftward shifting prisms may influence functioning within right parietal cortex, whereas rightward shifting prisms may influence functioning within left parietal cortex. This hypothesis is consistent with the model recently put forward by Pisella and colleagues (Pisella, Rode, Farné, Tilikete, & Rossetti, 2006) to explain the effects of prisms in neglect. Specifically, Pisella and colleagues (Pisella, Rode, Farné, Tilikete, & Rossetti, 2006) suggest that

rightward prism adaptation involves leftward realignment signals generated in the right cerebellum which are then transferred to the left PPC (the opposite network is involved in leftward prism adaptation, i.e. left cerebellum-right parietal cortex) via direct connections with the cerebellar dentate nucleus (Dum & Strick, 2003). In summary, these data, in combination with the findings from Berberovic and colleagues (Berberovic, Pisella, Morris, & Mattingley, 2004), support the notion that prism adaptation influences spatial attention.

In contrast, Morris and colleagues (Morris et al., 2004) found no evidence that prism adaptation influences visual attention in a visual search task in healthy individuals and in patients with neglect. Similar to previous studies, prior to prism adaptation patients with neglect were much slower and less accurate at detecting targets on the left side of the search display (e.g. Behrmann, Ebert, & Black, 2004). Surprisingly, following rightward prism adaptation there was no change in either the speed or the accuracy with which neglect patients detected targets on the left half of the search display. In addition, there was also no change in performance in healthy individuals following leftward or rightward prism adaptation.

One way to understand these discrepant findings is in terms of the differences between the tasks used to measure attentional performance. First, the studies that have found beneficial effects of prisms on attention required participants to detect the onset of a simple target stimulus (i.e. the temporal order judgment task and the COVAT). In addition, these studies required the participant to fixate centrally and not move their eyes. Therefore, generally speaking, the tasks in which prisms have been found to have a beneficial influence on spatial attention are largely restricted to situations in which a participant is required to utilize covert reflexive attention to indicate the onset of a relatively simple target stimulus. In

contrast, the study by Morris and colleagues (Morris et al., 2004) that failed to find any effects of prisms on attention required the participant to utilize voluntary attention to make a more difficult perceptual discrimination (i.e. finding a target embedded within a number of distracter items). Perhaps more importantly, recent studies suggest that patients with neglect have problems with spatial working memory that are not spatially lateralized (Ferber & Danckert, 2006; Husain et al., 2001; Malhotra et al., 2005). That is, neglect patients have been shown to be impaired on spatial working memory tasks in which the locations to be retained in memory are presented in either central space (Malhotra et al., 2005) or in right, putatively non-neglected, space (Ferber & Danckert, 2006). These deficits in spatial working memory have been linked to poor performance on search tasks (and on cancellation tests; Wojciulik et al., 2004) in which neglect patients continuously 'revisit' previously searched locations in ipsilesional space (Husain et al., 2001). Importantly, what these results imply is that prisms may not improve visual search (Morris et al., 2004) not due to a failure to change attentional orienting mechanisms, but rather as a consequence of the fact that the visuomotor transformations necessitated by prisms are unlikely to alter spatial working memory performance.

Critically, it may be the case that the beneficial effects of prisms arise through interactions within the dorsal vision-for-action stream and by extension, the dorsal attention network in the SPL/IPS – a region typically unaffected in many neglect patients. In contrast, functions that rely more heavily on the ventral attention network via the IPL/TPJ, perhaps including such things as spatial working memory, are less likely to demonstrate benefits from prisms. The SPL/IPS is known to be important for controlling attention, eye movements, and reaching movements (for reviews see Andersen & Buneo, 2002; Colby & Goldberg, 1999;

Corbetta & Shulman, 2002) making it an ideal candidate region to integrate visuomotor error signals that arise during prism adaptation, with attentional control signals. Interestingly, the effects of prisms have yet to be tested in patients with optic ataxia who have damage to the dorsal vision-for-action stream. If prism adaptation has beneficial effects on attentional deficits in neglect (Chapter 2), and these beneficial effects rely on the SPL/IPS, then patients with SPL/IPS lesions who have the same attentional deficits (Chapter 3) should fail to demonstrate any beneficial effects of prisms on their attentional performance (Chapter 4).

1.5 Focus of the present thesis.

To summarize, although prism adaptation has proven to be successful in reducing some of the symptoms of neglect, very little is known about the cognitive and neural mechanisms underlying these beneficial effects. One way in which prisms may operate in neglect patients is by influencing reflexive attentional orienting mechanisms. Chapter 2 examines the influence of rightward prism exposure on leftward reorienting and the rightward attentional bias in patients with RBD (with and without neglect). Chapter 3 will explore the influence of lesions of the dorsal vision-for-action stream and the dorsal attention network in the SPL/IPS on covert orienting performance. If the beneficial effects of prisms in neglect rely in part on the SPL/IPS then a patient with SPL/IPS lesions should fail to demonstrate any beneficial effects of prisms on their attentional performance. Thus, Chapter 4 examines the effects of prism adaptation on attention in a patient with optic ataxia. Finally, Chapter 5 concludes with a summary of the main findings of the present thesis and proposes a new theory to explain the beneficial effects of prism adaptation on attention in neglect, as well as directions for future research.

Chapter 2: The influence of prismatic adaptation on attentional deficits in right brain damage patients[1].

2.1 Introduction

Neglect is a common disorder resulting from right parietal lesions (Section 1.2), in which patients fail to attend to stimuli or events on the left side (Danckert & Ferber, 2006). Neglect is a debilitating disorder and its presence post stroke has been identified as a predictor of poor functional recovery (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001). As such, a great deal of research has focused on ways to rehabilitate neglect.

One technique for rehabilitating neglect is prism adaptation (Section 1.4; Rossetti et al., 1998). In a typical adaptation procedure the patient is asked to make a series of pointing movements while wearing prismatic lenses that shift perception 10° to the right (see Figure 3). Following exposure, patients demonstrate remarkable improvements on clinical tests such as line bisection and figure copying (Redding & Wallace, 2006; Pisella et al., 2006; Rossetti et al., 1998). Subsequent studies have shown that prisms improve postural imbalance, tactile perception, and mental imagery (Maravita et al., 2003; Rode, Rossetti, & Boisson, 2001; Tilikete et al., 2001). Finally, a recent study by Frassinetti and colleagues (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002) found the effects of prism adaptation to be long-lasting.

To further investigate the mechanisms underlying adaptation to prisms researchers have begun to examine the effects of adaptation in healthy individuals through the use of leftward shifting prisms which in healthy individuals creates neglect-like symptoms in line bisection and postural control (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Michel,

[1] A version of this chapter was originally published in *Neuroreport* (Striemer & Danckert, 2007).

Rossetti, Rode, & Tilikete, 2003). That is, following adaptation to leftward shifting prisms, healthy individuals bisect lines further to the right and shift their center of mass further to the right. Although prisms can reduce some symptoms of neglect and create neglect-like phenomenon in healthy individuals, the cognitive mechanisms underlying prism adaptation remain unknown.

One prominent symptom of neglect is impaired visual attention such that patients have difficulty reorienting attention to left space, in addition to demonstrating biases toward attending to the right (Section 1.2; Bartolomeo & Chokron, 2002). Prism adaptation may alleviate some symptoms of neglect by modulating the patients' ability to allocate and reallocate visual attention towards the left. One paradigm widely used to examine the effects of brain lesions on reflexive and voluntary visual attention is the COVAT (Section 1.2). In the COVAT, participants fixate centrally while attending to peripheral locations. In a single trial a cue directs the participants' attention to one of the peripheral locations. On so-called 'valid' trials, targets appear in the location previously cued. On so-called 'invalid' trials, targets appear in the opposite location resulting in an RT advantage (i.e., faster RT's) for validly cued versus invalidly cued targets. This RT advantage is typically represented as a cue effect size (CES) by subtracting the RTs to validly cued targets from the RTs to invalidly cued targets (i.e., a positive CES indicates an RT advantage for valid targets). To examine reflexive orienting, non-informative (i.e. 50% valid), abrupt onset peripheral cues are used to automatically attract attention to one location or another. In contrast, to explore voluntary orienting, informative (e.g. 80% valid), symbolic cues (e.g., a centrally presented arrow symbol pointing in one direction or another) are used to direct consciously controlled strategic orienting (Posner, 1980).

Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984) found that for both reflexive and voluntary orienting, left and right parietal patients displayed abnormally long RTs on invalidly cued trials when the cue first directed attention towards the ipsilesional field but the target appeared contralesionally. Interestingly, both groups of patients demonstrated equally fast RTs for ipsilesional and contralesional validly cued targets, indicating that parietal patients were impaired at 'disengaging' attention from an ipsilesional cue in order to reorient towards contralesional space. The magnitude of this disengage deficit was later found to be correlated with the severity of neglect (for a review see Losier & Klein, 2001; Morrow & Ratcliff, 1988). In addition, subsequent studies demonstrated that patients with neglect were more impaired at reflexive orienting (Bartolomeo, Sieroff, Decaix, & Chokron, 2001; Losier & Klein, 2001) which has led some researchers to suggest that neglect is primarily a deficit involving reflexive attention (Bartolomeo & Chokron, 2002).

In a recent study, it was demonstrated that prism adaptation influenced performance in a reflexive COVAT (Section 1.1.2) in healthy individuals (Striemer, Sablatnig, & Danckert, 2006). Most relevant to the current study was the observation that for reflexive covert attention, adaptation to leftward shifting prisms enabled participants to reorient attention more quickly from a right visual field cue towards a left visual field target (and vice versa for rightward prisms). For adaptation to both left and right shifting prisms, the effects were limited to the shortest (50ms) stimulus onset asynchrony (SOA) and to participants with a large RT advantage for validly cued targets evident prior to exposure to prisms. These reorienting effects were reminiscent of the directional disengage deficit observed by Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984) in patients with left and right parietal lesions, albeit with the opposite effects on RT. That is, parietal damage slowed the

ability to reorient attention in patients, whereas in healthy individuals prisms *facilitated* directional reorienting. Based on these data it was suggested that prisms influence visual attention and furthermore, that this may represent one of the mechanisms by which prisms exert their beneficial effects on neglect patients.

The purpose of the current experiment was to examine whether adaptation to rightward shifting prisms would reduce the disengage deficit in patients with RBD. To do this four patients with RBD (two with neglect) were tested on a reflexive COVAT paradigm before and after prism adaptation with their performance compared to a group of healthy controls (N=26) who performed the same task before and after a sham-adaptation procedure (i.e., in this procedure the participants wore lenses that did *not* induce any shift in visual perception). The hypothesis was that prior to adaptation, RBD patients would demonstrate a much larger cost for reorienting attention leftwards compared to rightwards (i.e., a disengage deficit). Following adaptation to rightward shifting prisms it was predicted that the disengage deficit would be reduced and fall closer to the mean and standard deviation of controls.

2.2 Methods

Participants

The 26 controls (8 male, 4 left handed, mean age= 20.07 yrs, SD=2.37) were undergraduate students from the University of Waterloo who participated in the study for payment. Clinical information for the four patients, including lesion location information, is presented in Table 1. Anatomical scans of each patient's lesion are presented in Figure 4. Patients were tested for clinical signs of neglect using a combination of line bisection, star cancellation, and figure copying tasks (Section 1.2; Table 1). A significant rightward bias in

line bisection was defined as any deviation from true center that was >5% of the total line length. To do this, the patients' bisection mark was measured in terms of the deviation away from true center (measured in millimetres; leftward deviations scored as negative, rightward deviations scored as positive). This deviation score was then converted to a percentage of the total line length. Impaired cancellation performance was defined as >10% omissions of left targets. Figure copying was scored based on a visual inspection of the patients' performance. Patients were considered to have neglect if they were impaired in at least two of the three tests. Two RBD patients did not present with neglect on any of the tests used. All participants provided informed consent prior to participating in the experiment and the experimental protocol was approved by the Office of Research at the University of Waterloo and the Tri-Hospital Research Ethics Board of Kitchener-Waterloo in accordance with the Helsinki declaration.

Table 1: Clinical details of four right brain damage (RBD) patients (two of whom have neglect; NP).

patient	age	sex	time post stroke (months)	lesion	Cancellation (% omitted targets)		figure copy	LB
					L	R		
NP1	55	M	22	F,T,P	66.67	33.33	+	9.11
NP2	55	M	11	F*,T,P	14.8	7.4	+	5.9
RBD1	71	M	12	Cau**	0	0	-	1.13
RBD2	80	M	8	M,P,O	0	0	-	-1.6

LB=line bisection task (rightward deviations are scored as positive). Cancellation performance represents the percentage of omitted left (L) and right (R) sided targets. Neglect on a figure copying task is indicated by the + symbol (absence of neglect on figure copying is indicated by -). P=parietal, F=frontal, T=temporal, O=occipital, Cau=Caudate nucleus, M=motor cortex. * indicates that NP2 had a frontal craniotomy; **indicates that RBD1 also has a small lesion in the left thalamus.

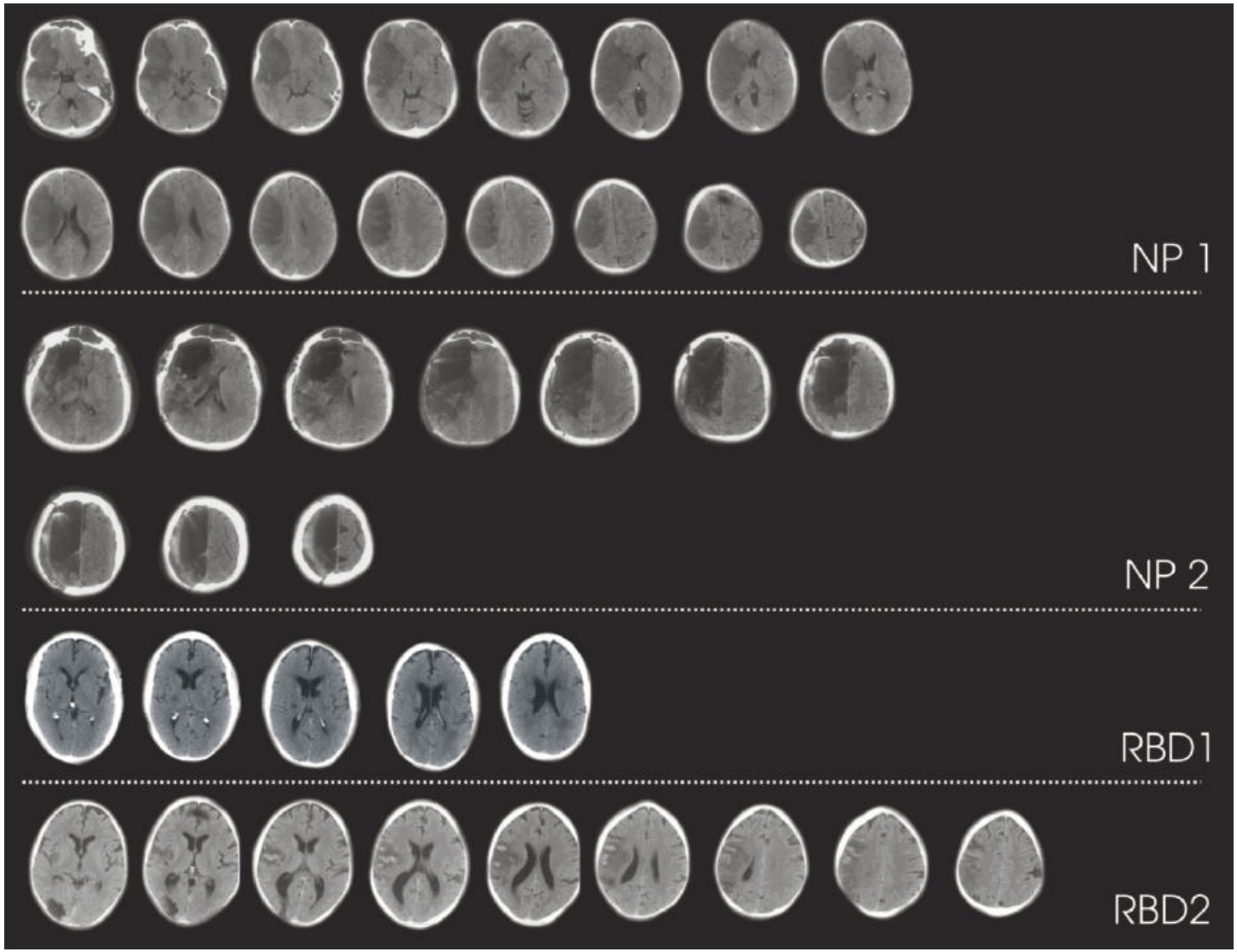


Figure 4: CT anatomical scans for the four right brain damaged (RBD) patients. The scans are presented in radiological convention with left and right reversed. Only the slices relevant to identifying each patients' lesion are presented.

Apparatus and procedure

COVAT

For the COVAT, non-informative (i.e., 50% valid) abrupt onset peripheral cues were used with target locations indicated by green circles subtending 2° and presented 12° to the left and right of fixation. A cue consisted of the brightening of one target location. Targets consisted of filled red circles presented within the location marker. Response times were measured by an external button press attached to a Pentium IV PC computer with a 19 inch CRT monitor (refresh rate 100Hz).

Participants maintained fixation throughout the COVAT. Patient fixation was observed directly by the experimenter. Each trial began with a fixation cross, after a variable time period one of the target locations was brightened. This cue remained present until the participant responded. After an SOA of either 50 or 150ms the target appeared at either the cued (valid) or uncued (invalid) location and remained on the screen until the participant responded or 3000ms elapsed. In addition, non-cued trials, in which targets appeared without a preceding cue were used to measure simple RTs in the absence of cues. Non-cued trials were presented randomly within the block of cued trials. Controls completed 180 trials presented in a single block, consisting of 160 cued trials (20 trials for each cue x target side x SOA combination) and 20 non-cued trials (10 left, 10 right). The task was completed once prior to and once following prism adaptation. Patients completed multiple smaller blocks of 50 trials, 40 cued trials (5 trials for each cue x target side x SOA combination) and 10 non-cued trials (5 left, 5 right) prior to and following adaptation. A short break (1-2 minutes) was allowed between blocks to decrease fatigue in the patients.

Prism adaptation

The prism adaptation procedure used was adapted from Rossetti and colleagues (Rossetti et al., 1998). Prior to exposure to prisms, and prior to the pre-prisms COVAT session, participants sat with their head in a chin rest and made five pointing movements to a subjective position straight-ahead of their body's midline with their eyes closed. The experimenter recorded the endpoints of these movements which were later used to calculate each participant's pre-adaptation notion of straight-ahead. Following the pre-prisms COVAT session patients wore wedge base prismatic lenses (Optique Peter, France) which shifted visual perception 10° to the right. Controls wore sham prisms which induced no visual shift in order to take into account practice effects when comparing the performance of the controls to the patients. All participants used their right hand to point during the exposure period. While wearing prisms they were asked to point to targets to the left and right of an objective straight-ahead position once every 2-3 seconds for a period of 5 minutes (leading to an approximate total of between 100 and 150 pointing movements). Immediately following adaptation participants closed their eyes again and pointed five more times to 'straight-ahead'. The endpoints of these pointing movements were recorded by the experimenter in order to determine the degree of adaptation to the prisms.

Thus the sequence of events in the experiment was as follows: 1) pre-prisms straight-ahead pointing, 2) pre-prisms COVAT, 3) prism adaptation session, 4) post-prisms pointing, 5) post-prisms COVAT.

Data analysis

Mean RTs were calculated for each trial type for each participant. For controls RTs were discarded if they were <150ms or more than 2 standard deviations above the participants' grand mean. For patients, RTs were discarded if they were <150ms or >1000ms. Reaction time data for controls were initially analyzed using a four-way ANOVA with session (pre, post), cue (valid, invalid), side of target (left, right), and SOA (50, 150) as within subject factors. In order to evaluate the effects of prisms on the RBD patients a five-way mixed factorial design ANOVA was carried out with session (pre, post), cue (valid, invalid), side of target (left, right), and SOA (50, 150) as within subject factors and group (controls, patients) as a between subject factor. Post hoc tests were carried out using Fisher LSD tests.

Data for left and right non-cued targets were analyzed separately for each group using paired samples t-tests.

In order to examine the effects of rightward prisms on the disengage deficit we also calculated CESs for leftward and rightward shifts of attention for each participant at each SOA. For leftward shifts we subtracted RTs to validly cued right targets from the RTs to invalidly cued left targets. For rightward shifts we subtracted the RTs to validly cued left targets from the RTs to invalidly cued right targets (Figure 5). For both left and right shift CES calculations the initial component of each trial type is identical – a shift of attention to a cue in the left or right visual field. The only difference is the cost in terms of *reorienting* attention in the opposite direction to detect invalidly cued targets (Striemer, Sablatnig, & Danckert, 2006). This method of calculating directional cuing effects contrasts with previous methods (i.e. Posner et al., 1984) which instead controlled for the side space in which the

target appeared as opposed to controlling for the side of the cue. Specifically, using this method the RT cost for leftward shifts of attention would be calculated by subtracting RTs for validly cued left targets from invalidly cued left targets (and vice versa for rightward shifts). This method of calculation relies on the assumption that cues in the left and right visual fields are equally efficient at attracting attention (Posner et al., 1984). However, several subsequent studies have demonstrated that neglect patients are also impaired at *orienting* attention towards contralesional space on validly cued trials (e.g. Sieroff et al., 2007; for a review see Losier & Klein, 2001). This suggests that left and right visual field cues are *not* equally efficient in attracting attention in patients with neglect. Importantly using this method to calculate cuing effects has the potential to *underestimate* the magnitude of the disengage deficit and may therefore classify a patient as 'normal' when in fact they may have a severe deficit in reorienting attention leftwards. Specifically, the disengage deficit would be masked by any RT differences between validly cued left and right visual field targets which are being used as a baseline comparison. Thus, in order to control for this discrepancy, directional cuing effects were calculated controlling for the side of space in which the cue, rather than the target, was presented.

To analyze the CES data planned comparisons were carried out using independent samples t-tests to compare the mean CES for the four RBD patients to the mean CES of the controls for leftward shifts of attention at each SOA pre and post prisms.

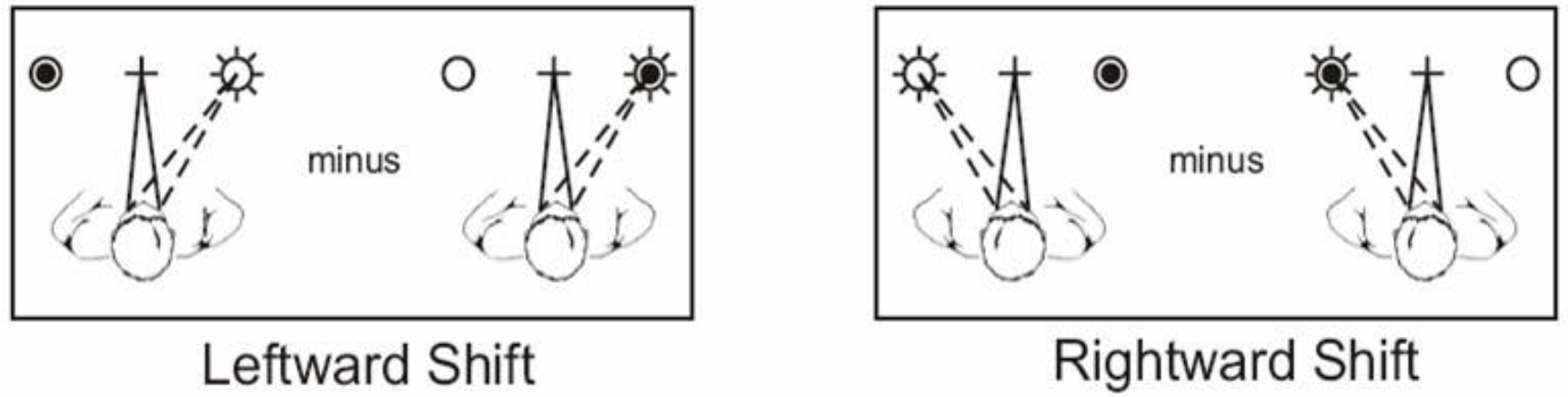


Figure 5: Schematic representation of the method of calculating directional cuing effects. To calculate a leftward shift of attention RTs to validly cued right targets were subtracted from invalidly cued left targets. To calculate a rightward shift of attention RTs to validly cued left targets were subtracted from invalidly cued right targets. Therefore, the only difference between the trials used to calculate a leftward or rightward shift is the location the target appears in the invalid trial.

Finally, to examine the difference between RTs to targets in left and right space for each cue type pre- and post-adaptation, symmetry ratios were computed using the following formula (Maruff, Hay, Malone, & Currie, 1995):

Symmetry Ratio = (right field RT– left field RT/ right field RT + left field RT)

Symmetry ratios determine the speed with which participants detect left versus right visual field targets in each cuing condition. Negative ratios indicate longer RTs for left space, whereas positive ratios indicate longer RTs for right space. The symmetry ratio data are presented graphically, but were not analyzed statistically as they concur with the CES and RT data.

Prism adaptation pointing data were analyzed by calculating the mean deviation from center for each participant prior to and immediately following the adaptation procedure. These data were converted into degrees of visual angle with leftward errors coded as negative and rightward errors coded as positive.

2.3 Results

Pointing data pre- and post-prisms for the controls and patients are presented in Figure 6. Reaction time data from the COVAT for the group of four RBD patients and the healthy controls are presented in Figure 7. Cue-effect size data pre- and post-prisms for the patients are plotted in relation to the mean and standard deviation of controls in Figure 8. Symmetry ratios prior to and following prism adaptation are presented in Figure 9.

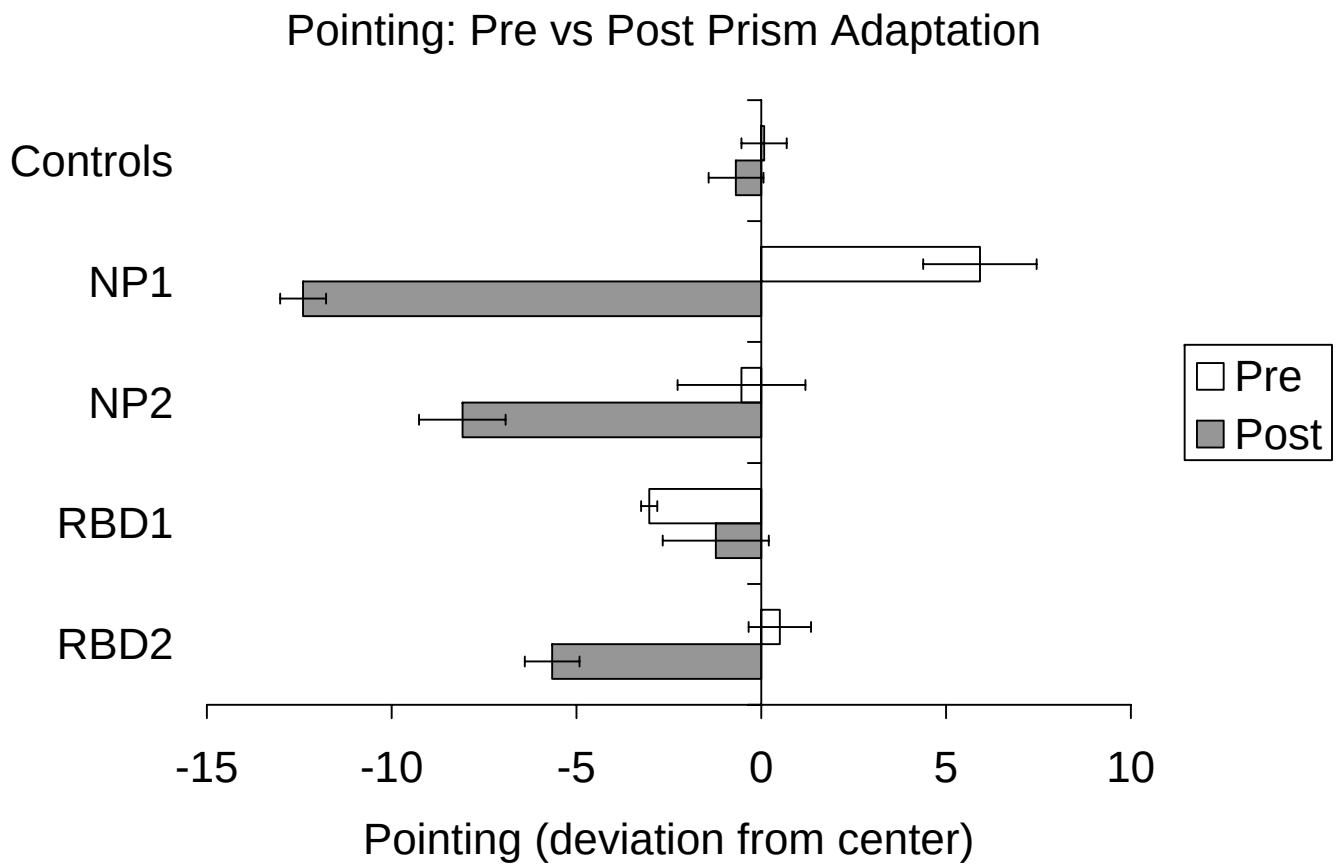


Figure 6: Prism adaptation pointing data. Pointing data (in degrees of visual angle ± SE) for the controls and each patient prior to (open bars), and following (grey bars) prism adaptation.

Controls

As expected, controls showed no shift in straight-ahead pointing following adaptation to sham prisms (pre- =.08° vs. post-adaptation=-.68°; t(24)=1.2, p=.23; Figure 6).

An ANOVA conducted on RT data revealed a significant cue x side of target x SOA interaction (F(1,25)=5.87, p<.05; Figure 7). Closer inspection showed that the difference in RT between valid and invalid trials at the 150ms SOA was larger for right (18ms) than left (7ms) targets (t(25)=2.99, p<.01). In addition, there was a significant session x SOA interaction (F(1,25)=9.49, p<.01) and a significant session x cue interaction (F(1,25)=4.52, p<.05). The session x SOA interaction indicated that following sham prisms RTs at the 150ms SOA decreased by 20ms compared with only an 8ms decrease at the 50ms SOA (t(25)=3.26, p<.01). The session x cue interaction indicated that post-exposure to sham prisms there was a non-significant trend towards a greater decrease in RTs for invalid trials (17ms) compared to valid trials (6ms; t(25)=1.63, p=.12) irrespective of the side of space in which the target appeared. These reductions in RT evident in the post-prisms session directly reflect practice effects and reinforces the need for a sham prisms control group in which practice effects of this kind can be detected and discriminated from the *directional* after-effects one would expect to see after exposure to rightward (or leftward) shifting prisms. In other words, what is critical to emphasize here is there were no *direction specific* effects (i.e., no field effects) involving session, indicating that the differences observed following sham prisms reflect a practice effect.

Analysis of non-cued targets prior to exposure revealed that controls were slightly faster to detect non-cued left (371ms) versus right (380ms) targets (t(25)=2.07, p<.05), a

difference that was no longer present following exposure to sham prisms (375ms left targets vs. 377ms right targets; t(25)=.49, *p*=.63).

Cue effect size data for controls was analyzed using a 3-way ANOVA with session (pre- vs. post-adaptation), direction of attention shift (left vs. right), and SOA (50ms, 150ms) as within subject factors (Figure 8). There was a main effect of session indicating that overall the CES in the controls was slightly reduced (24ms pre vs. 17ms post-adaptation) following sham adaptation (F(1,25)=4.5, *p*=.04). There was also a main effect of SOA with the CES at the 50ms SOA (29ms) being larger than CES at the 150ms SOA (12ms; F(1,25)=35.6, *p*<.001). No other main effects or interactions were significant.

Patients

Each patient's pointing data was examined separately using a paired samples t-test. In all but one patient (RBD1; t(4)=1.09, *p*=.34) there was a significant leftward after-effect in straight-ahead pointing post-adaptation (all t's >4.5, all *p*'s <.01; Figure 6).

The 5-way mixed factorial ANOVA revealed a four-way cue x target x SOA x group interaction (F(1,28)=12.643, *p*=.001). This interaction was driven by a larger difference between RTs for validly and invalidly cued left visual field targets at the 150ms SOA (7ms controls vs. 54ms RBD patients; t(28)=11.41, *p*<.001) compared to the 50ms SOA (29ms controls vs. 27ms RBD patients; t(28)=.48, *p*=.62) in the RBD group (Figure 7). Importantly, there was also a significant four-way session x cue x target x group interaction (F(1,28)=6.43, *p*=.017). This interaction indicated that prior to prism adaptation there was a large difference in RTs for validly and invalidly cued left visual field targets in the RBD group compared to controls (23ms controls vs. 72ms RBD patients; t(28)=11.89, *p*<.001).

Importantly, this difference was no longer present post prisms (14ms controls vs. 9ms RBD patients; $t(28)=1.21$, $p=.24$; Figure 7).

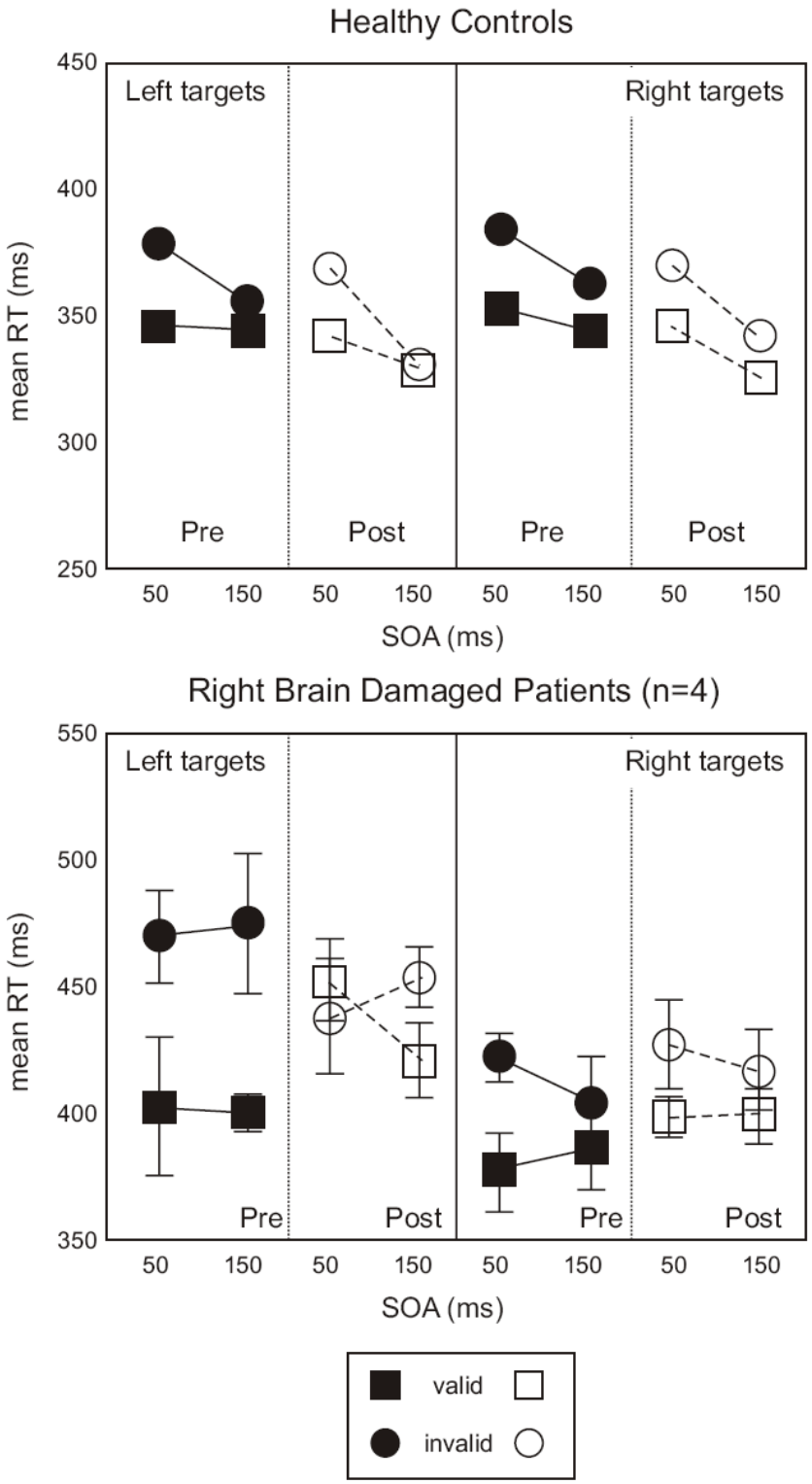


Figure 7: Mean response time (RT) data for healthy controls and the four right brain damage (RBD) patients. Presented as a function of cue validity (valid, invalid), side of target (left, right), and stimulus onset asynchrony (SOA; 50, 150ms), prior to (pre) and following (post) prism adaptation.

In addition, to explore the a priori hypothesis that prism adaptation would *reduce* the RT cost for leftward reorienting (i.e. the disengage deficit) directional CES's were examined using planned comparisons. Prior to exposure to prisms the RBD patient group demonstrated a disengage deficit such that leftward shifts of attention at both the 50ms (24ms controls vs. 94ms RBD patients; $t(28)=4.59$, $p<.001$) and 150ms SOAs (11ms controls vs. 89ms RBD patients; $t(28)=6.61$, $p<.001$) were significantly larger than controls (Figure 8). Based on previous findings (Striemer, Sablatnig, & Danckert, 2006) the specific hypothesis here was that the disengage deficit (i.e., leftward shifts) in patients with RBD would be significantly reduced following adaptation to rightward shifting prisms. To test this, the CES for leftward shifts of attention for the RBD patients post prisms was compared with the CES of controls post prisms at the 50ms and 150ms SOAs. Results showed that the RT cost for leftward shifts of attention for the RBD patients was no longer different from controls post prisms at the 50ms SOA (23ms controls vs. 39ms RBD patients; $t(28)=.928$, $p=.36$; Figure 8). More specifically, following prism adaptation the RT cost for leftward shifts of attention for three of four patients was within the mean and SD of controls (Figure 8). There was also a trend towards a reduced disengage deficit at the 150ms SOA for the RBD patients (89ms pre vs. 55ms post; $t(3)=1.29$, $p=.14$). However, the RT cost for leftward shifts of attention for the RBD patients at the 150ms SOA was still significantly larger than controls post prisms (5ms controls vs. 55ms RBD patients; $t(28)=3.26$, $p=.003$).

It is important to note that if the CESs are calculated controlling for side of target (i.e. Posner et al., 1984) instead of side of cue (Striemer, Sablatnig, & Danckert, 2006) the results are essentially the same. Prior to prisms, at the 50ms SOA RBD patients had a larger RT cost for leftward reorienting than controls (34ms controls, vs. 67ms RBD patients; $t(28)=1.78$,

p=.045; one tailed). However, following prism adaptation the controls now had a larger RT cost for leftward reorienting than the RBD patients (26ms controls vs. -14ms RBD patients; t(28)=2.34, *p*=.026) reflecting a significant reduction in the disengage deficit in the RBD group. Again, using the more traditional method of calculating cuing costs at the 150ms SOA results show that the RT cost for leftward reorienting in the RBD group was much larger than controls (11ms controls vs. 75ms RBD patients; t(28)=4.28, *p*<.001). Following adaptation this difference was somewhat reduced in patients (75ms pre vs. 33ms post; t(3)=1.25, *p*=.15 one-tailed) but continued to be significantly different than controls (2ms controls vs. 33ms patients; t(28)=2.35, *p*=.026).

Analysis of the non-cued trials indicated that prior to prisms, patients were slower to detect left non-cued targets compared to right non-cued targets (502ms left vs. 431ms right; t(3)=2.33, *p*=.05). This difference was also reduced following prism adaptation (450ms left vs. 434ms right; t(3)=.964, *p*=.41).

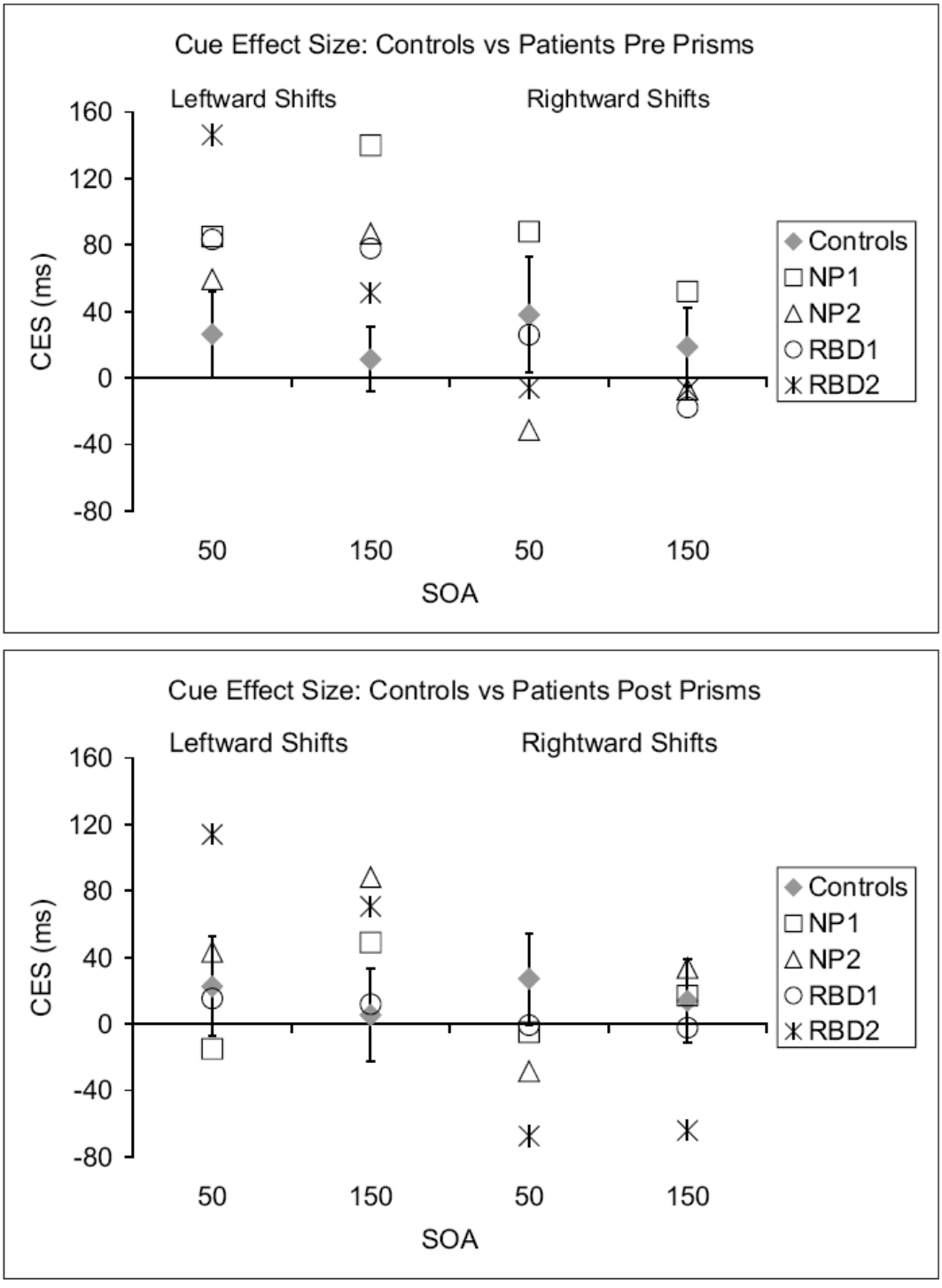
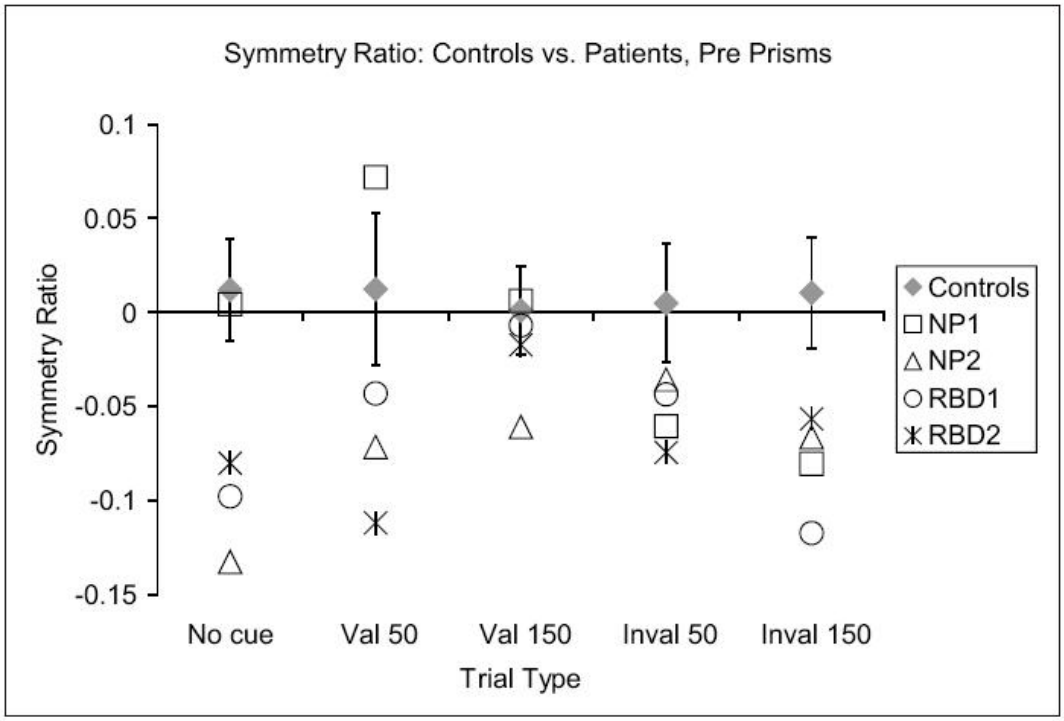


Figure 8: Cue-effect size (CES) data. Mean CES data in milliseconds for the four patients and the mean and standard deviation from the 26 controls as a function of attentional shift (left, right) and stimulus onset asynchrony (SOA). The top panel depicts the pre-adaptation data, and the bottom panel depicts the post-adaptation data. For information on how attentional shifts were calculated refer to Methods and Figure 5.

Finally, examination of the symmetry ratios (Figure 9) indicated that prior to prism adaptation patients were slower to respond to left versus right visual field targets (i.e. negative symmetry ratios) for no cue, valid, and invalid trials, especially at the 50ms SOA. Following rightward prism adaptation, the symmetry ratios for no cue, valid, and invalid trials at the 50ms SOA are much closer to the mean and SD of controls suggesting that the imbalance in RTs between the left and right visual fields has been reduced post prisms. Note that this effect is largest for invalidly cued targets at the 50ms SOA post prisms where three of the four patients are now within the mean and SD of controls. Specifically, prior to prisms there was a significant difference between RTs for invalidly cued targets at the 50ms SOA in the left and right visual fields (469ms left vs. 422ms right; $t(3)=4.85$, $p=.016$). This difference was no longer present post prisms (438ms left vs. 426ms right; $t(3)=.32$, $p=.76$), suggesting that prism adaptation influenced leftward reorienting. The only patient who did not fall within the mean and SD of controls was RBD2, the same patient who's disengage deficit did not fall within the mean and SD of controls following prism adaptation. However, this patient's disengage deficit was still reduced by 32ms following prism adaptation suggesting that prisms did have some beneficial effect on his attentional performance.



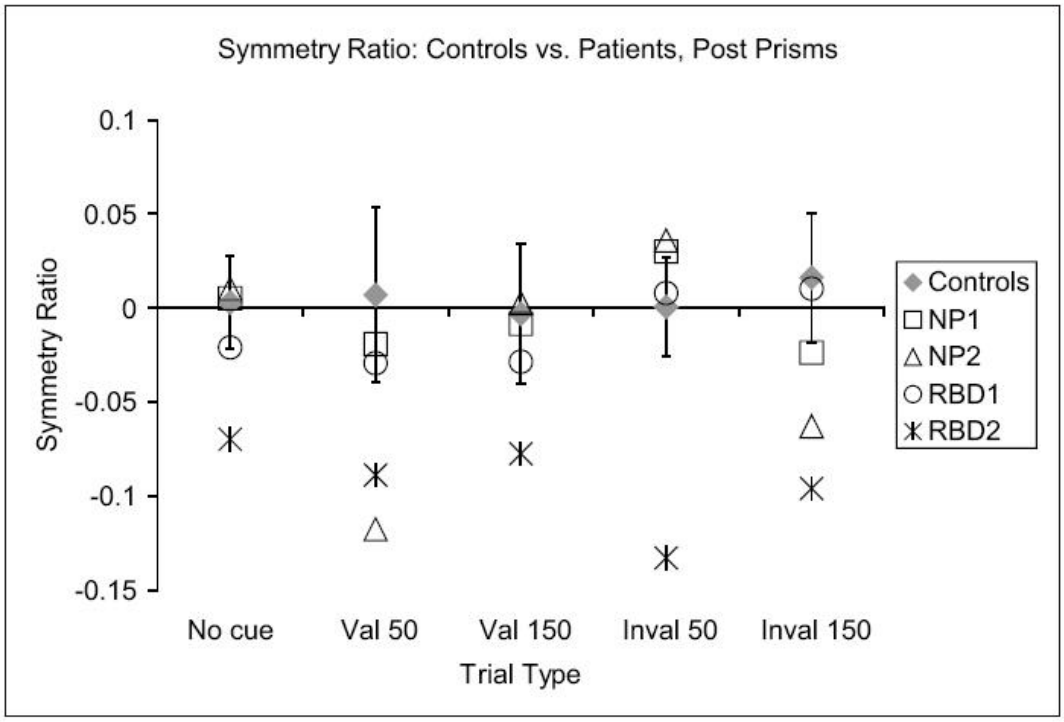


Figure 9: Symmetry ratios for controls (± SD) and patients before and after prism adaptation. These data are presented as a function of trial type (Val=valid, Inval=invalid) and stimulus onset asynchrony (SOA, 50, 150). Negative symmetry ratios are indicative of slower RTs for left visual field targets whereas positive symmetry ratios are indicative of slower RTs for right visual field targets.

2.4 Discussion

Previous research has demonstrated that adaptation to rightward shifting prisms is an effective way of alleviating some of the symptoms of neglect (Pisella et al., 2006; Redding & Wallace, 2006; Rossetti et al., 1998). Although prisms alter the performance of neglect patients, the mechanisms underlying these effects are largely unknown. Results from the current study clearly indicate that rightward shifting prisms substantially reduced the disengage deficit in all four patients with RBD. Indeed, post-adaptation at the 50ms SOA the disengage deficit for three of the four patients was reduced such that the CES for these patients now fell within the mean and SD of controls (Figures 8 & 9). Importantly, this reduction in the disengage deficit was significant regardless of whether the CES calculation controlled for side of cue or side of target. Thus rightward shifting prisms influence leftward attentional reorienting in RBD patients by enabling faster reorienting away from right spatial cues to detect left (contralesional) spatial targets. These results are similar to results in healthy individuals in which prisms *facilitated* reorienting at the earliest (50ms) SOA (Striemer, Sablatnig, & Danckert, 2006).

It should also be noted that prior to adaptation, left non-cued targets were detected more slowly than right non-cued targets, indicative of a rightward attentional bias (Section 1.2.1). Importantly, this rightward attentional bias was also reduced post prism adaptation. Thus prism adaptation successfully reduced both the disengage deficit and the rightward attentional bias.

Although the current results are clear cut, there are still some outstanding questions to be addressed. One patient (RBD1) failed to demonstrate a significant leftward after-effect in pointing to indicate his subjective notion of straight-ahead (Figure 6) but still demonstrated a

significantly reduced disengage deficit following prism adaptation. Although seemingly contradictory, Pisella and colleagues (Pisella, Rode, Farné, Boisson, & Rossetti, 2002) reported one patient who showed almost no pointing after-effect but demonstrated large and long-lasting changes in line bisection. Both their patient and RBD1 in the current study have restricted subcortical lesions involving the caudate nucleus. This suggests the caudate may not be important for modulating orienting behaviour post-adaptation, but may be vital in generating the pointing after-effect (see Fernandez-Ruiz et al., 2003), possibly through connections with the cerebellum.

Another discrepancy in the current study is that one patient's (RBD2) disengage deficit did not decrease as substantially as it did for the other patients. That is, while three of the four RBD patients had a CES that was within normal limits post-adaptation, the significant reduction in CES for patient RBD2 was not of a substantial enough magnitude to bring his performance to within the mean and SD of healthy individuals (Figure 8). There are several potential reasons for this. First, the patient's disengage deficit was by far the largest of the four patients pre-adaptation. This means that the patient needed to demonstrate a far greater degree of improvement than was required in the other patients in order to have his performance fall within the mean and SD of controls post-adaptation. Another potential explanation is related to the fact that the patients' lesion extended into occipital cortex. A recent study by Serino and colleagues (Serino, Angeli, Frassinetti, & Ladavas, 2006) found that lesions extending into occipital cortex were related to poorer recovery from neglect post-adaptation.

Finally, it is interesting to note that prisms reduced the disengage deficit in all four RBD patients regardless of whether they demonstrated signs of neglect. This adds to the

mounting body of evidence which suggests that the neglect syndrome is much more than simply a disorder of spatial attention. That is, recent research has demonstrated that patients with neglect are also impaired in tasks which require sustained (non spatial) attention, spatial working memory, and temporal perception (Danckert & Ferber, 2006; Danckert et al., 2007; Husain & Rorden, 2003; Robertson et al., 1997). It is the confluence of these impairments – of which biases in spatial attention represent an important component – that leads to the presence of neglect. The suggestion here is that without the other impairments – including impaired sustained attention, spatial working memory, and temporal perception – a bias in spatial attention alone will not be enough to produce the full neglect syndrome. In addition, just as a disorder of spatial attention alone is not sufficient to cause neglect, reducing deficits in spatial attention may not be sufficient to completely rehabilitate neglect (Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003). Finally, another important insight from this result is the suggestion that prisms may also be useful in rehabilitating attentional and spatial processing abnormalities present in patients with RBD without clinical signs of neglect.

These findings add to the accumulating body of evidence suggesting that prisms influence attentional processes perhaps via activation of regions in the right cerebellum and left temporal-parietal cortex which have been shown to correlate with the recovery from neglect post prism adaptation (Luaute et al., 2006). One remaining question relates to the neural correlates that underlie the beneficial effects of prisms on covert attention in neglect. In addition to the right cerebellum and the left temporal-parietal cortex, one region that may also play an important role in generating these beneficial effects is the SPL (Luaute et al., 2006), a region that is typically undamaged in patients with neglect (Coulthard, Parton, & Husain, 2006). The SPL is known to play an important role in visual attention, eye

movements, and visuomotor control (Astafiev et al., 2003; Colby & Goldberg, 1999; Corbetta & Shulman, 2002; Culham, Cavina-Pratesi, & Singhal, 2006), making it an ideal candidate region to integrate the visuomotor adaptation signals required for successful adaptation with attentional control signals. Therefore, in Chapter 4 the role of the SPL in creating the beneficial effects of prisms will be explored by investigating the effects of prism adaptation on covert visual attention in a patient with lesions to the SPL. Prior to this undertaking it was important to first demonstrate what kind of attentional impairments arise as a consequence of lesions to the SPL (Chapter 3).

The literature surrounding the impact of lesions of the SPL on covert attention is controversial. On the one hand, Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984) originally argued that damage to the SPL was associated with the disengage deficit. On the other hand, in a study which directly compared the effects of right TPJ and SPL lesions on covert attention, Friedrich and colleagues (Friedrich, Egly, Rafal, & Beck, 1998) argued that the SPL played no important role in reflexive covert attention or the disengage deficit. Given the current controversy, the important first step to answering the larger question in regards to the role of the SPL in generating the beneficial effects of prisms on visual attention, is to first seek to better understand the effects of SPL lesions on covert attention. To address this question covert visual attention was explored in two patients with optic ataxia arising from lesions largely restricted to the SPL and IPS.

Chapter 3: Deficits in covert visual attention in patients with optic ataxia[2].

3.1 Introduction

Lesions of the SPL and IPS often lead to a disorder known as optic ataxia – a disorder characterised by impaired reaching under visual guidance (Section 1.3; Perenin & Vighetto, 1988). Patients with optic ataxia typically misreach for peripheral targets, whereas actions in central vision are generally spared (for a review see Rossetti, Pisella, & Vighetto, 2003). In addition, traditional models of the disorder have suggested that the visuomotor deficits are not associated with perceptual or attention deficits (Perenin & Vighetto, 1988). Although the visuomotor abilities of optic ataxia patients have been studied extensively in the visual periphery, their ability to *direct attention* towards the periphery has not been studied as extensively (Michel & Henaff, 2004; Rossetti, Pisella, & Vighetto, 2003). In the current study the ability to direct attention in a reflexive or voluntary mode of orienting was examined in two patients with optic ataxia arising from lesions to the SPL.

Reflexive and voluntary attention were explored using the COVAT as described in Chapter 2 and Section 1.2. For reflexive orienting non-informative (i.e. 50% valid) abrupt onset peripheral cues were used with SOAs of 50 or 150ms. For voluntary orienting a predictive (i.e. 80% valid) central arrow cue was used with SOAs of 300 and 500ms. Different SOAs were used in the two tasks because cuing benefits for reflexive and voluntary orienting develop over different time courses. Specifically cuing benefits for reflexive orienting occur at SOAs shorter than 200ms, whereas cuing benefits for voluntary orienting occur at SOAs longer than 200ms (Muller & Rabbitt, 1989).

[2] Versions of this chapter were originally published in *Neuroreport* & *Attention and Performance XXII* (Striemer et al., 2007 and Pisella et al., 2007 respectively).

As outlined in Section 1.1.3 and Chapter 2, previous studies of covert attention in patients with parietal lesions *without* optic ataxia have demonstrated a deficit in 'disengaging' attention from ipsilesional cues in order to detect contralesional targets (Losier & Klein, 2001; Posner, Walker, Friedrich, & Rafal, 1984). Importantly, neuroimaging and monkey neurophysiology data have identified regions in the SPL and IPS that are important for attending to locations in space, and preparing and executing saccades and reaching movements (Andersen & Buneo, 2002; Astafiev et al., 2003; Corbetta & Shulman, 2002). Therefore, it is possible that lesions in the SPL in humans will disrupt both attention *and* visuomotor control.

3.2 Methods

Participants

Two patients with optic ataxia completed the voluntary and reflexive covert orienting tasks. Patient CF is a 27 year-old right-handed male who suffered bilateral lesions of the SPL at age 24, with the right hemisphere lesion being larger than the left (Figure 10). CF presented with Balint's syndrome (ocular apraxia, simultanagnosia and optic ataxia) immediately post stroke, but at the time of testing only displayed symptoms of optic ataxia in left visual space when reaching with either his left or his right hand (see Khan et al., 2005). CF has never displayed any clinical signs of neglect and has no visual field defects. Patient ME is an 88 year-old female tested eight months following a stroke which affected the right SPL with a minor extension into the angular gyrus (Figure 10). Initial bedside testing with ME demonstrated neglect which resolved by the time of current testing. ME has no visual

field defects and demonstrates optic ataxia in left visual space when reaching with either her left or her right hand.

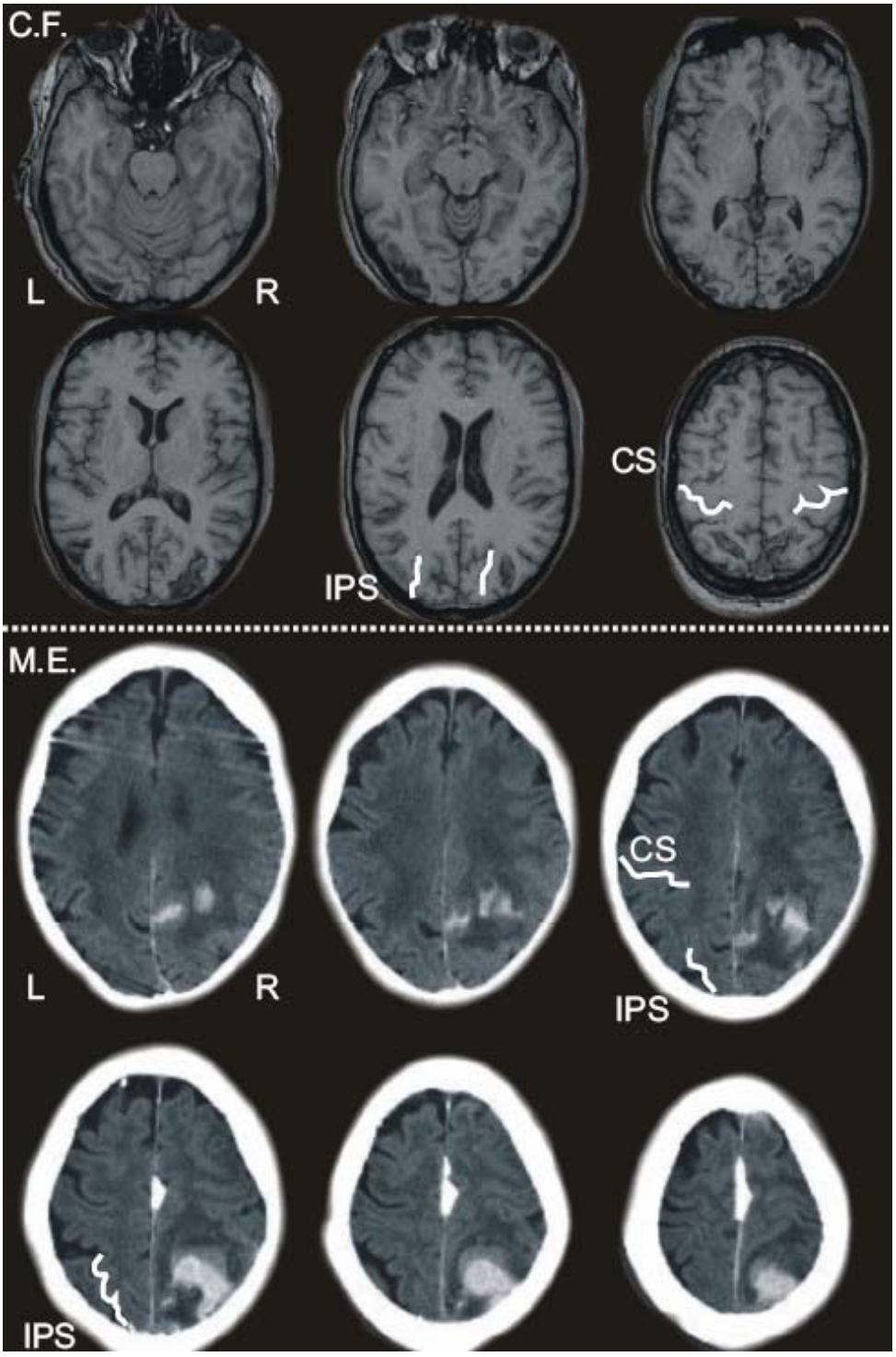


Figure 10: Anatomical scans of CF and ME. Upper panel: T1 MRI of CF's bilateral lesions to superior parietal lobule (SPL) and intraparietal sulcus (IPS). Lower panel: CT scan of ME's lesion of right SPL and IPS with a minor extension into inferior parietal cortex. CS=central sulcus; IPS=intraparietal sulcus.

Optic ataxia was assessed clinically by asking the patient to grasp a pencil placed in either peripheral or central vision while maintaining central fixation (Perenin & Vighetto, 1988). Both patients made reaching errors when grasping targets with either hand in the left space but not for grasping targets in central vision.

Sixty healthy individuals (22 male, 5 left-handed; mean age 20.8 years) completed the reflexive orienting task and 71 healthy individuals (26 male, 3 left-handed; mean age 19.8 years) completed the voluntary orienting task. These served as control groups for patient CF. In addition, six healthy elderly individuals (4 male, 1 left-handed, mean age 76.8 years, range 71-85) completed both tasks and served as elderly controls for patient ME. All controls had no history of psychiatric, neurological, or cognitive impairments. All persons gave informed consent prior to participation in accordance with the Helsinki declaration. All protocols were approved by the University of Waterloo Ethics Committee, the Tri-Hospital Research Ethics Board of Kitchener, and the French Ministry of Research.

Apparatus and procedure

For reflexive orienting a non-informative abrupt-onset peripheral cue was used. For voluntary orienting an 80% predictive central arrow cue was used. In both tasks, as in Chapter 2, target locations were indicated by green circles subtending 2° of visual angle, presented 12° to the left and right of fixation. Targets were filled red circles presented within the green circles. Response times were measured by button press of the right hand. Participants were seated 50cm from the monitor with their head in a chin rest. Stimuli were presented on Pentium IV computer with a 19 inch CRT monitor. Participants maintained fixation and while this was not monitored in controls, patients were monitored by an eye-

tracker (CF) or by the experimenter (ME). For voluntary orienting, after an SOA of 300ms or 500ms, targets appeared at the cued (valid) or uncued (invalid) location. For reflexive orienting SOAs of 50ms and 150ms were used (Muller & Rabbitt, 1989). In addition, non cued trials (targets appeared without cues) were included within the block in both tasks to examine RTs for simple target detection in the absence of cuing.

Data analysis

Mean RTs were calculated for each trial type for each participant. For controls, RTs less than 150ms or more than 2 standard deviations above the participants' grand mean were discarded. Reaction time data were analyzed separately for controls and patients using a three-way ANOVA with cue (valid, invalid), side of target (left, right), and SOA as within subject factors. Data from the patients was analyzed using the same procedure as controls with one exception. For patient CF, RTs were removed if they were below 150ms or above 1000ms (as in Chapter 2). However, given that patient ME was much older (88 years old) and slower to respond overall than CF, RTs were removed if they were below 150ms or above 2000ms. For both patients this resulted in the removal of less than five percent of trials. Post hoc tests were carried out using Fisher's LSD tests.

No cue trials were analyzed separately for controls and patients using paired samples t-tests.

In addition, to examine the cost for reorienting attention towards left vs. right space, cue effect sizes (CES's) were calculated. For leftward shifts of attention RTs to valid right targets were subtracted from RTs to invalid left targets. For rightward shifts of attention RTs to valid left targets were subtracted from RTs to invalid right targets (Section 2.2 & Figure 5;

Striemer, Sablatnig, & Danckert, 2006). In order to directly compare the RT cost for leftward reorienting in patients and controls, a modified t-test procedure developed by Crawford and colleagues was used (Crawford & Garthwaite 2002; Crawford & Howell, 1998). This procedure uses a modified version of the independent samples t-test in which the patient is treated as an individual sample that does not contribute to the estimate of the within group variance using the following formula (see Crawford & Garthwaite 2002; Crawford & Howell, 1998):

$$t = \frac{X_1 - X_2}{S_2\sqrt{(N_2 + 1)/N_2}}$$

In this formula X_1 represents the patients' score, X_2 the mean of the normative sample, S_2 the standard deviation of the normative sample, and N_2 the number of participants in the normative sample. The test statistic relies on the t-distribution with N_2-1 degrees of freedom. This allows the abnormality of an individual patient test score to be directly compared to a control group using the t distribution. This method is considered more conservative than the traditional Z-score approach (especially when smaller normative control samples are used) which tends to overestimate the abnormality of a patients' test score by assuming that the test scores of the control sample (and their variance) are normally distributed (Crawford & Garthwaite, 2002).

To examine the difference between RTs to targets in left and right space for each cue type symmetry ratios were calculated using the procedure outlined in Chapter 2 (Maruff, Hay, Malone, & Currie, 1995). Symmetry ratios determine the speed with which participants detect left versus right visual field targets in each cuing condition. Negative ratios indicate

longer RTs for left space, whereas positive ratios indicate longer RTs for right space. The CES data and symmetry ratio data are presented graphically, but were not analyzed statistically as they concur completely with the RT data. In all graphs CF's data is plotted with reference to the young control group, whereas ME's data is plotted with reference to the elderly controls.

3.3 Results

Healthy individuals: Reflexive orienting

Mean RTs are shown in Figure 11, directional cuing effects in Figure 12, and symmetry ratios in Figure 13. Younger controls showed a three-way cue x side of target x SOA interaction ($F(1,59)=6.3$, $p=.015$). At the 50ms SOA there was an equivalent RT advantage for valid over invalid targets when those targets appeared in either left or right visual space. In contrast, at the 150ms SOA there was no RT advantage for valid over invalid targets in left space (4ms; $t(59)=1.50$, $p=.14$), however there continued to be a significant RT advantage for valid targets in right space (19ms; $t(59)=7.14$, $p<.001$; Figure 11). Finally, younger controls were no faster at detecting non-cued targets on the left (377ms) vs. the right (383ms; $t(59)=1.9$, $p=.07$).

Elderly controls showed a main effect of cue ($F(1,5)=50.1$, $p=.001$) indicating that valid targets (426ms) were responded to faster than invalid targets (485ms) an advantage that was not modified by SOA or the side of space within which targets were presented. Finally, elderly controls responded more slowly to left (485ms) vs. right (465ms) non-cued targets ($t(5)=3.02$, $p=.03$).

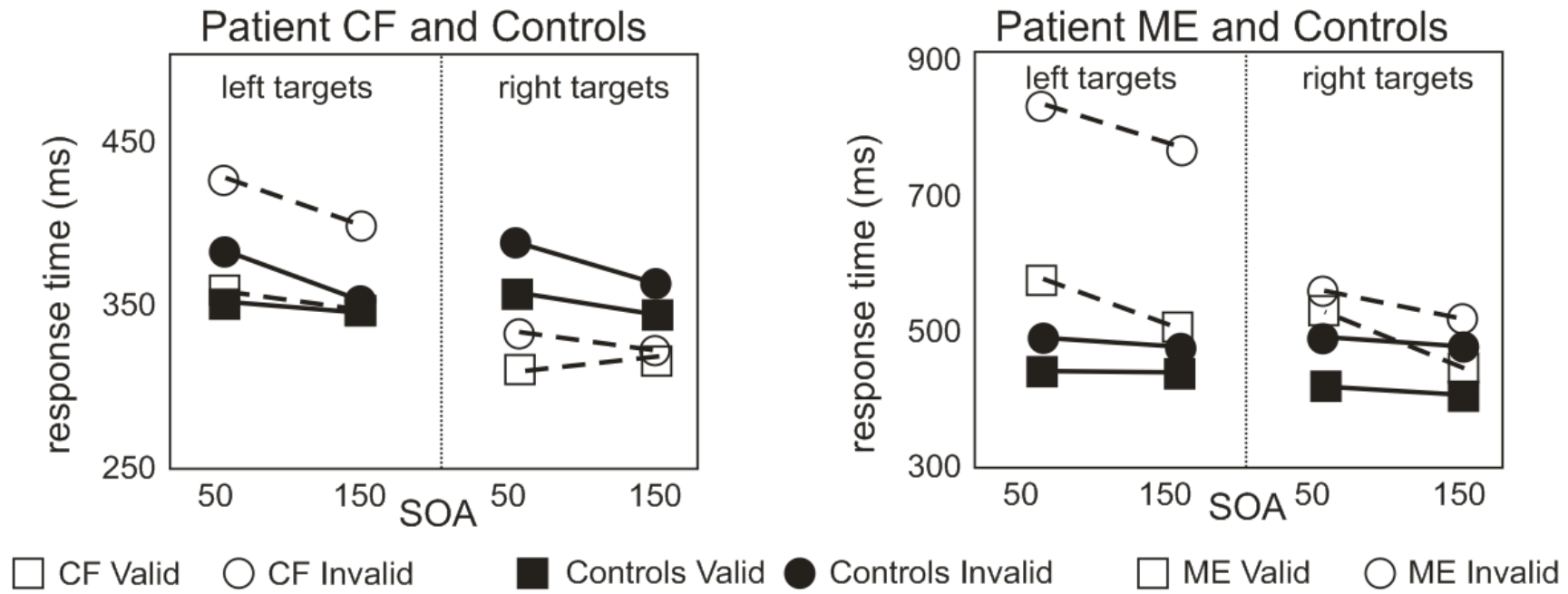


Figure 11: Reaction times (RTs) for reflexive orienting. Mean RTs for the young controls and CF (left) and elderly controls and ME (right).

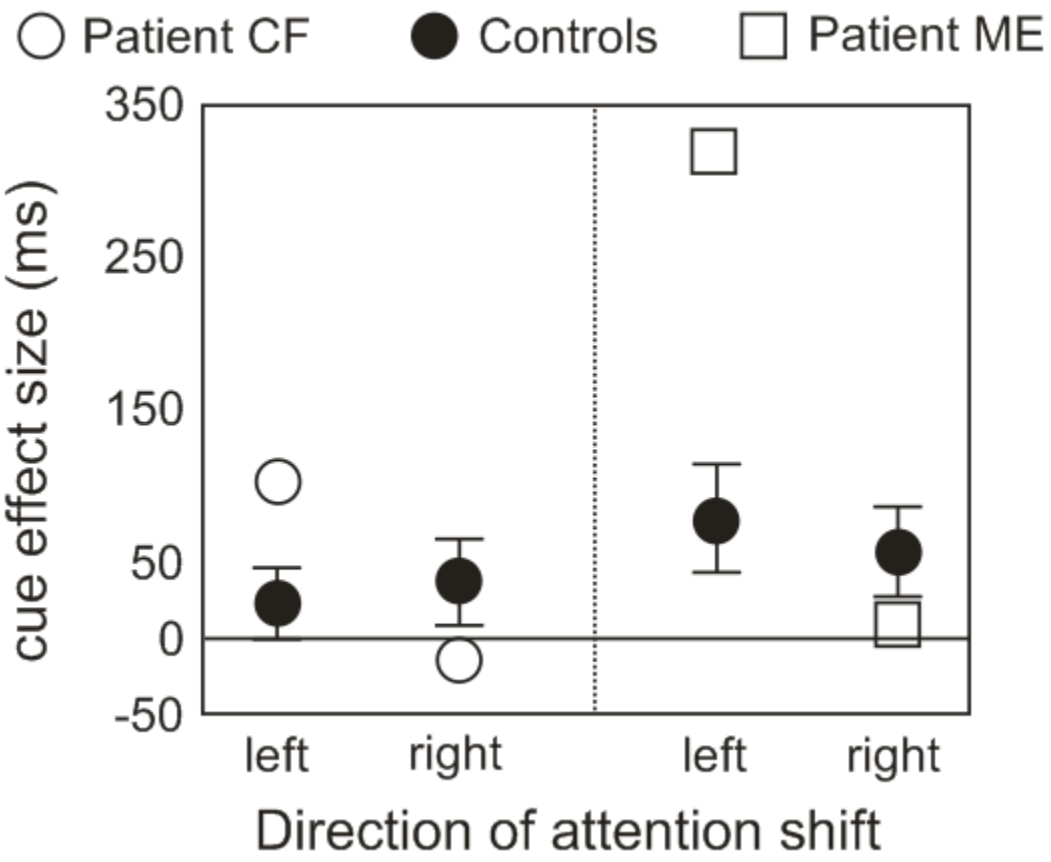


Figure 12: Cue effect sizes (CESs) for reflexive orienting. CESs for leftward and rightward attention shifts for both patients and their respective controls (mean ±SD).

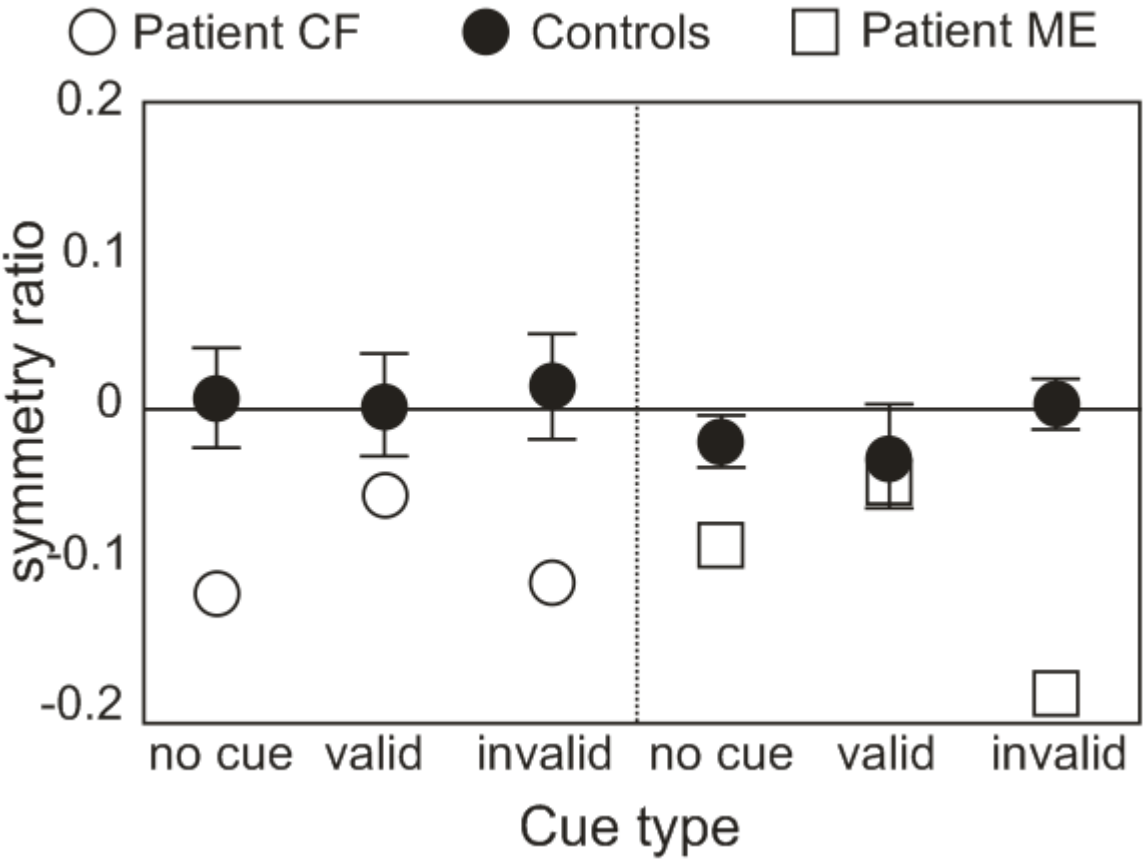


Figure 13: Symmetry ratios for reflexive orienting. Symmetry ratios for both patients in relation to mean (±SD) of their respective control groups. Positive ratios = longer RTs for right targets; negative ratios = longer RTs for left targets.

Patients: Reflexive orienting

Patient CF demonstrated a significant cue x side of target interaction ($F(1,310)=17.5$, $p<.001$) such that the difference in RTs between left and right visual field targets was larger for invalidly cued targets (82ms) compared to validly cued targets (42ms; $t(318)=10.55$, $p<.001$: Figure 11). CF was also slower to detect valid targets on the left (351ms) vs. the right (314ms; $t(318)=9.8$, $p<.001$) and to detect non-cued targets on the left (415ms) vs. right (327ms; $t(38)=5.6$, $p<.001$).

In addition, examination of the CES data using the modified t-test procedure (i.e. Crawford & Garthwaite 2002; Crawford & Howell, 1998) demonstrated that the RT cost for leftward shifts of attention for CF was significantly larger than controls (14ms controls vs. 95ms CF; $t(59)=3.39$, $p<.001$; Figure 12)[3].

Patient ME showed a strikingly similar pattern of performance to patient CF. Results showed a significant cue x side of target interaction ($F(1,150)=13.9$, $p<.001$) such that the RT difference for left and right visual field targets was larger for invalidly cued targets (257ms) compared to validly cued targets (48ms; $t(158)=10.55$, $p<.001$; Figure 11). She was also slower to detect valid targets on the left (538ms) vs. right (490ms; $t(158)=2.5$, $p=.015$) and was slower to detect non-cued targets on the left (573ms) vs. the right (479ms; $t(33)=2.7$, $p=.01$).

Examination of the CES data using the modified t-test procedure indicated that ME's RT cost for leftward reorienting was significantly larger than that of the elderly control group (69ms elderly controls vs. 308ms ME; $t(5)=6.25$, $p=.002$; Figure 12)[4].

[3] Note that if the CES for CF is calculated controlling for side of target (i.e. Posner et al., 1984) the result is the same (16ms controls vs. 66ms CF; $t(60)=2.59$, $p=.012$).

[4] Note that if the CES for ME is calculated controlling for side of target (i.e. Posner et al., 1984) the result is the same (44ms elderly controls vs. 260ms ME; $t(6)=9.56$, $p<.001$).

Healthy individuals: Voluntary orienting

Mean RTs are shown in Figure 14, directional cuing effects in Figure 15, and symmetry ratios in Figure 16. Young controls showed main effects of cue, side of target, and SOA (F's >5, all *p's* <.025). Valid targets (300ms) were detected faster than invalid targets (331ms), left targets (313ms) were detected slightly faster than right targets (318ms), and RTs were faster at the 500ms SOA (312ms vs. 319 at the 300ms SOA; Figure 14). There was no difference between RTs for non-cued trials in left and right space (left 382ms vs. right 389ms; t(70)=1.9, *p*=.07).

Elderly controls showed main effects of cue, and SOA (F's >9, *p's* <.03). Valid targets (377ms) were responded to faster than invalid targets (433ms) and targets at the 300ms SOA (395ms) were responded to faster than targets at the 500ms SOA (415ms). There was a significant side of target x SOA interaction (F(1,5)=9.5, *p*=.03) such that left targets (430ms) were responded to more slowly than right targets (398ms) at the 300ms SOA (t(6)=6.7, *p*<.001; Figure 14). Elderly controls were also slower to respond to left (494ms) vs. right (464ms) non-cued targets (t(5)=2.9, *p*=.03).

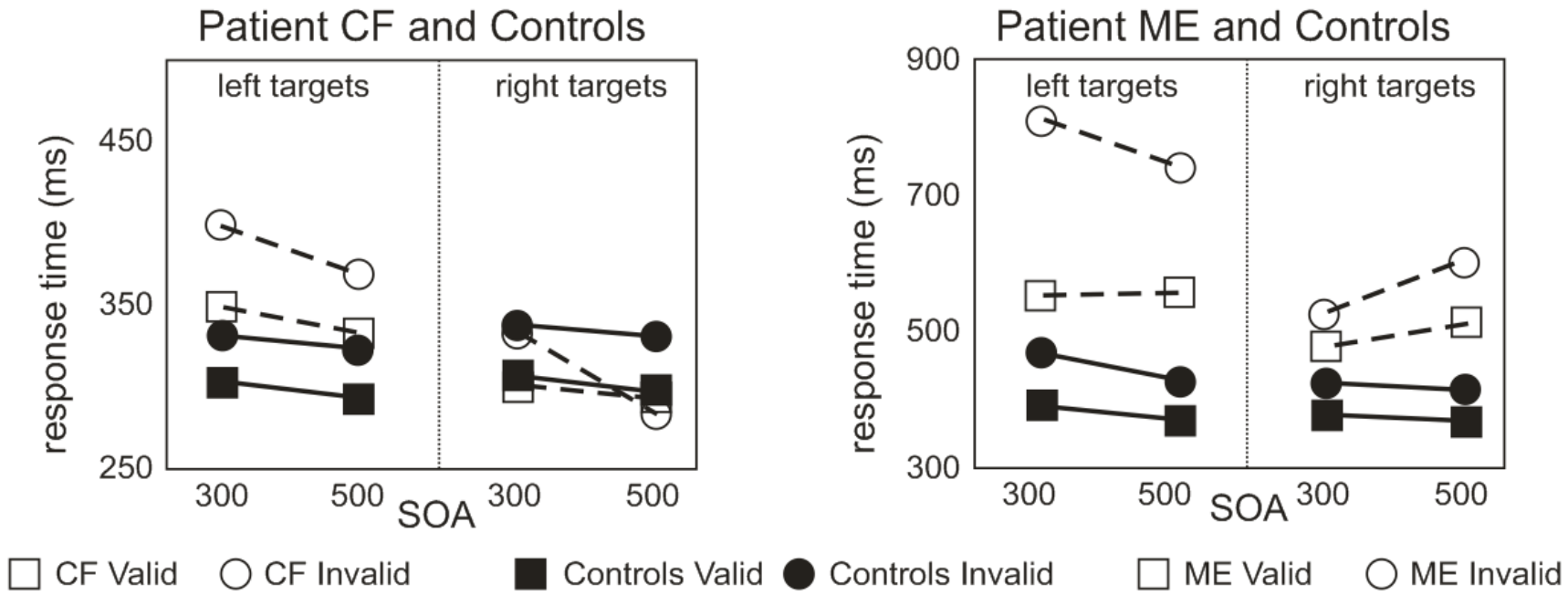


Figure 14: Reaction times (RTs) for voluntary orienting. Mean RTs for the young controls and CF (left) and elderly controls and ME (right).

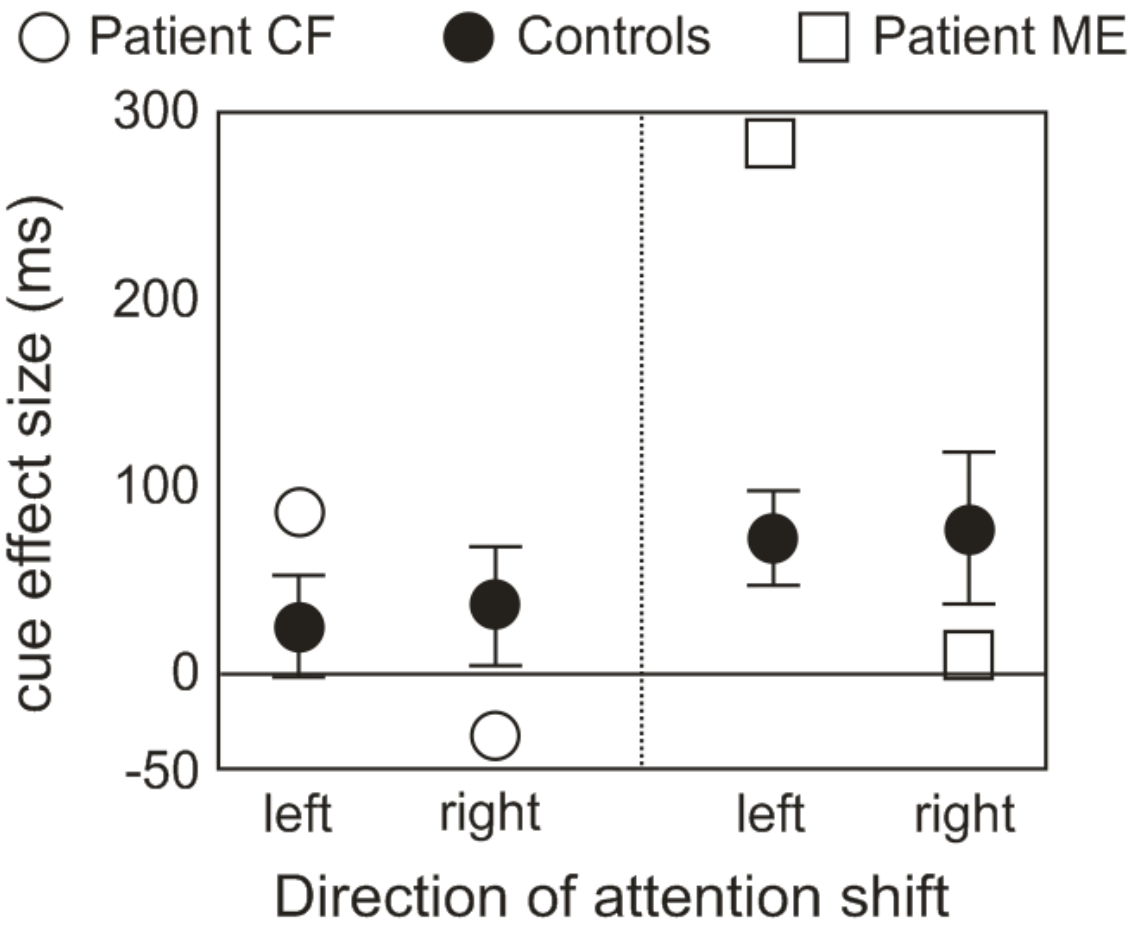


Figure 15: Cue effect sizes (CESs) for voluntary orienting. CESs for left and right attention shifts for patients and their respective controls (mean ±SD).

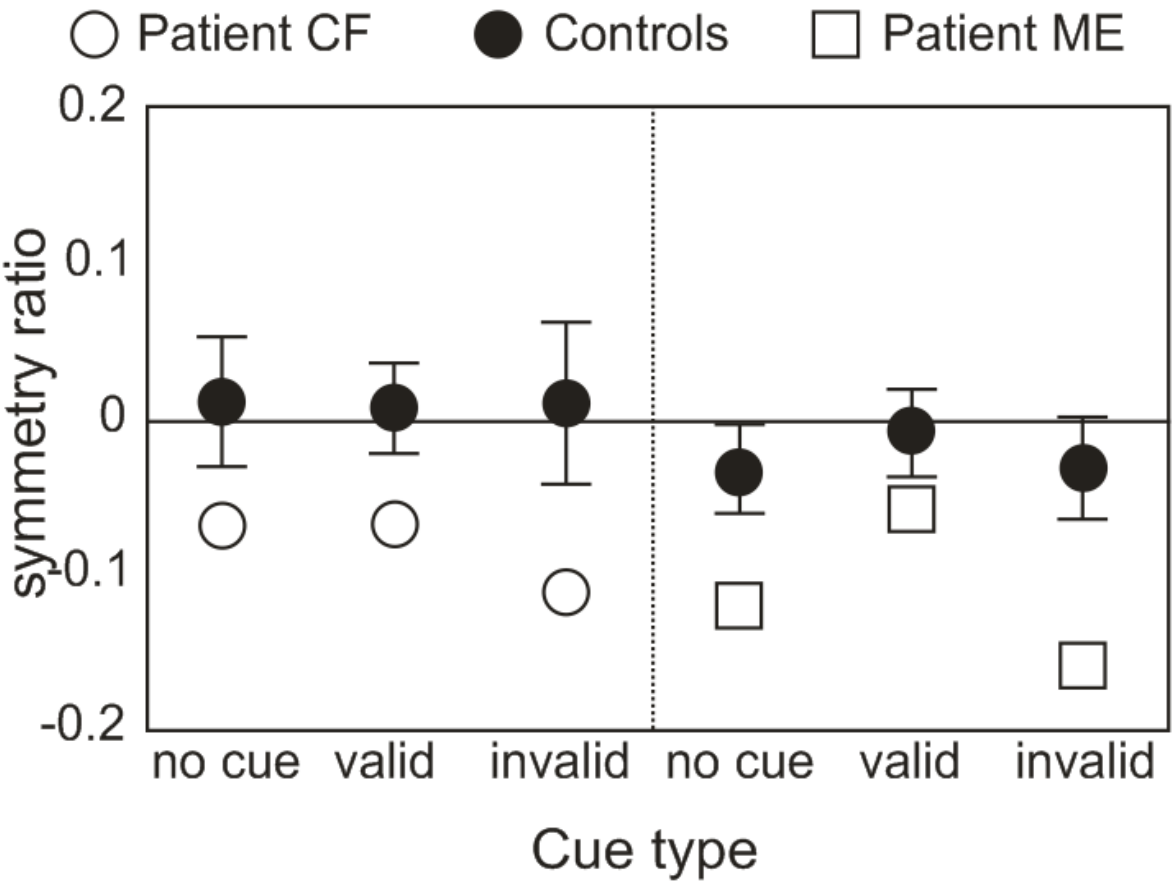


Figure 16: Symmetry ratios for voluntary orienting. Symmetry ratios for patients in relation to mean (±SD) of controls. Positive ratios = longer RTs for right targets; negative ratios = longer RTs for left targets.

Patients: Voluntary orienting

Patient CF's analysis showed a significant cue x side of target interaction ($F(1,305)=4.3$, $p=.04$) such that the RT difference for left and right targets was larger for invalidly cued targets (76ms) compared to validly cued targets (44ms; $t(312)=7.08$, $p<.001$; Figure 14). CF was also slower to detect valid targets on the left (341ms) vs. the right (297ms; $t(305)=9.6$, $p<.001$) and was slower to detect non-cued targets on the left (428ms) vs. the right (373ms; $t(37)=3.0$, $p=.005$).

Finally, analysis of the CES data using the modified t-test procedure indicated that CF's RT cost for leftward reorienting was much larger than controls (26ms controls vs. 87ms CF; $t(69)=2.28$, $p=.029$; Figure 15).[5]

Patient ME's analysis revealed a similar pattern of performance with a significant cue x side of target interaction ($F(1,343)=11.4$, $p<.001$). This interaction indicated that the RT difference for left and right visual field targets was larger for invalidly cued targets (212ms) compared to validly cued targets (60ms; $t(350)=12.11$, $p<.001$; Figure 14), In addition, ME was slower to detect valid targets on the left (555ms) vs. right (495ms; $t(343)=4.8$, $p<.001$) and was slower to detect non-cued left (733ms) vs. right (575ms) targets ($t(33)=2.4$, $p=.023$).

[5] Note that if the CES for CF is calculated controlling for side of target (i.e. Posner et al., 1984) he is not significantly different from controls (30ms controls vs. 43ms CF; $t(70)=.635$, $p=.26$). Although this implies that CF is not impaired, the vast majority of the evidence strongly supports the notion that he is impaired at directing voluntary attention towards left space. Specifically, he is much slower at reorienting leftwards when the CES calculation controls for side of cue (see results above). This is driven by two factors. First, CF is significantly slower for detecting left versus right invalidly cued targets (see above for results). Second, he is also slower to detect *validly* cued left and right visual field targets (see results above and Figures 14 & 16). In contrast, there was no difference in RTs for controls when comparing validly or invalidly cued targets in the left and right visual fields (i.e. the cue x side of target interaction was not significant, $F(1,70)=.770$, $p=.38$). Importantly, this second factor (an RT difference between validly cued left and right targets) actually serves to *underestimate* the magnitude of the disengage deficit in CF when it is calculated in the traditional manner (Section 2 .2). Finally, the symmetry ratio data clearly indicate that CF is much slower at detecting *any* target on the left compared to controls. This effect is largest for invalidly cued trials when attention has to be reoriented from a cue on the right to a target on the left (see results above; Figure 16). In summary, the weight of evidence conclusively supports the view that CF is greatly impaired at directing voluntary attention towards left visual space – a problem that is clearly not evident in the control group.

Analysis of the CES data using the modified t-test procedure indicated that ME's RT cost for leftward reorienting was much larger than the elderly controls (72ms controls vs. 282ms ME; $t(5)=7.71$, $p<.001$; Figure 15)[6].

Overall, CES's for both patients were larger for leftward than rightward shifts of attention compared to the mean and SD of the appropriate control groups (Figures 12 & 15). In addition, symmetry ratios for both patients were negative in all conditions indicating slower responses for left targets (Figures 13 & 16). In both patients, this was most pronounced for the no cue and invalid cue conditions.

3.4 Discussion

Optic ataxia has traditionally been considered a deficit of visuomotor control independent of perceptual or attention deficits (Perenin & Vighetto, 1988). However, the present results clearly demonstrate that patients with optic ataxia also have marked deficits in orienting and reorienting attention. Specifically, both patients were dramatically slower to detect any target in their left (ataxic) field, regardless of cue type. This resulted in negative symmetry ratios in all cue conditions that were well outside the mean and SD of controls, indicative of a left spatial deficit. This deficit was most evident for invalid trials when attention had to be disengaged from ipsilesional (i.e. right) cues (Figures 12 & 15). One explanation for the dramatic slowing of responses to all cue types in the ataxic field would be a decrease in salience for contralesional stimuli. That is, when a cue or target appears in the ataxic field, attention may not be captured to the same extent as it is for ipsilesional stimuli. A decrease in salience is consistent with what is known about the various functions supported

[6] Note that if the CES for ME is calculated controlling for side of target (i.e. Posner et al., 1984) the results are the same (66ms elderly controls vs. 222ms ME; $t(6)=11.62$, $p<.001$).

by the IPS. For example, neurons in LIP of the monkey IPS (Figure 1 in Chapter 1) show increased firing rates only to task-relevant stimuli, reflecting a role for this region in representing the behavioural salience of contralateral stimuli (Gottlieb, Kusunoki, & Goldberg, 1998).

Interestingly, similar to patients with spatial neglect (Section 1.2 & Chapter 2; Bartolomeo & Chokron, 2002), both patients in this study had difficulty disengaging attention from ipsilesional cues as well as demonstrating a rightward attentional bias when detecting non-cued targets. Previous studies suggest that the disengage deficit results from lesions to the TPJ and not the SPL (Friedrich, Egly, Rafal, & Beck, 1998). However, the current results question this conclusion given that neither patient's lesion extends into the TPJ. It is important to emphasize that although both CF and ME have a deficit in reorienting attention similar to neglect patients, they also have marked deficits in *orienting* attention. That is, they are much slower to detect valid and non-cued targets in their ataxic (left) visual field.

One question raised by the current study is how the attention impairments in optic ataxia seen here may relate to deficits in visuomotor control. Recent research suggests that several regions within SPL and the IPS are important for directing attention, motor planning, pointing, reaching, and grasping within a particular region of space (Andersen & Buneo, 2002; Astafiev et al., 2003; Corbetta & Shulman, 2002). Given that regions in the SPL are important for both spatial attention and the control of actions, lesions to this region could lead to peripheral attention deficits that may interact with the deficits in visuomotor control that are characteristic of optic ataxia. Although the link between peripheral attention and action in optic ataxia is unclear, the current results strongly suggest that future studies must

consider these attention deficits when examining visuomotor control in these patients (Pisella et al., 2007).

In addition, the current study indicates that the SPL and the IPS play an important role in controlling both reflexive and voluntary attention. In the next chapter the question of whether or not the SPL plays an important role in generating the beneficial effects of prism adaptation will be addressed. That is, patient CF was examined for performance of a covert orienting task before and after a period of exposure to prisms to determine whether prism adaptation could reduce *the same attentional deficits* (i.e. rightward attentional bias, difficulty with leftward reorienting) that were altered in the RBD group tested in Chapter 2.

Chapter 4: Bilateral parietal lesions disrupt the beneficial effects of prisms on visual attention[7].

4.1 Introduction

As discussed earlier (Section 1.2), the most common form of neglect – neglect of left space from lesions of the right IPL/TPJ – represents a debilitating disorder with poor functional outcomes for the patient. Recent work making use of prism adaptation has provided some promising results in terms of rehabilitating the spatial deficits of these patients. As yet, however, little is known about the cognitive and neural mechanisms that support recovery of function in some neglect patients post-adaptation to rightward shifting prisms.

One way in which prisms may exert beneficial effects in neglect is by altering dysfunctional attentional orienting mechanisms. As shown in Chapter 2, rightward shifting prisms were able to reduce both the disengage deficit, and the rightward attentional bias (i.e., the classic attentional components referred to in models of the neglect syndrome) evident in a group of four RBD patients (two with neglect; Chapter 2). Specifically, after adaptation to rightward-shifting prisms, the RT cost associated with leftward shifts of attention (i.e. the disengage deficit) was reduced in all patients to such an extent that three of the four patients now performed within one SD of a group of healthy controls. In addition, the RT difference between non-cued left and right targets was also dramatically reduced post-adaptation, indicative of a reduced rightward attentional bias. These results provide a mechanism by which prisms may exert their beneficial effects in neglect and indeed in RBD patients without neglect who can be shown to have demonstrable impairments in the ability to

[7] A version of this chapter is currently in press in *Experimental Brain Research* (Striemer et al., in press).

allocate attention towards contralesional space (as was also the case for patient CF; see Chapter 3).

One candidate brain region that may mediate the beneficial effects of prism adaptation in neglect patients, (i.e. the after-effects on visual attention), is the SPL, a region typically undamaged in neglect patients that is known to play a pivotal role in attention (Chapter 3) and eye and limb movements (Buneo & Andersen, 2006; Corbetta & Shulman, 2002). Furthermore, the SPL receives inputs from the cerebellum (Dum & Strick, 2003), a structure that is critical for demonstrating successful adaptation to prisms (Pisella et al., 2005; Weiner, Hallett, & Funkenstein, 1983). Thus, it may be the case that the beneficial effects of prisms are generated, in part, by interactions between the cerebellum and the SPL.

If the SPL contributes to the beneficial after-effects of prisms, then a patient with bilateral SPL lesions may well be able to adapt to prisms – a process that presumably relies on fronto-cerebellar networks (Kurata & Hoshi, 1999; Pisella et al., 2004; Pisella, Rode, Farné, Tilikete, & Rossetti, 2006; Pisella et al., 2005) – but should fail to demonstrate any beneficial after-effects of prisms on tasks such as the COVAT. However, if the SPL is *not* important for generating the beneficial effects of prisms, then a patient with bilateral SPL lesions should be able to adapt to the prismatic shift *and* demonstrate beneficial after-effects of prisms. To explore this hypothesis patient CF (Chapter 3) was asked to perform a reflexive COVAT before and after a period of exposure to rightward shifting prisms. As outlined in the previous chapter, CF demonstrated an impairment in the ability to orient and reorient attention towards his left (ataxic) visual field (Chapter 3; Pisella et al., 2007). That is, he has difficulty attending to the same visual field in which he has problems with reaching and grasping (Blangero et al., in press; Khan et al., 2005). Although CF has bilateral lesions of

the SPL/IPS, MRI scans show that the right hemisphere lesion is larger than the left (Figure 10). Furthermore, based on his behavioural deficits both on clinical tests of optic ataxia and on the COVAT (Chapter 3), CF performs much like an RBD patient such that his attention and reaching deficits are restricted to his left visual field.

To evaluate the effects of prisms on attention in CF he completed the same procedure used in the previous study with RBD patients (Chapter 2). That is, his performance on a reflexive orienting version of the COVAT before and after adaptation to rightward shifting prisms was compared to a group of controls who underwent sham (no visual shift) exposure. As in the previous study examining the effects of rightward prism adaptation on attention in RBD patients (Chapter 2), the sham prisms group was used as an index of 'normal' performance independent of directional prism exposure. Using sham prisms enables the practice effects and any motor activity effects to be taken into account by comparing CF post-adaptation to sham controls post-adaptation. Thus, any effects that appear in CF but not controls post prisms must be related to the *directional* adaptation effects and not to simple practice effects.

To summarize, the current study was designed to investigate whether the SPL is important for generating the beneficial effects of prisms on attention seen in patients with RBD not involving the SPL (Chapter 2). If the SPL is *not necessary* to observe the beneficial effects of prisms on attention then CF should demonstrate a reduced rightward attentional bias and disengage deficit similar to the RBD patients in the previous study (Chapter 2). That is, he should perform more similarly to the healthy controls that have undergone sham (no visual shift) adaptation. However, if the SPL *is necessary* to demonstrate the beneficial effects of prisms on attention then CF's disengage deficit and rightward attentional bias

should remain unchanged following adaptation to rightward shifting prisms (contrary to the performance of the RBD patients in Chapter 2) such that his performance is still severely impaired relative to controls.

4.2 Methods

Participants

Twenty-six individuals (8 male, 4 left handed, mean age= 20.1 yrs, SD=2.4) recruited from the University of Waterloo participated as controls. Note that this was the same control group used in Chapter 2. For a description of patient CF refer to Section 3.1. The current testing session took place two weeks after the testing session reported in Chapter 3. All persons gave informed consent prior to participation in accordance with the Helsinki declaration. All protocols were approved by the University of Waterloo Ethics Committee, and the French Ministry of Research.

Apparatus and procedure

The apparatus and procedure used to examine reflexive covert orienting were identical to those reported in Chapter 2 (Section 2.2). Participants completed the COVAT once prior to and once following adaptation to either rightward shifting prisms (patient CF) or sham prisms (controls). The prism adaptation procedure was identical to that used in Chapter 2 (Section 2.2). CF wore wedge base prisms inducing a 10° rightward shift while controls wore sham prisms which induced no shift in visual perception. All participants used their right hand to point during exposure.

Data analysis

Mean RTs were calculated for each trial type for each participant. For controls, RTs were discarded if they were below 150ms or more than 2 standard deviations above the individual's grand mean. For CF, RTs were discarded if they were below 150ms or more than 1000ms (as in Chapter 3). For all participants (including CF) this accounted for less than 5% of trials. Reaction time data were analyzed separately for CF and controls using a 4-way ANOVA with session (pre-, post-adaptation), cue (valid, invalid), side of target (left, right) and SOA (50, 150) as within subject factors. Post-hoc analyses were carried out using Fisher's LSD tests.

In addition, to examine the cost in RT associated with left and right shifts of attention, directional cue effect sizes (CES's) were calculated as outlined in Chapter 2 (Section 2.2 and Figure 5). This analysis is not reported here as it completely supported the same conclusions as the RT analysis. In order to evaluate the effects of prisms on CF's ability to reorient attention the modified t-test procedure developed by Crawford and colleagues was used (Crawford & Garthwaite , 2002; Crawford & Howell, 1998; Section 3.2). The specific hypothesis tested here was that if rightward prism adaptation decreases CF's disengage deficit, then his RT cost for leftward reorienting should not be significantly different from controls post prisms.

Symmetry ratios were also calculated to compare RTs for left and right visual field targets pre- and post-adaptation using the procedure outlined in Chapter 2. Pointing data were analyzed by calculating the mean deviation from center for each participant pre- and post-adaptation. Data were converted into degrees of visual angle with leftward errors coded as negative and rightward errors coded as positive.

4.3 Results

Figure 17 depicts prism adaptation pointing data for controls and CF. Mean RTs for each trial type pre- and post-adaptation for controls and CF are depicted in Figures 18 and 19. Cue effect size data and symmetry ratios for controls and CF are presented in Figures 20 and 21.

Controls

Given that the control group used here was the same control group that was used in Chapter 2, the same data analyses will not be repeated. Instead, RT data for the controls are presented in Figure 18 (reproduced from Figure 7). For the analysis of the control data refer to Section 2.3.

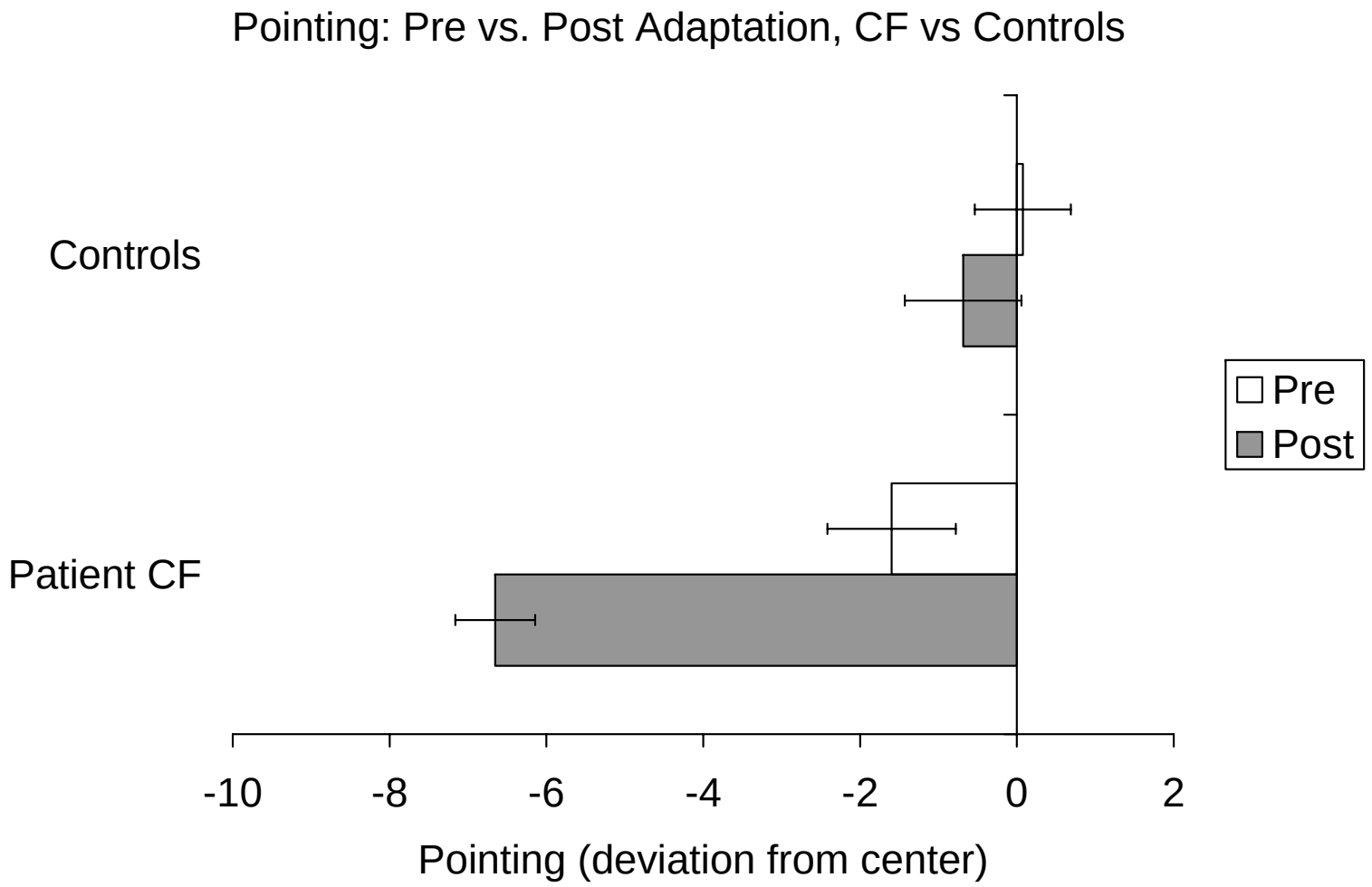


Figure 17: Prism adaptation pointing data. Straight-ahead pointing data for CF and controls prior to and after prism adaptation. Error bars represent standard error.

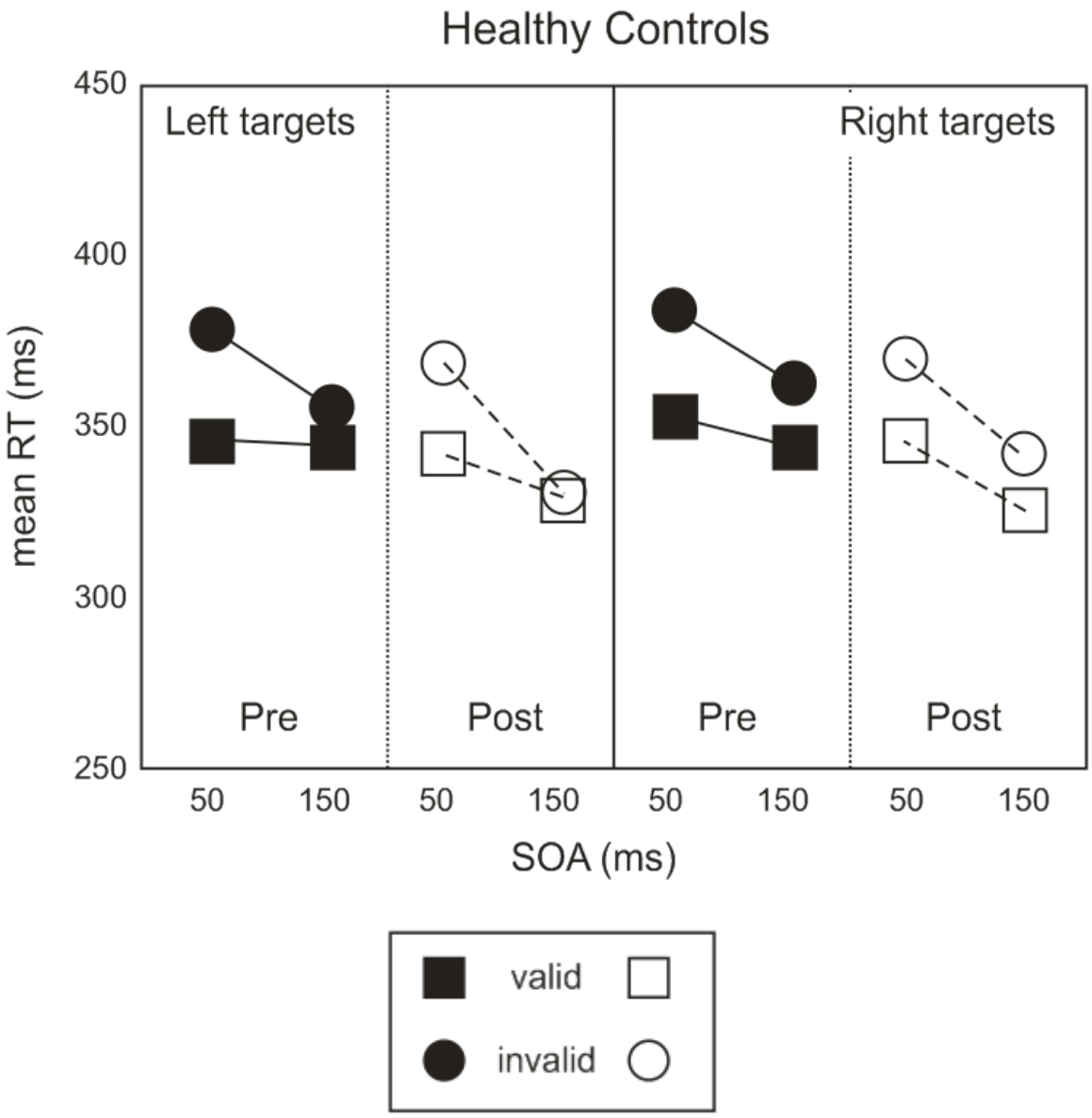


Figure 18: Mean response time (RT) data for controls. Depicts the mean RTs for healthy controls as a function of cue validity (valid, invalid), side of target (left, right), and stimulus onset asynchrony (SOA; 50, 150ms), prior to (pre) and following (post) sham adaptation (taken from the upper panel of Figure 7).

Patient CF

Patient CF showed a significant leftward shift in straight-ahead pointing post-adaptation (-1.59° pre vs. -6.65° post; $t(9)=7.14$, $p<.001$) indicating that he successfully adapted to the prisms (Figure 17).

Analysis of CF's RT data pre-adaptation revealed a significant cue x side of target interaction ($F(1,218)=19.83$, $p<.001$) such that while CF was slower to react to left versus right visual field targets overall, the effect was largest for invalid versus valid trials (i.e., the classic disengage deficit; $t(229)=12.66$, $p<.001$; Figure 19). In addition, prior to adaptation CF was much slower to detect non-cued left (395ms) versus right (330ms; $t(9)=4.18$, $p<.01$) targets (i.e., a rightward attentional bias). This is the same pattern of performance that CF demonstrated in the previous study (Chapter 3; Figure 11), indicating that his attentional deficits were stable over time.

Analysis of CF's data pre- and post-adaptation revealed a significant cue x side of target interaction ($F(1,302)=55.98$, $p<.001$) which indicated that the difference in RTs for left and right visual field targets was larger for invalidly cued targets (87ms) compared to validly cued targets (20ms; $t(318)=21.26$, $p<.001$; Figure 19). There was also a significant session x side of target interaction ($F(1,302)=4.36$, $p<.05$) resulting from a larger overall decrease in RTs for left visual field targets (33ms) versus right visual field targets (15ms) post-adaptation (Figure 19; $t(317)=5.70$, $p<.001$). The session x cue x side of target interaction, however, failed to reach significance ($F(1,302)=2.38$, $p=.12$), indicating that prisms had no *differential* effects on valid versus invalid trials (Figure 19).

In addition, after adaptation, CF continued to be much slower to detect non-cued left (365ms) versus right (305ms) targets ($t(9)=3.83$, $p=.01$). That is, the magnitude of his rightward attentional bias was unchanged following prisms.

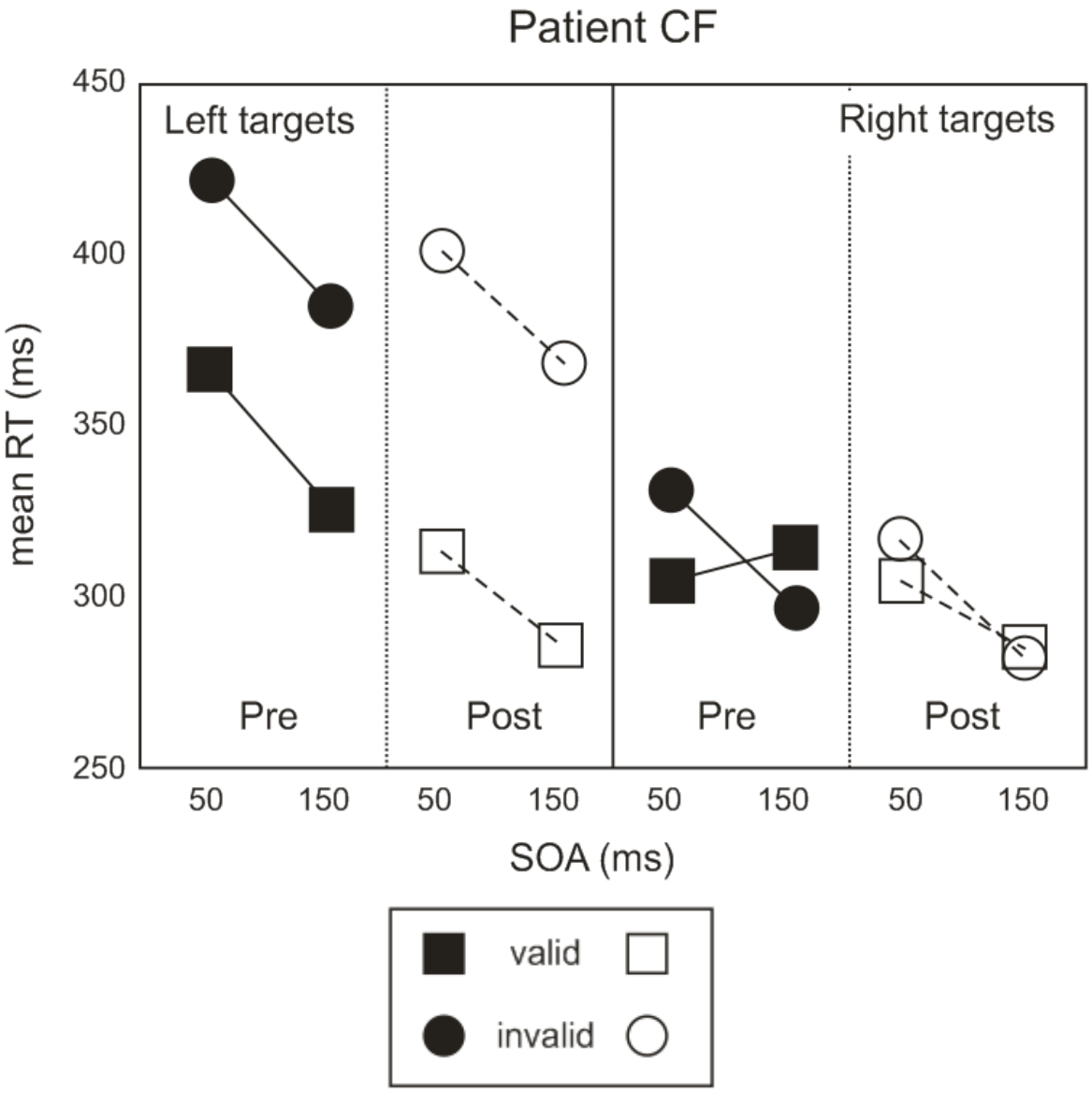


Figure 19 Mean response time (RT) for CF: Depicts the mean RTs for patient CF as a function of cue validity (valid, invalid), side of target (left, right), and stimulus onset asynchrony (SOA; 50, 150ms), prior to (pre) and following (post) adaptation to rightward shifting prisms.

Directional CES's were analyzed using the modified t-test procedure (i.e. Section 3.2; Crawford & Garthwaite, 2002; Crawford & Howell, 1998). The CES data (Figure 20) support the same conclusions as the RT analysis. Prior to exposure, CF demonstrated a larger CES for leftward shifts of attention (i.e. a disengage deficit) compared to controls (19ms controls vs. 95ms CF; $t(25)=3.31$, $p=.003$). However, prisms failed to reduce CF's disengage deficit such that it continued to be larger than either the cost of rightward reorienting for CF (Figure 20) or the cost of leftward reorienting for the healthy controls (14ms controls vs. 90ms CF; $t(25)=2.583$, $p=.016$). More importantly, unlike our previous findings in patients with RBD (including two patients with neglect; Chapter 2), CF failed to demonstrate a reduction in his cost for leftward reorienting (Figure 20)[8].

Finally, symmetry ratios for controls and CF pre- and post-adaptation (Figure 21) indicated that there was a slight, non-significant reduction in CF's symmetry ratio for valid trials post prisms (i.e. the session x cue x side of target interaction was not significant). Importantly there was no reduction in CF's symmetry ratios for either invalid or no cue trials. This provides further support that prism adaptation had no influence on CF's deficit in leftward reorienting or his rightward attentional bias.

[8] Note that if CES is calculated controlling for side of target CF's RT cost for leftward reorienting is still significantly larger than controls post prisms (13ms controls vs. 86ms CF; $t(26)=3.90$, $p<.001$).

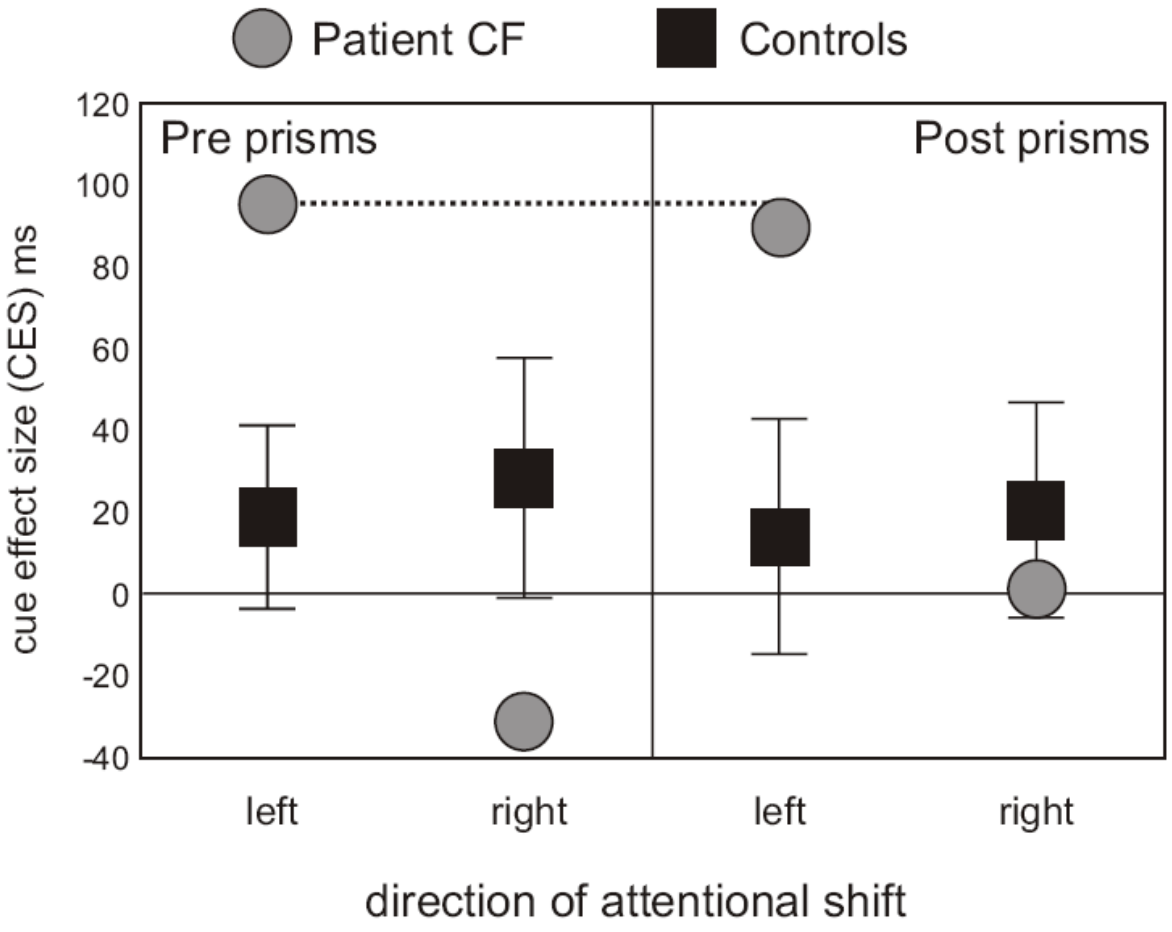


Figure 20: Cue effect size (CES) data for CF and controls. Cue effect size (CES) data for patient CF in comparison to the mean (±SD) of the control group for leftward and rightward shifts of attention prior to and following prism adaptation. The dashed line is intended to demonstrate that the magnitude of CF's disengage deficit does not change post-adaptation.

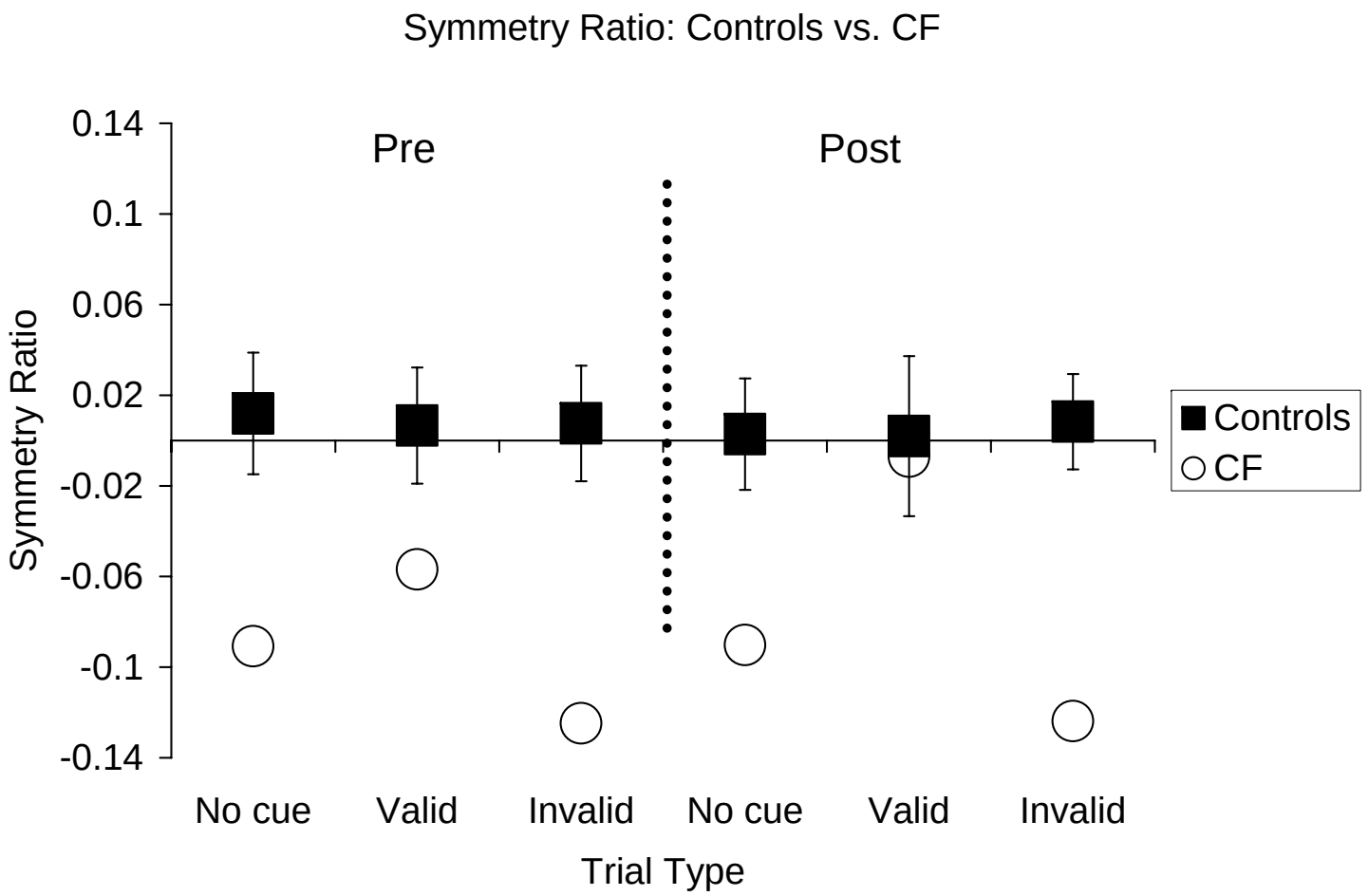


Figure 21: Symmetry ratios for controls (± SD) and CF before and after prism adaptation. These data are presented as a function of trial type. Negative symmetry ratios are indicative of slower RTs for left visual field targets whereas positive symmetry ratios are indicative of slower RTs for right visual field targets.

4.4 Discussion

Prior to prisms CF demonstrated a disengage deficit and a rightward attentional bias, replicating earlier findings (Chapter 3), suggesting that his pattern of impairment is stable over time. It is important to note that this pattern of performance closely resembles that of RBD patients without SPL lesions (Chapter 2). Following adaptation to rightward shifting prisms – the same technique that successfully rehabilitated the disengage deficit and rightward attentional bias in four RBD patients (Chapter 2) – CF continued to demonstrate a large leftward disengage deficit and rightward attentional bias. That is, despite the fact that CF had the *same* attentional deficits as the RBD patients in the previous study, he failed to demonstrate any of the same beneficial effects of prisms (Figure 20). When interpreted in this context, the current findings suggest that the SPL plays a crucial role in generating the beneficial effects of prisms on attention observed in patients with right parietal lesions that spare the SPL. These findings add to the growing body of literature which suggests that some patients may adapt to prisms without demonstrating any beneficial effects (Morris et al., 2004; Pisella, Rode, Farné, Boisson, & Rossetti, 2002; Pisella, Rode, Farné, Tilikete, & Rossetti, 2006).

One criticism that could be raised concerning the current findings is that CF showed an overall speeding of left versus right sided targets post-adaptation which could be construed as a beneficial effect of prisms (Figure 21). While it is possible that this effect is related to prisms as opposed to simply reflecting a practice effect in CF, this effect should not necessarily be construed as 'beneficial'. What is important here is not the change in overall RTs post prisms, or the non-significant change in RTs to left versus right valid targets, but the overall *pattern* of RTs which continued to be indicative of impaired attention for left

space. Given that there was no change in CF's overall *pattern* of performance post prisms (i.e. no decrease in the disengage deficit or the rightward attentional bias), these results strongly imply that no beneficial effects of prisms were present.

One important question that remains to be addressed is how the SPL might contribute to the beneficial effects of prisms. CF's bilateral SPL lesions make any direct link between the beneficial effects of prisms with either the left or right SPL somewhat difficult to interpret. Nevertheless, the direction of his deficits strongly imply that the larger right SPL lesion is responsible for his current deficits both in terms of visual attention and optic ataxia, while the lesion to his left SPL may be responsible for the lack of any observed benefits of prisms. While this is necessarily speculative, several different lines of research provide some support for this hypothesis. First, although the SPL is not necessary for successful adaptation to right prisms (Pisella et al., 2004), lesions to the right cerebellum or the left ventral premotor cortex do prevent adaptation to rightward shifting prisms (Clower et al., 1996; Kurata & Hoshi, 1999; Pisella, Rode, Farné, Tilikete, & Rossetti, 2006; Pisella et al., 2005). Taken together this suggests that the *adaptation* to prisms relies on cerebellar and frontal regions that do not rely directly on the SPL. It may be the case then, that adaptation to rightward shifting prisms involves leftward realignment signals that are transferred from the right cerebellum (Pisella et al., 2005) to the left PPC and ventral premotor cortex via direct connections with the dentate nucleus in the cerebellum (Dum & Strick, 2003).

Furthermore, the leftward realignment signals transferred to the left IPL are crucial for the *adaptation* to prisms (Clower et al., 1996; Rossetti et al., 1998), whereas the leftward realignment signals which are subsequently relayed to the left SPL during rightward prism adaptation may be crucial for generating the *beneficial after-effects* of prisms by enabling

neglect patients to begin to re-explore contralesional (left) space. This re-exploration of left space may also serve to re-activate undamaged parietal regions in the right hemisphere, including the SPL which is known to be important for directing visual attention, as well as eye and reaching movements to contralateral (left) space. In support of this hypothesis, a recent PET imaging study by Luaute and colleagues (Luaute et al., 2006) found that changes in activation in the right SPL were correlated with the recovery from neglect following prism adaptation.

To conclude, the current results show that the SPL (left, right, or both) is important for generating the beneficial effects of prisms, although the exact role of the SPL in generating these effects remains somewhat unclear.

Chapter 5: General Discussion

Corbetta and colleagues (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta & Shulman, 2002) suggest that there are two separate but interacting attention systems within the PPC. The dorsal attention network in the SPL/IPS is important for directing attention towards a specific location in space whereas the ventral attention network in the right IPL/TPJ serves as a circuit breaker which interrupts the current focus of attention in order to signal the dorsal attention network to reorient attention towards salient or behaviourally relevant stimuli in the environment. Lesions to the ventral attention network in the IPL/TPJ result in spatial neglect – a disorder in which patients behave as if the left half of their world has ceased to exist (Danckert & Ferber, 2006; Heilman, Watson, & Valenstein, 1993; Husain & Rorden, 2003; Mesulam, 1999). In contrast, lesions of the dorsal attention network in the SPL/IPS typically result in optic ataxia – a disorder in which visually guided reaching is disrupted (Perenin & Vighetto, 1988; Karnath & Perenin, 2005). The specific goal of the present thesis was to investigate the cognitive and neural mechanisms underlying the effects of prism adaptation (Section 1.4) – a visuomotor adaptation procedure – on reducing spatial attentional deficits in patients with parietal lesions.

5.1 Summary of research findings.

One way in which prism adaptation may benefit patients with neglect is by altering damaged attentional orienting mechanisms (Section 1.4.1). Results from Chapter 2 indicated that rightward prism adaptation reduced both the RT cost for leftward reorienting (i.e. the

disengage deficit) and the rightward attentional bias in a group of four RBD patients, two of whom had neglect. These findings have a number of important implications. First, they add further support to previous work (Berberovic, Pisella, Morris, & Mattingley, 2004; Striemer, Sablatnig, & Danckert, 2006) suggesting that prism adaptation influences visual attention. Second, the fact that prism adaptation reduced attentional deficits in RBD patients *without* neglect suggests that just as the disengage deficit and the rightward attentional bias are not restricted to neglect patients, neither are the beneficial effects of prisms. Finally, and perhaps most importantly, these results suggest that one of the ways in which prism adaptation may ameliorate neglect symptoms is by reducing both the disengage deficit and the rightward attentional bias, two of the hallmark attentional deficits in neglect.

Following the demonstration that prisms reduce attentional deficits following RBD, one key question that remained unanswered was in regards to the neural correlates supporting these beneficial effects. One candidate brain region that may be important for generating these beneficial effects is the SPL, a region which is not commonly damaged in neglect (Coulthard, Parton, & Husain, 2006), and is known to be important for controlling eye movements, reaching movements, and attention (for reviews see Andersen & Buneo, 2002; Colby & Goldberg, 1999; Corbetta & Shulman, 2002; Culham, Cavina-Pratesi, & Singhal, 2006). This makes the SPL an ideal region to integrate the visuomotor error signals generated during exposure to prisms with attentional control signals. Although the beneficial effects of prisms may depend on the SPL (Luaute et al., 2006), previous research has not extensively examined the effects of SPL lesions on the control of visual attention. Therefore Chapter 3 examined reflexive and voluntary covert attention in two patients with optic ataxia.

The results from Chapter 3 indicated that patients with optic ataxia were slower to

detect targets in their ataxic visual field regardless of cuing condition. More specifically, both patients had a disengage deficit and a rightward attentional bias similar to patients with neglect (e.g. Chapter 2), despite the fact that neither patient demonstrated any symptoms of neglect. Furthermore, both patients were very slow to *orient* attention towards their ataxic field on validly cued trials, a finding which is not always observed in neglect (Losier & Klein, 2001).

Importantly, a previous study by Friedrich and colleagues (Friedrich, Egly, Rafal, & Beck, 1998) suggested that the disengage deficit was related to TPJ damage, and that SPL lesions had no influence on reflexive attention or the disengage deficit (Section 1.1.3). The data from Chapter 3 challenge these conclusions and instead suggest that the dorsal attention network in the SPL/IPS (Section 1.4) is important for controlling both the orienting *and* reorienting of reflexive and voluntary attention. These findings are consistent with Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984) who originally linked the disengage deficit to SPL damage. In addition, these data are consistent with the notion that the IPS contains a salience map of contralateral space (Gottlieb, Kusunoki, & Goldberg, 1998; Kusunoki, Gottlieb, & Goldberg, 2000). That is, lesions of the SPL/IPS result in a decrease in the salience of stimuli appearing in the contralesional space which in turn impairs the ability of optic ataxia patients to orient towards those stimuli. These data also challenge the long held assumption that optic ataxia occurs independently from perceptual and attentional deficits (Pisella et al., 2007). Given that these patients have difficulty attending to stimuli that appear in the same visual field in which they exhibit visuomotor control problems it will be important for future research to determine to what degree these two deficits are related.

Finally, these data also suggest that deficits in visuospatial attention alone are not sufficient to explain the lack of awareness for contralesional stimuli in neglect as patients with optic ataxia can display the same attentional deficits, without displaying any neglect symptoms. Although neglect has traditionally been considered a disorder of spatial attention, several recent studies have demonstrated that neglect patients have a range of deficits including difficulty maintaining non-spatial attention over time (Husain, Shapiro, Martin, & Kennard, 1997), deficits in spatial working memory in non-neglected space (Ferber & Danckert, 2006; Husain et al., 2001; Pisella, Berberovic, & Mattingley, 2004), and problems estimating the passage of time itself (Danckert et al., 2007). This suggests that neglect involves a combination of deficits in both spatial attention and deficits that are not restricted solely to the neglected (left) visual field. The important point here is that deficits in visuospatial attention alone are considered to be insufficient to cause neglect. Instead, neglect is thought to result from a combination of both spatial attention deficits and 'non-spatial' or 'non-lateralized' deficits (for reviews see Danckert & Ferber, 2006; Husain & Nachev, 2007; Husain & Rorden, 2003).

The novel hypothesis put forward in Chapter 2 was that prism adaptation may reduce attentional deficits by influencing mechanisms in the SPL (Luaute et al., 2006), a region not commonly damaged in neglect. After establishing that damage to the dorsal attention network in the SPL/IPS did indeed result in attentional deficits identical to those of patients with neglect (i.e. Chapter 3), the work outlined in Chapter 4 intended to determine whether or not a patient with an SPL/IPS lesion could demonstrate the same *beneficial effects* of prisms as patients with neglect (i.e. Chapter 2). Results indicated that although CF was able to adapt to prisms, he failed to demonstrate any beneficial effects of prisms on his attentional

performance. Specifically, following prism adaptation there was no reduction in either his rightward attentional bias or his disengage deficit. These results support the notion that the SPL plays an important role in generating the beneficial effects of prisms on attention (Luaute et al., 2006).

5.2 Neural circuits underlying the beneficial effects of prism adaptation on attention in parietal patients.

As highlighted in the introduction, there is still a great deal of debate as to what specific function(s) the parietal cortex serves in controlling behaviour. Some authors emphasize the critical role the PPC plays in attention (Colby & Goldberg, 1999; Corbetta & Shulman, 2002; Driver & Mattingley, 1998), whereas others suggest that the PPC serves primarily as a sensorimotor interface for the control of actions (Andersen & Buneo, 2002; Buneo & Andersen, 2006; Buneo, Jarvis, Batista, & Andersen, 2002; Goodale & Milner, 1992; Milner & Goodale, 2006). Here it will be argued that prism adaptation affects attention primarily by influencing the dorsal vision-for-action pathway that extends from the primary visual cortex (i.e. V1) to the PPC – a pathway which is typically undamaged in neglect.

Prior to exposure to prisms many neglect patients demonstrate a shift in the egocentric reference frame such that subjective judgements of straight-ahead are shifted to the right of true centre (e.g. Rossetti et al., 1998). Realignment signals necessary for adjusting visuomotor commands to accommodate the shift induced by prisms are then generated in the ipsilateral cerebellum (Pisella et al., 2005) and transferred to left PPC (Clower et al., 1996; Clower, West, Lynch, & Strick, 2001; Pisella, Rode, Farné, Tilikete, & Rossetti, 2006). Any shift in straight-ahead judgements may then initially be the result of altered processing within this network. Additional after-effects, of the kind demonstrated for

covert attention here, may rely on redressing the imbalance between left and right SPL activity (Corbetta et al., 2005; Luaute et al., 2006). That is, realignment signals processed in left PPC that shift the egocentric reference frame to the left (a direct consequence of exposure to prisms) may then encourage the patient to explore more of left visual space – a process normally achieved by the right SPL. Thus, the beneficial effects of prisms on attention may arise as by-product of changes in exploratory motor behaviours which have been shifted leftwards (see Redding and Wallace, 2006).

Importantly, this theory can explain the findings in patient CF (Chapter 4) who has attentional deficits in his left (ataxic) visual field due to a right SPL lesion. Specifically, CF was able to adapt to the prismatic shift because his right cerebellum was intact, however he was not able to demonstrate significant beneficial effects of prisms either because leftward realignment signals were not able to influence processing within his damaged left SPL, or because any changes in spared regions of left PPC would have no influence on processing in the damaged right SPL. In short, this theory suggests that the SPL (left, right, or both) plays an important role in generating the beneficial effects of prisms.

5.2.1 Mechanisms subserving the influence of prism adaptation on attention.

Although the SPL may be critical for generating the beneficial effects of prisms by shifting exploratory motor and attentional biases leftward, the specific mechanism by which prisms induce beneficial effects on attention remains unclear. In this section a novel theory is put forward that explains the beneficial effects of prisms on attention through links between common neural circuits subserving motor control and shifts of attention in the dorsal attention network and the dorsal vision-for-action pathway in the SPL/IPS.

To reiterate, during rightward prism adaptation the participant must adjust their pointing movements *leftward* to compensate for the rightward shift in vision. This leftward shift in motor behaviours easily explains the beneficial effects of prism adaptation on tasks that require the patient to perform exploratory motor behaviours with their adapted hand such as manual line bisection, target cancellation, and figure copying (Farné, Rossetti, Toniolo, & Ladavas, 2002; Pisella, Rode, Farné, Boisson, & Rossetti, 2002; Rossetti et al., 1998). That is, using the adapted hand will encourage the patient to move further leftward thereby reducing line bisection errors, increasing the number of targets cancelled on the left, and allowing the patient to reproduce a greater number of details from the left side of figures they are asked to copy[9].

In addition, rightward prism adaptation has also been shown to shift exploratory eye movements leftward into neglected space (Dijkerman et al., 2003; Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003) and to reduce oculomotor biases (Angeli, Benassi, & Ladavas, 2004; Serino, Angeli, Frassinetti, & Ladavas, 2006) in patients with neglect. Importantly, such changes in eye movements may rely on common mechanisms and neural networks that subserve the beneficial effects of prism adaptation on covert attention. Rizzolatti and co-workers (Rizzolatti, Riggio, Dascola, & Umilta, 1987; Rizzolatti, Riggio, & Sheliga, 1994; Sheliga, Craighero, Riggio, & Rizzolatti, 1997; Sheliga, Riggio, & Rizzolatti, 1995) have argued in favour of a 'premotor' theory of attention which posits that covert shifts of attention are simply eye movements that are planned but not executed, thus reducing the cognitive act of directing one's attention covertly to an inherently motor process. Support for this theory comes from studies which have demonstrated that RTs to detect targets in a covert

[9] It is interesting to note that even though neglect patients are able to reproduce a greater number of details from the left sides of figures they are asked to copy, many of those details are still distorted, suggesting that their ability to copy the figures is still impaired following prism adaptation (see Figure 2a in Rossetti et al., 1998).

attention task are reduced when a saccade or reaching movement is required to the same location as the target, versus when the saccade or reach is directed to a location in the opposite direction (Sheliga, Craighero, Riggio, & Rizzolatti, 1997). Further support comes from studies which have shown that perceptual discrimination of targets is facilitated when a saccade or reach is planned to the target location versus a non-target location (Deubel & Schneider, 1996; Deubel, Schneider, & Paprotta, 1998).

It is possible that prism adaptation may influence the ability to reorient attention by altering circuits in the SPL/IPS that control the ability to plan and execute eye movements, even in circumstances in which the intended movement is not actually executed (i.e. covert shifts of attention). Specifically, if it is easier for patients to generate leftward eye movements following adaptation (e.g. Dijkerman et al., 2003; Ferber et al., 2003) then this could also influence the ability to *plan* leftward eye movements which according to Rizzolatti and colleagues (Rizzolatti, Riggio, Dascola, & Umilta, 1987; Rizzolatti, Riggio, & Sheliga, 1994; Sheliga, Craighero, Riggio, & Rizzolatti, 1997) is the process by which covert shifts in attention occur.

Although prism adaptation can reduce attentional deficits and improve performance on clinical tests of neglect, not all aspects of neglect are aided by prisms. Ferber and colleagues (2003) examined one patient with neglect who explored, via eye movements, only the right side of chimeric faces (faces depicted as smiling on one side, with a neutral expression on the other) prior to exposure to prisms. The patient demonstrated the classic perceptual bias observed in neglect on this task (Mattingley et al., 1993), such that he chose faces depicted as smiling on the right half as appearing ‘happier’ on 96% of trials. After prisms there was a dramatic leftward shift in exploratory eye movements so that he now

explored previously neglected regions of the chimeric faces. Despite this improvement he continued to exhibit the same perceptual preference for choosing faces smiling on the right as appearing happier, just as he had done prior to prisms (Ferber, et al., 2003; see also Dijkerman et al., 2003). These findings provide striking evidence that prism adaptation can influence exploratory motor biases (i.e. eye movements) without altering perceptual biases.

Importantly, the dissociation between the beneficial effects of prisms on exploratory motor biases but not perceptual biases highlights an important insight into the mechanisms underlying the effects of prisms in neglect. Specifically, the dissociation suggests that prisms may influence attention via motor circuits in the SPL/IPS, but may fail to alter perceptual biases that are likely being driven by interactions between spatial attention mechanisms in the SPL/IPS, and perceptual processes controlled by the ventral visual stream in the inferior temporal cortex. Importantly, the IPL/TPJ is thought to play a crucial role in integrating information from the dorsal and ventral visual streams (Husain & Nachev, 2007; Milner & Goodale, 2006). Given that damage to the IPL/TPJ results in neglect, and therefore disrupts integration between the dorsal and ventral visual streams, prisms may be able to influence attention and exploratory motor biases through the dorsal vision-for-action stream, but may fail to alter perceptual biases subserved by ventral stream mechanisms or at the very least reliant on interactions between the dorsal and ventral visual streams.

5.3 Directions for future research.

The research findings presented in the current thesis could serve as the impetus for several future lines of research. The findings from Chapter 2 indicated that prism adaptation reduced deficits in reflexive attention in RBD patients. It would also be of interest to examine

the effects of prism adaptation on voluntary covert attention (i.e. using a predictive central arrow cue) in order to determine whether or not the effects of prisms are specific to reflexive attention as the current research seems to imply, or if the beneficial effects of prisms also extend to voluntary modes of orienting. If the beneficial effects of prisms extended to voluntary covert attention it would be consistent with the theory that the effects of prisms in neglect arise via interactions between the dorsal vision-for-action pathway and the dorsal attention network in the SPL/IPS which is thought to control the allocation of attention – both reflexively and voluntarily – to a particular location in space (Chapter 3; Corbetta & Shulman, 2002).

A previous study by Morris and colleagues (2004) found no beneficial effects of prisms on visual search in neglect which could be construed as evidence that prisms do not influence voluntary attention. However, patients with neglect also have deficits in spatial working memory in non-neglected space that may underlie their poor performance on visual search tasks (Ferber & Danckert, 2006; Husain et al., 2001). Specifically, during cancellation and search tasks patients with neglect will continuously 'revisit (i.e. re-fixate)' previously searched target locations treating them as new locations. Importantly, the number of revisits correlates with the number of missed targets on the left half of the search display. That is, the greater the number of revisits to previously searched target locations, the greater the number of items omitted on the left side of the cancellation or search task (Husain et al., 2001). Thus, it may be the case that the lack of beneficial effects of prisms in visual search (Morris et al., 2004) may stem from the inability of prisms to influence spatial working memory, and not from an inability to influence voluntary attention per se. This prediction could be tested by conducting a study that examines the influence of prisms on visual search in neglect while

monitoring patients' eye movements. If the absence of beneficial effects of prisms in visual search is related to revisiting behaviour (an indicator of poor spatial working memory performance), then patients with neglect should continue to revisit previously searched target locations following prism adaptation. Interestingly, given previous work demonstrating dissociations between exploratory eye movements and perceptual biases post prisms (Dijkerman et al., 2003; Ferber et al., 2003), one might also expect that a greater portion of the left side of visual search displays would be explored post prisms, while target detection on the left and revisiting behaviour remain unaltered.

The results from Chapter 3 indicated that the SPL/IPS is important for controlling the orienting and reorienting of both reflexive and voluntary attention. These results are intriguing because even though the patients tested in the study had no clinical signs of neglect, they have the *same attentional deficits* as patients with neglect, without the loss of awareness for contralesional stimuli that is characteristic of neglect. These data provide an interesting perspective on the organization of the parietal cortex. Whereas previous studies suggested that reflexive attention and the disengage deficit were related specifically to the TPJ (Friedrich et al., 1998), these data suggest instead that the SPL/IPS (i.e. the dorsal attention network) plays an important role in the control of visual attention. However, the IPL/TPJ (i.e. the ventral attention network) which is damaged in neglect must subserve a different function that, when damaged, results in problems with visual awareness, and not specifically visual attention (for a review see Husain & Nachev, 2007). In order to obtain a more thorough understanding of the functional organization of the PPC future studies could benefit by directly contrasting performance on tasks that measure different aspects of spatial attention, as well as 'non-spatial' or 'non-lateralized' functions (e.g. sustained attention, time

perception; Danckert et al., 2007; Husain et al., 1997) in patients with neglect and patients with optic ataxia without signs of neglect. These studies could help provide important insights into the functional roles of different regions of the PPC, as well as the pathophysiology of neglect and optic ataxia.

One other important finding from Chapter 3 was the fact that contrary to previous work which has argued that optic ataxia is a disorder independent from any perceptual or attention deficits (e.g. Perenin & Vighetto, 1988), both CF and ME were clearly impaired at orienting and reorienting attention towards their ataxic visual field. Importantly, it may be the case that these patients' difficulties with reaching and grasping in the periphery are related, in part, to deficits in visual attention. Specifically, these patients may be unable to reach towards targets in the periphery because they are unable to adequately attend to them (Pisella et al., 2007). Therefore, future studies should examine the relationship between deficits in visual attention and reaching errors in the ataxic visual field in patients with optic ataxia.

Finally, in the current chapter it was argued that the beneficial effects of prisms in neglect result primarily from the influence of prisms on neural circuits subserving attention and motor control in the SPL/IPS. A number of testable hypothesis emerge from this. Specifically, if prism adaptation influences neglect symptoms by altering circuits in SPL/IPS that control attention and action then, prism adaptation should be able to decrease other symptoms of neglect that involve a directional motor component. For example, many patients with neglect are slower to initiate leftward than rightward movements, a deficit which has been termed 'directional hypokinesia' (Coulthard, Parton, & Husain, 2006; Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Mattingley, Bradshaw, & Phillips, 1992; Mattingley, Husain, Rorden, Kennard, &

Driver, 1998). If prism adaptation influences mainly visuomotor processes then prisms should enable neglect patients to initiate leftward movements more quickly thereby reducing directional hypokinesia. Alternatively, prism adaptation should have relatively little influence on the so called ‘non-spatial’ or ‘non-lateralized’ deficits which may not be linked directly to visuomotor processes. Specifically prism adaptation should have minimal effects on spatial working memory (Ferber & Danckert, 2006; Husain et al., 2001), sustained temporal attention (Husain, Shapiro, Martin, & Kennard, 1997; Robertson et al., 1997), or time estimation deficits (Danckert et al., 2007).

In short, data from the present thesis have led to a number of important discoveries which will serve as a catalyst for future studies that will help determine the cognitive and neural organization of the PPC, as well as the pathophysiology of neglect and optic ataxia.

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