Perceptual and Memory Deficits in Unilateral Neglect

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

Unilateral neglect is a disorder in which patients behave as if the left half of space has ceased to exist. The disorder typically arises from right hemisphere brain damage involving the inferior parietal and superior temporal cortices. Classic models of neglect have suggested that the disorder represents impaired attentional functioning. More recently, research has suggested that the heterogeneous symptoms of neglect can not be fully explained by attentional deficits alone. This thesis first examined performance on both visual working memory and attention tasks in patients with right brain damage, some of whom presented with neglect. Results showed severe deficits in both domains. Next, prism adaptation, a treatment long understood to improve attention in neglect, was used to examine whether the technique could improve performance in domains not specifically related to attention. Results showed that prisms failed to meaningfully improve severe deficits in time perception and spatial working memory. Such deficits outside spatial attention may be the result of damage to perceptual systems. The final experimental chapter examined the potential for saccadic adaptation, an analogue of prism adaptation previously shown to induce some perceptual change, to influence both perception and action in ways relevant to neglect. Here, healthy individuals performed the classic saccadic adaptation paradigm, with performance on a line bisection and landmark task used as indices of action and perception respectively. The task was not found to measurably influence either domain. Overall, the thesis supports recent research that claims that neglect involves independent deficits, involving more than attention. Specifically, it provides evidence that working memory and perceptual deficits are not strongly coupled to spatial attention.

Dedication

This is dedicated my ever supportive wife, Annette.

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Chapter 1

General Introduction

Unilateral spatial neglect is a disorder commonly resulting from damage to the right inferior parietal or superior temporal cortex (Vallar & Perani, 1986; Karnath, Ferber & Himmelbach, 2001; Karnath & Rorden, 2012; Mort et al., 2003; Buxbaum et al., 2004; Verdon, Schwartz, Lovblad, Hauert & Vuilleumier, 2010). Spatial neglect is characterized by a heterogeneous collection of deficits, the most prominent of which is an inability to respond to information on the contralesional side of space (Driver & Mattingley, 1998; Halligan, Fink, Marshall & Vallar, 2003; Heilman, Watson & Valenstein, 1993). People with the disorder are spatially biased away from contralesional space in their search behaviour (Husain et al., 2001; Wojciulik, Husain, Clarke & Driver, 2001), grooming and eating (Halligan et al., 2003; Kerkhoff, 2001), drawing (Halligan, Marshall & Wade, 1989), posture (Rode, Tiliket & Boisson, 1997), and perceptual judgment of spatial extent (Dijkerman et al., 2003; Striemer & Danckert, 2010a). The disorder is debilitating, and is associated with poor rehabilitative outcomes (Cassidy, Lewis & Gray, 1998; Ringman, Saver, Woolson, Clarke

& Adams, 2004). Less than half of patents show improvements in the weeks after a neglect inducing stroke, and a small minority fully recover (Farnè et al., 2004).

Most theoretical accounts of the neglect syndrome describe it as either a deficit of the deployment of spatial attention, or one of impaired awareness. More specifically, either an inability to report, respond, or orient attention toward stimuli in left space (Driver & Mattingley, 1998; Halligan et al., 2003; Heilman et al., 1993), or a general loss of environmental awareness that can at it's most extreme, cause a person to act as if the entire contralesional half of their world has ceased to exist (Mesulam, 1981). The spatial-attention based model does a good job of explaining many of the deficits displayed on clinical tests of neglect. For example, object cancellation (a variant of visual search tasks) and figure copying are arguably influenced by the patient's ability to deploy attention across the page. Where attention cannot effectively be directed, mistakes or omissions are made. For example, the line-bisection task — in which the patient is asked to place a mark at the perceived midpoint of a horizontal line — an inability to attend to the left endpoint is a plausible explanation for impaired performance (Typically marks are placed a long way to the right of true centre; Wilson, Cockburn & Halligan, 1987).

Attentional accounts of neglect typically invoke two kinds of impairment; first, an ipsilesional bias such that attention is preferentially oriented toward right space, and second, a reorienting deficit such that neglect patients have difficulty disengaging attention from stimuli in right space in order to reorient towards the left. Originally associated with the related phenomenon of extinction — the failure to report a contralesional stimulus when presented simultaneously with an ipsilesional stimulus — the 'disengage deficit' describes a general attentional "stickiness" where-by rightward stimuli attract and capture attention

to the exclusion of leftward stimuli (for a review, see Losier & Klein, 2001). Posner and colleagues 1984 used a covert orienting task in which participants must detect peripheral targets that can be validly or invalidly cued (i.e., cue and target presented at the same or opposite locations respectively; Posner, 1980). On this task, neglect patients are disproportionately slower to respond to left sided targets following a right sided cue — as if they have trouble disengaging from a right sided cue. Similarly, in a visual search task, performance in contralateral space is driven by the number of ipsilesional distractors (Eglin, Robertson & Knight, 1989). This coincides with a general body of research that supports the notion that a crucial function of the right inferior parietal cortex is to disengage attention from its current focus and reorient toward a new, salient location (for a review, see Corbetta, Kincade & Shulman, 2002; and Corbetta & Shulman, 2011).

Given the debilitating nature of the disorder a broad range of rehabilitation protocols have been attempted (for a review, see Luauté et al., 2006). Perhaps because of the heterogeneity of the symptom profile in neglect, most rehabilitation strategies have met with varied success (Danckert & Ferber, 2006). Both caloric stimulation, in which water, often ice-cold, is injected into the patient's ear canal, and neck muscle vibration, quickly orient the patient's torso, head, eyes, and attention to the stimulated side, reducing several of the behavioural deficits for a short time (~20 minutes; Adair, Na, Schwartz & Heilman, 2003; Karnath, Christ & Hartje, 1993; Karnath, Fetter & Dichgans, 1996; Rubens, 1985). Unfortunately, these exercises are aversive and their short-term effects prevent them from being useful as treatments. A much more promising rehabilitation technique based on prismatic glasses has more recently been shown to have broader, and longer lasting effects in neglect (Rossetti et al., 1998; Rossi, Kheyfets & Reding, 1990). When patients with

neglect are adapted to a rightward visual shift, the after-effects on several behavioural measures are profound, and last considerably longer than the adaptation period (Farnè, Rossetti, Toniolo & Làdavas, 2002; Frassinetti, Angeli, Meneghello, Avanzi & Làdavas, 2002; Pisella, Rode, Farnè, Boisson & Rossetti, 2002; Rossetti et al., 1998). Judgment of straight-ahead and line bisection performance becomes closer to true centre, object cancellation, and figure copying improves (Rossetti et al., 1998). Beyond these clinical tests, exploratory eye movements demonstrate a reduction in rightward bias (Danckert & Ferber, 2006; Ferber, Danckert, Joanisse, Goltz & Goodale, 2003), and even visual imagery (Rode, Rossetti & Boisson, 2001), and postural balance (Tilikete et al., 2001) are improved by the technique.

Despite the long list of symptoms that prisms have been shown to ameliorate, more recent randomized controlled trials have failed to show prisms as an efficacious rehabilitation treatment (Nys, De Haan, Kunneman, De Kort & Dijkerman, 2008; Turton, O'Leary, Gabb, Woodward & Gilchrist, 2010). Additionally, when an effort is made to examine attention and perception more directly, the ameliorative effects seem to be somewhat less clear. Some direct measures of attentional biases have been shown to be affected by prisms, such as covert shifts of attention (Striemer & Danckert, 2007; Nijboer, McIntosh, Nys, Dijkerman & Milner, 2008), and extinction (Serino, Bonifazi, Pierfederici & Làdavas, 2007), while other, perhaps more naturalistic measures of attention, such as serial visual search, have failed to show an effect (Morris et al., 2004). Similarly, while several studies have shown that prisms induce a shift in voluntarily eye movements towards previously neglected space, perceptual judgments can remain just as biased toward right space as before (Dijkerman et al., 2003; Ferber et al., 2003). Taken together this research suggests

there is a dissociation between occulomotor "looking" and perceptual "seeing," with prisms restoring the former but not the latter (Striemer & Danckert, 2010b).

The dissociation between after effects that influence actions and those that influence perception invokes the dual visual pathways hypothesis of Goodale and Milner (Milner & Goodale, 2006). Information from primary visual cortex (V1) projects to two streams, one projecting to the superior, posterior parietal cortex that is important for the visual guidance of action (the so-called dorsal 'how' pathway) and another that projects from V1 to inferotemporal cortex and is important for perceptual processing (the so-called ventral 'what' pathway; Milner & Goodale, 2006). Prisms have been shown to primarily influence processing within the dorsal stream (Luauté et al., 2006; Danckert, Ferber & Goodale, 2008; Corbetta, Kincade, Lewis, Snyder & Sapir, 2005; Clower et al., 1996). In this framework, prisms will primarily influence behaviours supported by the superior parietal lobule and intraparietal sulcus, areas well within the dorsal stream that are typically undamaged in neglect. Instead, damage to the inferior parietal/superior temporal gyrus leads not only to the neglect syndrome, but also severely reduces (or even eliminates) the brain's ability to integrate dorsal and ventral stream processing (Striemer & Danckert, 2010b). Similarly, given that prisms operate primarily on the dorsal stream, this is likely to limit the influence the technique can have on functioning within the ventral system responsible for higher level perceptual judgments. This thesis outlines three experiments chosen to examine perceptual biases, as well as related working memory deficits, with the goal of providing insight into the greater breadth of cognitive deficits underlying neglect beyond spatial attention.

Experiment 1 explores the relationship between visual working memory and spatial at-

tention in neglect. It examines the hypothesis that these two domains represent separate, but interacting deficits. Experiment 2 employs prism adaptation in right brain damaged (RBD) participants to explore the effects of prisms on two domains — spatial working memory and temporal estimation — that are critical for developing accurate perceptual representations of the world. This chapter contributes to the growing evidence that prisms fail to influence domains of processing important for the construction of perceptual representations. Experiment 3 develops a procedure for using saccadic adaptation to explore the possibility that modifying eye position sense would lead to more generalized change in perceptual and motor biases. This preliminary work was conducted in healthy individuals.

The evidence presented in this thesis expands on previous work that has identified deficits in neglect that purportedly go beyond dorsal, spatial attention networks (Striemer & Danckert, 2010b; Robertson et al., 1997; Husain, Shapiro, Martin & Kennard, 1997). Here, working memory and temporal perception are demonstrated to be impaired in patients with right brain damage, many of whom presented with symptoms of neglect, and these deficits do not appear to be strongly linked to performance on spatial attention tasks. Specifically, working memory impairments, including memory of visual characteristics like colour or colour-location bindings, are degraded in the patients, and not in ways predictable from their attention deficits. Further, prism adaptation, a procedure known to have an effect on spatial action systems, did not produce reliable improvement in the large spatial working memory and time perception deficits observed in the patients. Lastly, saccadic adaptation successfully altered eye movement parameters, but was not found to influence perceptual or motoric judgments of centre in the healthy participants. The potential future research directions involving saccadic adaptation, and more generally, the observed percep-

tual and working memory deficits, are discussed, with the focus on better understanding the breadth of underlying cognitive deficits in neglect.

Chapter 2

Exploring the relationship between visual working memory and attention in neglect.

As discussed earlier, most traditional models of neglect describe the disorder as a deficit of spatial attention. A disorder driven by a difficulty in disengaging attention away from stimuli and events in right-space (Posner, Walker, Friedrich & Rafal, 1984), an attentional 'stickiness' that results from disruption to inferior parietal cortex — a region known to be important for effective attentional disengagement and re-orienting (Corbetta et al., 2002). This characterization of neglect as an attentional disorder, however, does not fully capture the range of symptoms observed in neglect — particularly on tasks that are not direct measures of attention, and for which performance may be degraded for other reasons. For

example, lateralized failures on object cancellation tasks (i.e., omissions of left-sided targets) could be couched as a consequence of a spatial attention deficit. However, revisiting behaviour (i.e., re-cancelling old targets as if they were new), commonly observed on the non-neglected, 'good' side of space (Husain et al., 2001; Parton et al., 2006), suggest something more nuanced is occurring. Even eliminating targets as they are cancelled, thereby removing their potential to re-capture attention, improves but does not fully remediate revisiting behaviour on the task (Mark, Kooistra & Heilman, 1988).

In fact, a great deal of research over the past few decades has highlighted aspects of neglect that clearly go beyond spatially lateralized deficits of attention. For example, neglect patients tend to have difficulties with sustained attention (Robertson, Tegnér, Tham, Lo & Nimmo-smith, 1995), even when operating in a non-spatial modality (Robertson et al., 1997). For example, the attentional blink — a measure of temporal, selective attention — is exaggerated in neglect. When presented with a rapid series of stimuli with two embedded targets separated by varying temporal intervals, neglect patients require up to three times as much time, relative to controls, between targets in order to identify both correctly (Husain et al., 1997). In addition to these non-lateralized attention deficits, recent work has highlighted deficits of spatial working memory for stimuli in central or right, putatively non-neglected space (Husain et al., 2001; Danckert & Ferber, 2006; Malhotra et al., 2005; Striemer, Ferber & Danckert, 2013).

Non-lateralized selective attention, and sustained attention, are strongly correlated with both neglect severity and recovery over time (Husain & Rorden, 2003). Further, remediation of these non-spatial deficits can improve spatial neglect symptoms (Robertson et al., 1995). This has lead some to go so far as to speculate that the non-spatial deficits are

the driving factor behind the persistence and clinical relevance of neglect (Husain & Rorden, 2003). In other words, a bias in spatial attention is overcome by the brain's adaptive mechanisms, *unless* it is accompanied by other deficits of attentional deployment that prevent the brain from recognizing the errors. More conservatively, these recent discoveries indicate that, despite the fact that lateralized attentional deficits seem to represent a cornerstone feature of the neglect syndrome, they, alone, fail to compose a complete picture of the disorder.

Furthermore, recent attempts at rehabilitating neglect have shown that while spatial attention can be improved, a range of perceptual biases remain unaltered. As noted earlier, several aversive and invasive treatments intended to trigger attentional re-orienting to left space have been tried, with little clinical effectiveness. The most promising treatment has been prism adaptation, because it is non-aversive, and because it has been shown to produce effects lasting much longer than the treatment duration (Rossetti et al., 1998; Farnè et al., 2002; Frassinetti et al., 2002). Unfortunately, while prism adaptation produces striking changes in spatial attention (Striemer & Danckert, 2007; Nijboer et al., 2008), researchers have begun to recognize an increasing number of neglect deficits that are not improved by prism adaptation (Rousseaux, Bernati, Saj & Kozlowski, 2006; Striemer & Danckert, 2010b). Many of these findings make use of perceptual tasks, such the perceptual judgment of spatial extent (Dijkerman et al., 2003; Striemer & Danckert, 2010a), and chimeric faces tasks(Ferber et al., 2003; Sarri, Kalra, Greenwood & Driver, 2006). It may be the case then that prisms operate on neural systems important for the deployment of attention, but have little to no effect on those mechanisms needed to form accurate perceptual representations.

Part of the deficit involved in maintaining accurate perceptual representations may be driven by working memory impairments. As mentioned earlier, neglect patients have deficits of spatial working memory generally, even in "non-neglected," right or central space (Husain et al., 2001; Danckert & Ferber, 2006). In this context, it is important to clarify the relationship between spatial working memory and spatial attention. The two systems appear to be independent and functionally unique, generally residing in ventral and dorsal visual systems, respectively, although there is some functional overlap and mutual interaction (Awh & Jonides, 2001). Specifically, in healthy people, mechanisms of spatial attention provide a rehearsal-like function to maintain information held in working memory (Awh & Jonides, 2001).

This arguably creates three possible causes of the apparent spatial working memory problems in neglect; namely, that they may actually be directly caused by attention deficits, they may be caused by the disruption of access to attentional resources by working memory systems, or, finally, they may arise independently, from damage to regions specifically necessary for working memory function. In the first case, it is possible that the neurological architecture of working memory is healthy, but spatial attention deficits prevent patients from performing adequately on the tasks, producing the appearance of spatial working memory deficits. This seems less-likely, as patients maintain the ability to orient to rightward and central targets effectively. However, we can not rule out the possibility that subtle pathological orienting deficits exist for central and right space that, in turn, impact upon spatial working memory. If this was the case, though, we might expect these deficits to improve as a result of improvement in attention deficits, and this does not appear to be the case (Striemer & Danckert, 2010b; Striemer & Danckert, 2010a; Ferber et al., 2003;

Sarri et al., 2006). In the second case, of disrupted access to attention by working memory networks that would then prevent patients from utilizing spatial attention as a rehearsal mechanism. This could be due to a compromise of the dorsal and ventral stream connectivity, arising from the neglect-inducing lesion. Unlike the case of direct causation described above, if disrupted communication between the two systems is the problem, improvement in spatial attention may not have any impact on spatial working memory deficits. The third possibility, where working memory deficits are fully independent of spatial attention deficits, would have this same property, and therefore, cannot be clearly differentiated from a problem of disconnection in the existing research.

To overcome this problem, a new version of the working memory task was created to minimize the possible reliance on spatial attention rehearsal mechanisms. Rather than asking participants to remember and recall strictly spatial information, memory for target colour (or a combination of colour *and* spatial location), was tested. Placing the primary requirement of the task on colour processing reduces reliance on spatial attention and places any possible rehearsal mechanism requirements within the ventral stream, reducing the likelihood that measured deficits would be the result of the hypothesized disrupted communication between the dorsal and ventral streams. If attention and working memory deficits are indeed independent in neglect, then deficits of a similar degree of severity would be expected on this task as have been seen in past research employing a purely spatial WM task. That is, WM deficits will be evident even when the involvement of spatial attention is low.

2.1 Method

2.1.1 Participants

Patients and controls performed a standard covert orienting task as a measure of spatial attention and a visual working memory task (both described below). The covert orienting task was performed by two groups, a group of eight neurological patients, recruited from the Neurological Patient Database (Funded through the Heart and Stroke Foundation of Ontario, https://uwaterloo.ca/neurological-patient-database), who showed symptoms of neglect in pre-testing (3 male, 2 left handed, mean age of 66; Table 2.1), and a healthy older control group of eight individuals recruited from the University of Waterloo's Research on Aging Participant pool (3 male, handedness untested, mean age of 74). All of the neurological patients were at least 9 months post injury. The study was approved by the University of Waterloo's Office of Research Ethics, and the Tri-Hospital Research Ethics board. The two groups were not strictly age-matched, but did not significantly differ with respect to age ($t(12.5) = 1.8$, $p = 0.10$). The visual working memory task was performed by these same two groups plus an additional control group of 9 healthy young adults recruited from the University of Waterloo's Research Experience Group, and were compensated for participation with course credit (6 Females, mean age of 20).

Patients were also tested for signs of neglect using three standard clinical tests: line bisection, star cancellation, and figure copying (Wilson et al., 1987). Figure copying was coded qualitatively as having or lacking signs of neglect. For the bisection task, participant's bisection marks were recorded as deviations from centre as a percentage of total

line length. Impaired performance was defined as a bias of greater than 5% of line-length. For star cancellation, the percentage of missed targets on the left side of the page was recorded, and impaired performance was defined as $> 10\%$ omission of left-sided targets. Three of the patients scored as impaired on all tasks, and these participants also scored highest quantitatively on the bisection and cancellation tasks (Table 2.1). Only one patient no longer demonstrated neglect on any task at time of testing.

2.1.2 Apparatus and Procedure

Visual Working Memory Task

The visual working memory task was a modification of the one used by Emrich and Ferber (2012). It was presented on a Dell Latitude D820 Laptop with Windows XP and executed by Matlab on the built-in 8.5x13" screen. Instead of squares and a colour wheel surrounding central fixation, as used by Emrich and Ferber (2012), the colour wheel was replaced with a vertical colour bar and all stimuli appeared to the right of centre in order to minimize the impact of spatial attention deficits on working memory performance (Figure 2.1).

A trial sequence for the visual working memory task was as follows: a fixation cross was presented for 500ms, followed by a memory sample which consisted of either 1, 2, or 3 squares of different colours presented, vertically aligned, to the right of fixation for 500ms. The coloured squares could appear in any one of 16 different locations in the vertical column. Following the memory sample, a blank delay, containing only the fixation cross, was displayed for 1000ms. Following the delay, a probe display was presented that consisted of the colour bar and black outlines of the previously presented squares acting

	Age	Sex	Handedness	CES	VWM(1)	VWM(2/3)	Stars	Copying	Bisection
487	61	F	Right	23.0	0.15	0.04	0	+	2.2
35	51	F	Right	27.0	0.15	0.04	17	+	0.1
489	66	M	Left	31.0	0.25	0.08	0	+	1.0
171	71	F	Left	112.0	0.13	0.00	0	-	1.4
454	70	M	Right	221.5	0.23	0.17	0	+	6.3
213	65	F	Right	NA	0.2	0.30	100	+	7.3
396	85	M	Right	NA	0.3	0.55	87	+	8.1
465	63	F	Right	NA	0.3	0.45	97	+	12.9

Table 2.1: Table presents demographic data, measures of attention (CES) and visual working memory, as well as performance on the three clinical measures of neglect by the patient group (described in Results). "CES" indicates the leftward cue-effect-size on the COVAT test (RT difference between valid and invalidly cued leftward targets). "VWM(1)" is the average probability a patient guesses the target colour in the single target condition (increased values indicate more guessing). "VWM(2/3)" is the average probability a patient selects one of the distractor colours (high values indicate a colour-location binding deficit). Values for "Stars" are coded as the percentage of leftward stimuli missed on the Star Cancellation task. Neglect observed in figure copying is coded as a "+" under "Copying." Line bisection performance is recorded as the bias, in terms of percentage of line length, with positive values indicating rightward bias, under "Bisection."

as placeholders, marking the locations of the previously presented memory sample (i.e., probes did not contain any colour information; Figure 2.1) One of the placeholders was identified as the target by a bold-ed outline, distinguishing it from the non-targets (A line thickness of 8 pixels vs. 4 pixels). Participants were asked to indicate, by external mouse input, the colour of the initial square indicated by the bold-ed placeholder (Figure 2.1). Unlimited time was given, and the participant could make changes to their response an unlimited number of times until they were satisfied they had accurately indicated the colour. Note that in the single square condition, there were no non-target squares, and there would only be one outline, so the task was essentially to remember the colour of a single stimuli without any need to remember locations. In the two and three square conditions, only one of the two or three probes was highlighted, and the participant would be required to recall the colour of the target that had been presented at that particular location (Figure 2.1).

Covert Orienting of Attention Task

The covert orienting task (Posner (1978); Posner (1980)) was identical to that used by Striemer and Danckert (2007) and was run on the same computer as the visual working memory task described above. It was programmed and run in Superlab (Cedrus Software). Participants were presented with 100 trials. A single trial sequence consisted of a fixation cross with peripheral landmarks (empty green circles 12° to right and left of centre, each subtending 2°). This stimulus was followed by the appearance of a peripheral cue (1050–1550ms), which consisted of the brightening of one landmark. After an SOA of 50 or 150ms, targets, which consisted of red circles presented within the landmark, appeared either at

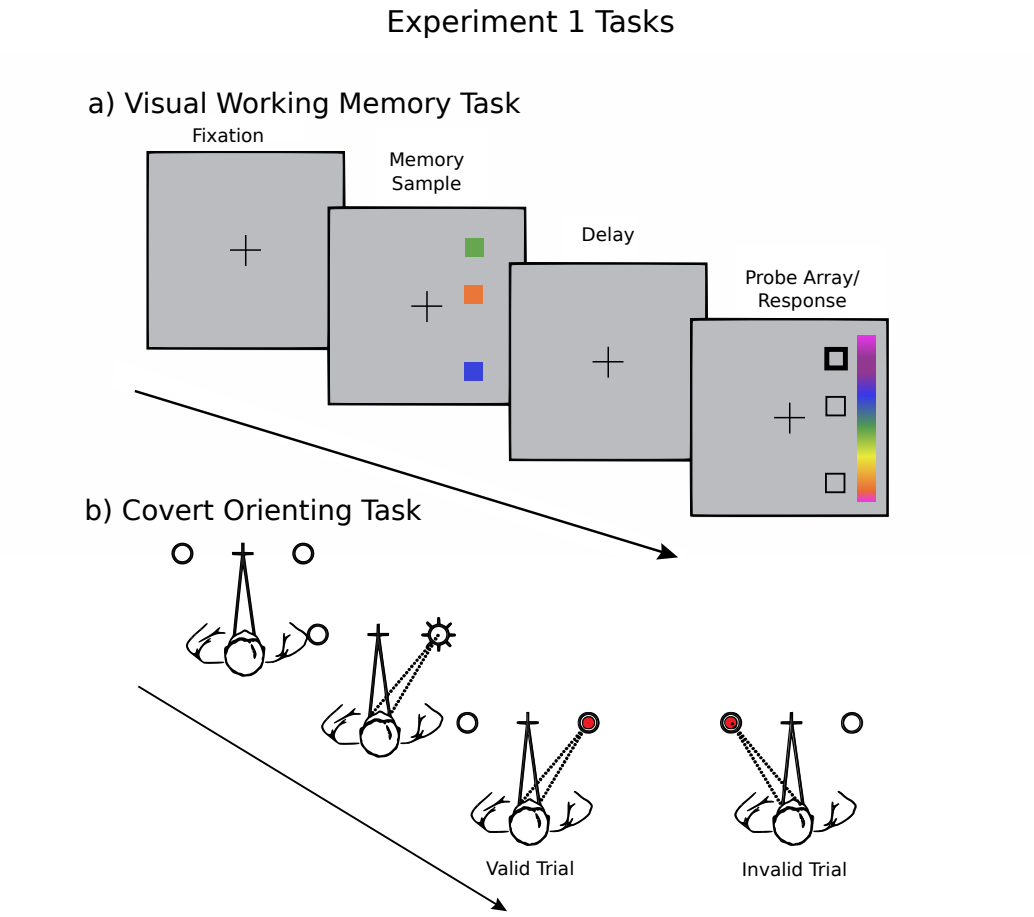


Figure 2.1: Figure depicts both visual working memory (above) and covert orienting (below) tasks. The three-square condition of visual working memory task is depicted.

the cued location (valid trials) or at the opposite location (invalid trials; Figure 2.1). Cues were non-informative, and 20% of trials were non-cued (40 validly cued trials, 40 invalid trials, and 20 non-cued trials, per participant). Targets appeared equally often on the left and right sides. Participants maintained fixation throughout the task. This was monitored by the experimenter and verbal feedback was given periodically to encourage participants to maintain fixation.

2.1.3 Data Analysis

Visual Working Memory Task

The visual working memory task recorded the exact colour value selected by the participant. From this, several measures were calculated: the probability that the response represented an attempt at selecting the correct colour (P_T), one of the non-target colours (P_{NT}, in the two and three square conditions), or simply represented a random guess (P_G), was calculated with the probabilistic model described in Emrich and Ferber (2012) and Bays, Catalao and Husain (2009) (Figure 2.2).

For each trial, these measures were calculated based on the physical location of the participant's response relative to the true colour of the target square on the colour bar. First, a probability that the participant indicated the correct target colour, P_T, was made relative to the magnitude of the location on a Gaussian distribution centred around the exact target colour. If the trial type included more than one initial box, then the probability that the response was made to a non-target, P_{NT}, was calculated in the same way but based on the colours of the non-target squares. Lastly, the probability that the patient guessed

randomly is based on a flat distribution, however the above distributions were chosen so that this was effectively the remainder (i.e., $P_G = 1-(P_T+P_{NT})$). To compute an estimate of the precision of target responses, the SD of the probability model used to compute the above three components was also recorded. This provides a measure of the spatial response precision of those trials where the patient successfully recalls and reports a viewed colour (i.e., P_T and P_{NT}), providing a basic measure of perceptual-motor ability, relevant to the task.

Covert Orienting of Attention Task

For the covert orienting task, response times were recorded and cue-effect sizes (CES) were calculated for each trial category to measure the effects of leftward and rightward re-orienting. Leftward cue-effect size, the measure of importance with regards to neglect, was calculated by subtracting reaction times (RTs) to validly cued, right-sided targets from RTs to invalidly cued, left-sided targets, separately for each SOA. Both trial types involve right-sided cues, and the difference represents the increased latency required to re-orient attention leftward.

Significance was defined as $p < 0.05$ throughout the thesis. Where independent samples t tests are used, unless otherwise specified, the Welch approximation of the degrees of freedom for unequal variance was used. Except where noted, all analysis was completed using R(R Core Team, 2014), with various additional packages (Wickham & Francois, 2015; Lawrence, 2013; Wickham, 2007; Konietschke, Placzek, Schaarschmidt & Hothorn, 2014; Wickham, 2009).

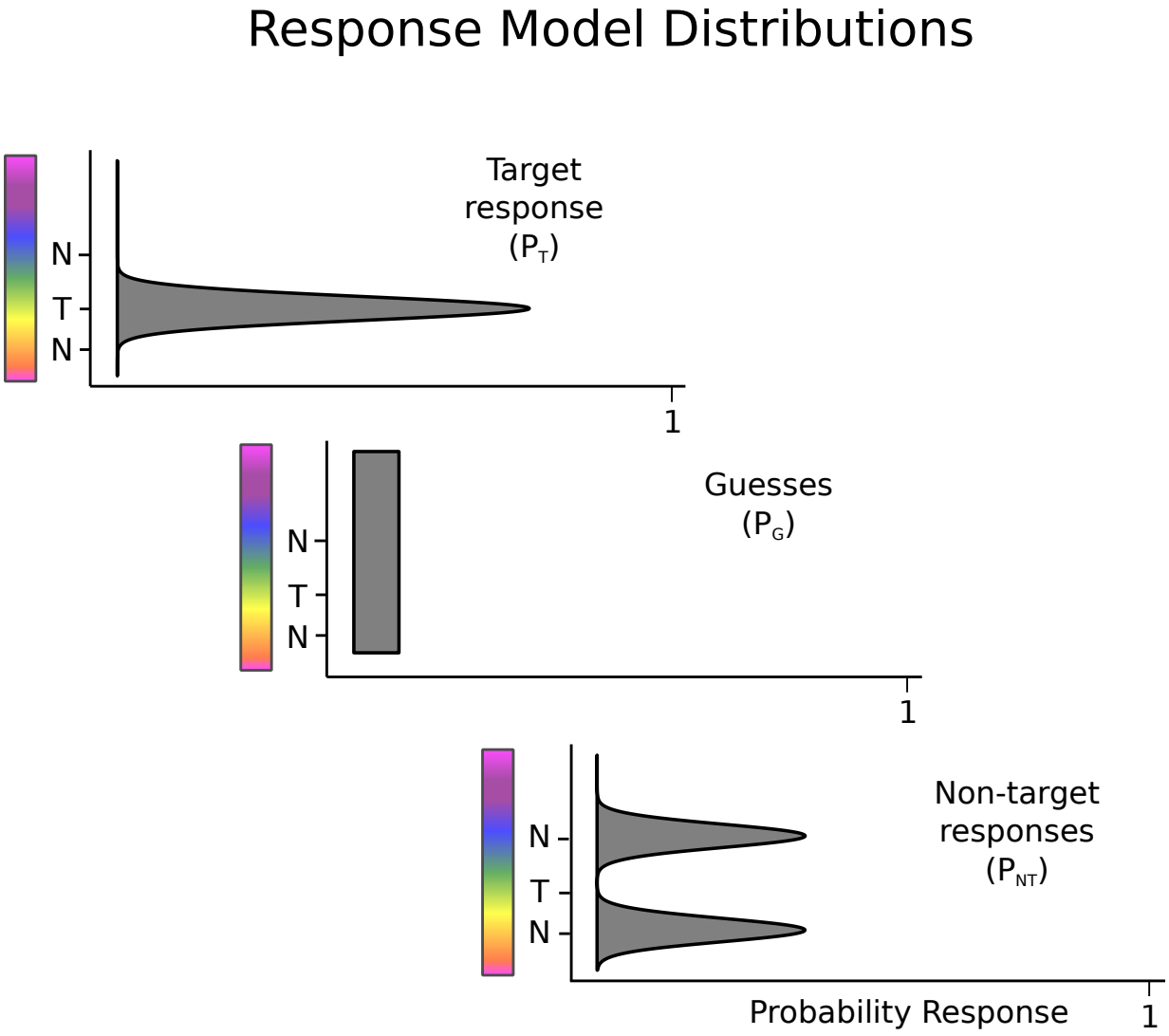


Figure 2.2: Figure depicts the three probability distributions used to calculate the three values.

2.2 Results

2.2.1 Visual Working Memory

Response Precision

Response precision was compared between the three groups and three conditions using a mixed between and within-measures ANOVA (Figure 2.3). Response precision was positively skewed, but was sufficiently normal when log transformed (e.g., Shapiro-Wilk $w = 0.98$, $p = 0.9$). While there was a significant effect of the number of squares condition ($F(2, 44) = 14.7$, $\mathrm{p} < 0.001$), the effect of group did not reach significance ($F(2, 22) = 3.19$, $\mathrm{p} = 0.06$). The interaction between the two was also non-significant ($F(4, 44) = 0.88$, $\mathrm{p} = 0.4$). *Post hoc* multiple comparisons, using Tukey's HSD, indicated that the near-significant group effect was the result of a possible age effect between young adults and patients ($\overline{M}_{\mathrm{diff}} = 0.6$, $\mathrm{p} = 0.05$). While the other age-related contrast was not significant (i.e., young adult and older control groups, $\overline{M}_{\mathrm{diff}} = 0.4$, $\mathrm{p} = 0.3$), the critical comparison, between patients and older controls, did not demonstrate an effect of neurological damage on response precision ($\overline{M}_{\mathrm{diff}} = -0.23$, $\mathrm{p} = 0.6$).

Single Square Condition

When considering response probabilities, the single square condition of the VWM task was analyzed separately, as it represents an arguably distinct challenge to participants, and the outcome variables are different when compared with trials that contain non-target distractors (i.e., the single square condition lacks a P_{NT} measure). It does not require the

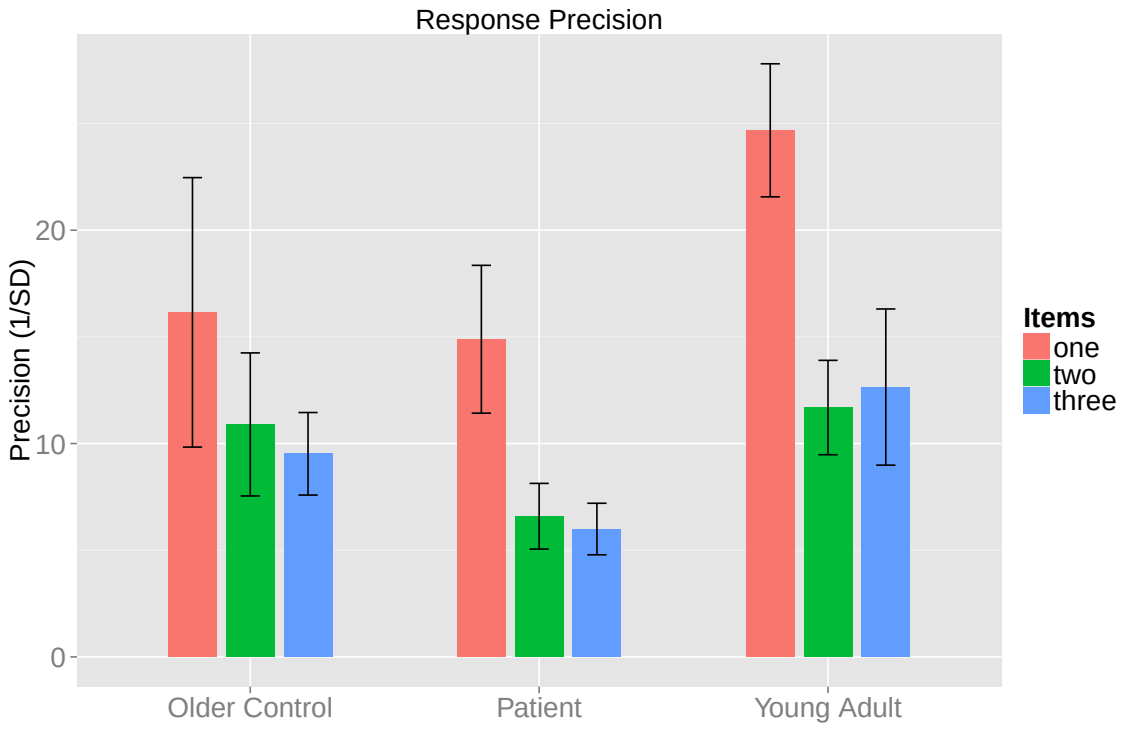


Figure 2.3: Figure depicts the precision of responses (coded as 1/SD of the response distribution, so higher values indicate better performance). The groups do not statistically differ in their ability to manually indicate their response precisely.

participant to encode distinct spatial locations, or to bind colour and spatial location, so it is more purely a measure of an individual's ability to precisely encode and recall a target colour.

Because the single square condition has no non-targets, and therefore no P_{NT} (i.e., $P_T = (1-P_G)$), there is effectively only one dependent variable and the choice of which probability to use for analysis is arbitrary. For convenience, P_T is used here as the dependant variable. As can be seen in Figure 2.4, the two healthy groups perform nearly perfectly by this metric. A one-way ANOVA containing all three group means was significant ($F(2) = 38$, $p < 0.001$). Tukey's HSD tests were performed to compare the means, and the two healthy groups, who appear to have been performing at ceiling, did not differ on this metric ($\overline{M}_{\text{diff}} = 0.02$, $p = 0.56$). However, the patients performed significantly worse than both young adults and older controls ($\overline{M}_{\text{diff}} = 0.17$, $p < 0.001$, and, $\overline{M}_{\text{diff}} = 0.19$, $p < 0.001$, respectively).

Two and Three Square Conditions

In the multi-square conditions, three outcome probability estimates were produced. As was the case for the one square condition, these probability estimates sum to one, and as such represent only two unique values. Here, two types of failures were chosen for the analysis — the probability of guessing (P_G), and the probability of indicating a non-target distractor (P_{NT}; Figure 2.5)

The two dependant variables were analyzed separately, rather than in a multivariate analysis, as the characteristics of the data violate many of the assumptions of standard

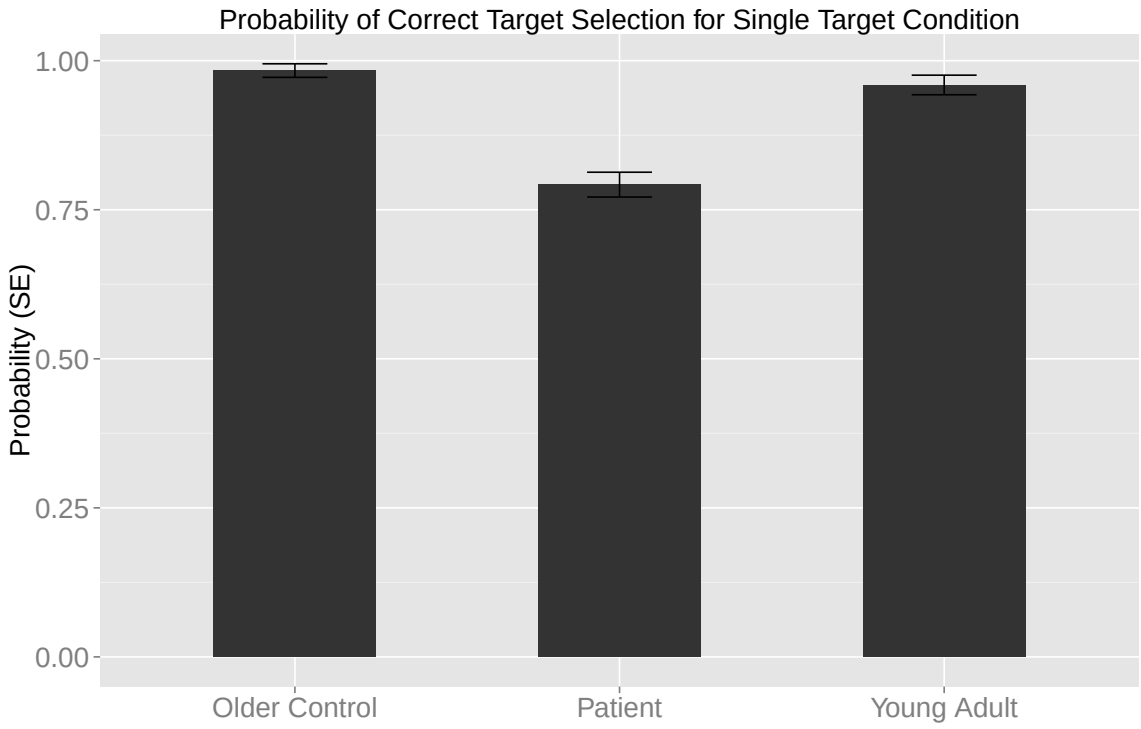


Figure 2.4: Figure depicts the probability of correct selection for the single square condition (i.e., the inverse of the probability of guessing, so higher values are more accurate). The two healthy groups perform at ceiling, with the patient group responding less reliably.

multivariate tests and the limited sample size would render any result tenuous at best. This limits the ability to compare the two outcomes, but provides clearer answers to the distinct questions each measure addresses.

The restricted range of both probability scores, and high frequency of near-zero outcomes produced a highly skewed and non-normal distribution that could not be normalized. As a result, the results of the 2 and 3 target conditions were collapsed, and analysis was performed with non-parametric tests.

Guessing

The Kruskal-Wallis rank sum test was used for the non-parametric omnibus model of P_G, and it did not indicate differences between groups ($\chi^2(2) = 2.89$, $p = 0.2$). Non-parametric relative effects using Tukey contrasts were performed in a "one-sided" fashion, assuming age and injury would only impair performance (Using Nparcomp, Konietschke et al., 2014). The Patients did not significantly differ from either the young adults ($t(8) = 2.20$, $p = 0.08$), nor older controls ($t(8) = 0.19$, $p = 0.8$). Additionally, the two healthy groups did not differ from one another ($t(8) = 0.86$, $p = 0.5$).

Non-target Selection

As was done for the guessing data, analysis was performed on the collapsed means of the two and three target trials. Here, however, the Kruskal-Wallis omnibus test was significant ($\chi^2(2) = 7.5$, $p < 0.05$). Multiple comparison tests yielded significant differences between the patients and the two healthy groups ($t(12) = 2.47$, $p < 0.05$, for older con-

trols, and $t(8) = 3.9$, $p < 0.05$, or young adults). The two healthy groups, however, did not significantly differ from one another ($t(8) = 0.54$, $p = 0.6$).

2.2.2 Covert Orienting Task

Analysis of the covert orienting data was limited given that three of the patients failed to respond to any left-sided targets (note: these patients also presented with the most severe neglect symptoms). Leftward cue-effect sizes (CES) were calculated for each participant in the patient group and older controls. Overall, both groups exhibited significant cue effects, indicating significant cost for reorienting attention to invalidly cued targets ($t(4) = 2.16$, $p < 0.05$, for the patients, and $t(7) = 2.48$, $p < 0.05$ for the older controls). To examine group differences in covert orienting, a mixed ANOVA was performed with group as the between-subjects factor and SOA as the within-subjects factor. An effect of group approached significance ($F(1) = 3.7$, $p = 0.08$), while SOA and the interaction were non-significant ($F(1) = 0.5$, $p = 0.49$, and $F(1) = 0.02$, $p = 0.8$, respectively). Considering the size of the patient group in this analysis ($n = 5$), it is unlikely that the sample variance provides a good estimate of the population, so the groups were also compared using a non-parametric Kruskal-Wallis test, collapsing across SOA, and this did indicate that patients exhibited larger leftward CES than the older controls ($\chi^2(2) = 4.2$, $p < 0.05$).

Figure 2.6 depicts the CES of the 5 patients over the range of performance observed in the healthy controls (bands represent 1 and 2 standard deviations). As can be seen in the figure, three of the patients performed within the range of healthy controls. In contrast, two other patients demonstrated leftward CESs that were well outside the range of the healthy

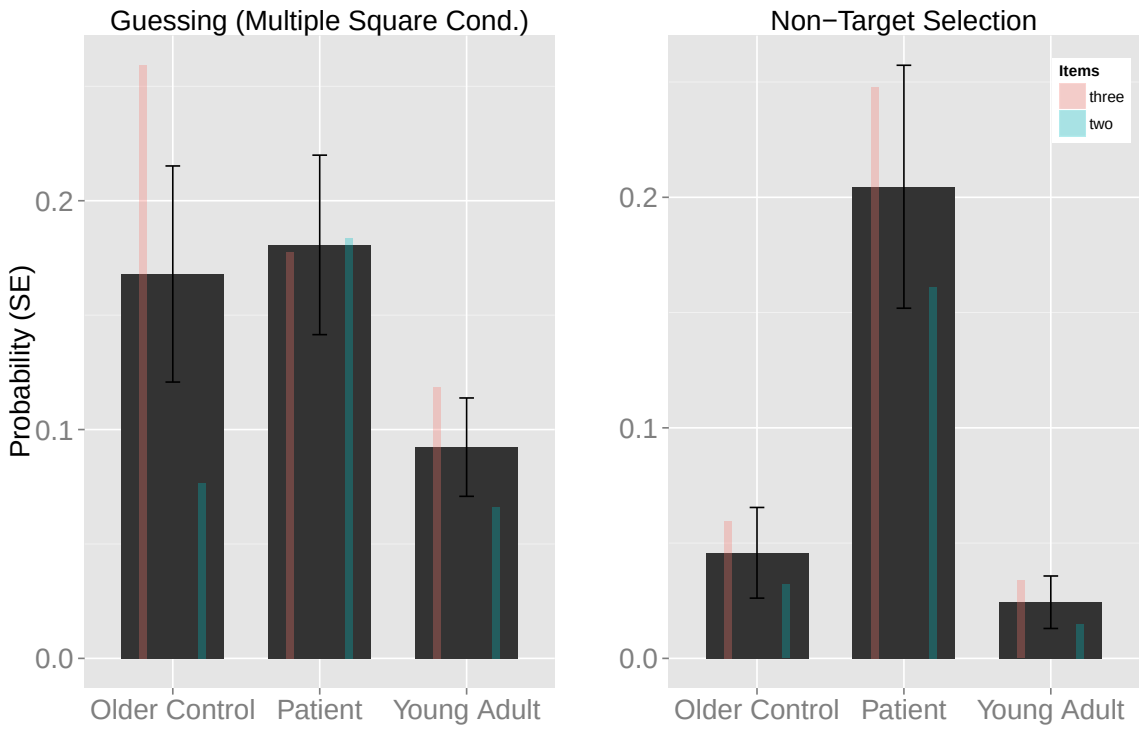


Figure 2.5: Figure depicts non-target probability means (right) and guessing probability means (left) for the multi-square conditions (i.e., 1 and 2 non-target distractors). Overlaid on the collapsed means are the contributing means in the 2 (blue) and 3 (red) square conditions. While the groups did not differ statistically when guessing, patients selected non-target colours more frequently than the two healthy groups.

older controls. It is also worth noting that one of the two, Patient 171, did not show any signs of neglect on the clinical tests, and the other, Patient 454, exhibited moderately neglecting symptoms when compared with their cohort. This patient (454) produced a bisection bias above our threshold, though only at 6%, a near median performance for the group, and produced errors in figure copying, but did not miss any left-sided targets in the star cancellation test. It also should be noted that Patient 171 did not show a similarly large rightward CES, so it cannot be said that the result was a deficit of general covert re-orienting, but, indeed, reflects a lateralized deficit (CES_R of -22 and 11 for 50 and 150ms SOA respectively). For Patient 454, it was less clear (CES_R of -263 and -21 for 50 and 150ms SOA respectively; negative values indicate faster invalid trials).

2.2.3 Comparing Visual Working Memory and Covert Orienting

Group Level Comparison

In order to explore the relationship between visual working memory and covert orienting, a generalized linear model was fit predicting group affiliation based on the demonstrated deficits from the two tasks. Specifically, a logistic regression was computed based on predicting group with just CES in an initial model, and then sequentially adding the two visual working memory deficits (P_{NT}, and P_G from the single target condition) in a second and third step. This order was chosen in order to examine visual working memory as a predictor of the patient group beyond (i.e., partialled on) the attentional deficits measured with the covert orienting task. In order to model the complete data set of 8 patients, the patient CES data was "Winsorized," substituting values of 2 standard deviations greater

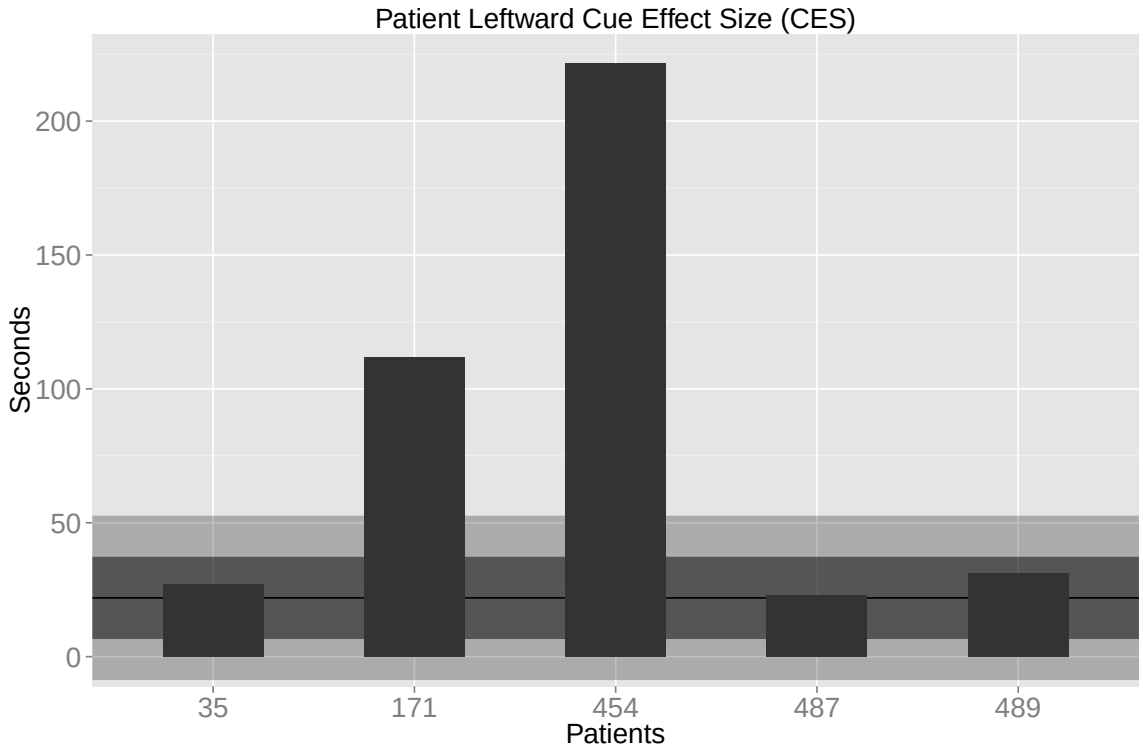


Figure 2.6: Figure depicts left CES of each of the 5 patients that were able to perform the COVAT. Larger values indicate difficulty re-orienting leftward after a rightward attentional cue. Dark and lighter horizontal bands are overlaid that indicate 1 and 2 standard deviations around the mean normative performance of the older controls.

than the group mean for the three patients who failed to orient leftward. This procedure emphasizes any contribution of CES, at the risk of over-emphasizing it, and in doing so, makes later estimates of visual working memory contributions more conservative.

Because P_{NT} and P_G could not be normalized, each was transformed via a median split into categorical factors representing "good" and "poor" performance. The analysis of deviance indicated that CES, on it's own, significantly predicted group affiliation (see Table 2.2). The addition of P_{NT} was not significant, but P_G did significantly describe group, when partialled on both CES and P_{NT}. No interactions were significant.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL			15	22.18	
CES	1	8.62	14	13.56	0.0033
P_{NT}	1	1.12	13	12.44	0.2908
P_G	1	12.44	12	0.00	0.0004

Table 2.2: Analysis of deviance table. Each row represents the change in deviance of the model with the addition of one term. Pr(>Chi) is the probability of obtaining a greater scaled deviance statistic than the observed under the null hypothesis (new term has true parameter of zero). Both CES and P_G result in statistically significant model improvement.

Individual Patient Comparison

When comparing patients on a case by case basis, they can be divided into 3 groups based on covert orienting results; non-responders (3), large deficit (2), and near normal range CES (3). The three non-responders were the most densely neglecting patients on the clinical tests, and demonstrated strong deficits on the visual working memory task. This was particularly apparent in the measure of non-target selection, where these three performed considerably worse than the rest of the group (Table 2.1).

The two patients exhibiting a large deficit on CES did not stand out with similarly extreme performance deficits on the visual working memory task. When the two are compared with the three normal range CES patients, as can be observed in Table 2.1, Patient 454 performed slightly worse than the median on both visual working memory measures, while Patient 171, who, as mentioned previously, as the only one in the group to score negatively on all three clinical measures of neglect, was actually the most accurate participant. Similarly, the near normal range CES patients did not stand out as different from their cohort on either visual working memory deficit.

2.3 Discussion

2.3.1 Visual Working Memory Task

The response precision data indicates that the patients were able to perform the basic task of indicating a colour to a similar degree of proficiency as the healthy groups, demonstrating that basic perceptual representations were intact, and that they are able to perform the perceptual-motor response as effectively as controls when they are able to recall the correct visual information (Figure 2.3).

Guessing

When examining the apparent reliability of patient responses, the data appears to indicate that neglect patients fail to recall the colour of the stimuli and respond in a way that indicates more prevalent guessing, in the single square condition (i.e., P_G, Figure 2.4).

Interestingly, this effect was not significant in the multi-square condition (Figure 2.5). In the single square condition, both healthy groups performed near ceiling. When non-targets are introduced in the multi-square conditions, all groups appear to fail more often, but for the healthy groups the bulk of the new errors appear to come from guessing (Figure 2.5). Deficits in the patients were not as clear cut. This may represent a different underlying failure, as guessing likely represents a failure of memory for target colour, while non-target selection represents a more complicated interaction, as discussed below.

The lack of a significant group difference in guessing for the multi-target condition may, nevertheless, reflect limited sensitivity of the task variant. The single square condition may be more effectively tuned to measure simple visual working memory failures (i.e., guessing), as that is the only type of failure in the condition. The parameters of the task meant that the healthy groups performed near ceiling, and so demonstrated less variability, perhaps allowing for more sensitive statistical contrast with the patient group.

Binding Errors

When participants were asked to perform the same VWM task in the presence of distractor "non-targets", two things change: there is an increase in memory load, as patients are asked to remember more items over the delay, and some of that information must be associated, as patients must now bind colours and locations in working memory across the delay interval (Wheeler & Treisman, 2002). That is, in addition to remembering more than a single colour, patients needed to remember the relative spatial arrangement of those colours in order to answer correctly. As a result, two types of errors can be committed. A failure

to recall a colour (a guess), or a mis-identification of one of the non-target distractors as belonging to the indicated spatial position (non-target response).

Patients were more likely to demonstrate colour-location binding errors than controls (Figure 2.5). There are many potential explanations for this, the most obvious being failures of binding information from the two domains in working memory. This type of cross-domain cognitive process has previously been shown to be degraded in parietal and neglect patients (Humphreys, Hodsoll and Riddoch (2009); Pisella, Berberovic and Mattingley (2004)). When more than one square is presented in the memory sample, colour information must be explicitly associated with spatial location in memory and stored over the delay. If all of the colours are effectively encoded and recalled, but a failure to bind the colours to spatial location occurs, participants will select a distractor colour about half of the time in the two-target condition, and two thirds of the time in the three-target condition.

The other event that can lead to this type of error is a simple failure to recall the complete set of presented colours. If the target colour cannot be recalled, but others can, it is possible the participant may be inclined to select one of the distractor colours, or something close to it, simply due to cognitive anchoring. This experiment is not able to clearly disambiguate the two causes. However, if the large impairments observed here were caused by patients forgetting target colours, then it seems likely that such frequent recall failures would have also lead to a similarly large increase in the amount of guessing. As guessing did not appear to stand out in this condition, binding errors are the more likely culprit.

2.3.2 Covert Orienting

Conclusions about the covert orienting data is more limited, as only five of the eight patients were able to perform the task, and only two of them performed well outside the healthy range — although it is reasonable to suggest that the three patients who failed to detect any left sided targets also performed well outside the normal range. The three patients unable to complete the covert orienting task also exhibited the strongest symptoms of neglect on the clinical measures. As a result, the analysis is based on only the subset of moderately neglecting patients. Nevertheless, as a group, those patients able to complete the task did perform more poorly than the healthy controls, so it is unlikely that those two extreme cases are artifacts of chance. Moreover, the non-parametric comparison is un-affected by the large magnitude of deficit in those two cases, as it is based on rank-order, lending more support to the notion that the groups as a whole are, in fact, different.

Nevertheless, others have typically found clearer alignment between clinical results and orienting performance (Posner et al., 1984; Morrow & Ratcliff, 1988; Losier & Klein, 2001), so it is likely that experimental constraints limited sensitivity. For example, the two short stimulus onset timings were chosen to prevent the need for eye movement monitoring (i.e., at 150ms SOA, targets appear before eye movements can be initiated), but this may have limited cue effect size sensitivity by reducing the opportunity for complete attentional orienting. Also, patients were asked to perform only 100 trials to avoid undue fatigue, but this may have limited the power of the experiment, as other research has utilized considerably more trials (e.g., Posner et al., 1984; Morrow & Ratcliff, 1988; Danckert & Maruff, 1997).

In contrast, it is also well established that the paper and pencil clinical tests of neglect have limited sensitivity and, by their nature, are not capable of capturing the complete spectrum and heterogeneity of deficits across patients (Danckert & Ferber, 2006). Participant 171, for example, had demonstrated neglect in a clinical setting previously, but at the time of testing, no longer showed symptoms on the clinical tests. Despite this, considering the large leftward re-orienting deficit demonstrated on the covert orienting task, it would be premature to claim complete recovery. It is more likely that this is a case where the three clinical tests used here are poorly matched with remaining deficits; an extreme example of a general reality that paper and pencil tasks alone will present an incomplete picture, and as a result, will not always agree with measures of other components of the disorder.

The three patients who were unable to complete the covert orienting task *did* effectively show striking deficits of leftward orienting, but the task was not able to quantify their performance, reducing the power of the above analysis. Nevertheless, these strongly biased patients also demonstrated the most severe deficits on the clinical tests of neglect, further supporting the connection between leftward re-orienting on the covert orienting task, and the clinical measures.

2.3.3 Comparison of the Tasks

The logistic regression indicated that one of the two deficits of visual working memory — guessing in the single target condition — significantly described group affiliation, even when partialled on covert orienting performance. If visual working memory deficits were merely

consequences of a deficit of spatial attention, then one would not expect a measure of visual working memory to uniquely describe the patient group above and beyond an established measure of the attentional deficit (i.e., leftward covert re-orienting). It is possible, but unlikely, that the visual working memory test used here is a more sensitive, if indirect, measure of attention deficits than the covert orienting task — a well tested and direct measure of attention. Fortunately, the relationship can also be examined by considering the patients on a case-by-case basis.

The three most severely neglecting patients demonstrated consistently degraded performance on all tasks, lending support to the claim that the clinical, visual working memory, and covert orienting tasks are all affected by a common underlying deficit. However, the remaining five patients presenting with moderate-to-weak neglect symptoms present a much less consistent relationship (Table 2.1). One patient presents with a very large leftward CES, along with degraded performance, relative to peers on most of the remaining tasks; while another presents the opposite picture, doing exceedingly well on the non-covert orienting tasks. Generally, CES rank matches line bisection performance, though, this is not without exception. However, in only the one case, mentioned above, does covert orienting and visual working memory performance appear to be consistent. This lack of a reliably similar performance across the range of the two tasks hints at the decoupled nature of the two domains in neglect.

Most rehabilitation techniques implemented in neglect focus on remediating impairments of attention. If attention deficits are indeed distinct from working memory impairments as suggested here and elsewhere (e.g.; Husain et al. (2001); Danckert and Ferber (2006); Striemer et al. (2013)), then this rehabilitation strategy will fail to address this

domain, and may leave patients with untreated symptoms. The next chapter addresses this question by examining the effects of a prominent rehabilitation technique on non-attentional biases.

Chapter 3

Prism adaptation does not improve deficits in spatial working memory or temporal estimation.

The previous chapter demonstrated that the working memory deficits observed in neglect are not constrained strictly to the spatial domain, and are unlikely to be a direct effect of an inability to utilize spatial attention — either due to spatial attention deficits specifically, or an inability to access those networks for spatial rehearsal (Awh & Jonides, 2001). This working memory deficit joins several perceptual deficits demonstrated in neglect that stand apart from the traditionally described deficits of spatial attention.

As discussed earlier, one of the most promising and well studied treatments for the remediation of neglect is the use of short term adaptation to leftward shifting prisms

(Rossetti et al., 1998; Luauté et al., 2006). While much of the research into prism adaptation has focused on changes in spatial attention (Striemer & Danckert, 2007; Nijboer et al., 2008; Schindler et al., 2008), their effectiveness may not extend to more integrated, perceptual tasks such as serial visual search (Morris et al., 2004).

Visual search involves successive steps that make use of several systems, including perceptual judgment of stimulus identity, and, spatial memory of searched locations. While patients do not seem to have trouble discerning the stimulus types used in visual search, eye-tracking research has demonstrated that even young, healthy, individuals can occasionally fixate, or even interact with targets, but still fail to identify them (Rich et al., 2008; Solman, Cheyne & Smilek, 2012), highlighting that reduced perceptual judgment can play a role in diminished search performance. Diminished performance could also come from the search algorithm itself. People do not search targets in a completely random order, necessitating a role for spatial working memory in directing search based on previously visited locations. The revisiting behaviour observed when neglect patients perform object cancellation tasks suggests a sub-optimal memory of those locations (Wojciulik et al., 2001; Husain et al., 2001).

The reliable effect of prisms on remediating spatial attention deficits, along with the simultaneous lack of obvious efficacy on perceptual and search tasks, indicate that their target of action may be primarily within the dorsal visual stream. The two visual stream hypothesis places spatial attention and action (where and how) within the dorsal stream, passing from visual areas in occipital cortex into superior regions of the parietal lobe (Milner & Goodale, 2006). Conversely, it places perception, and working memory of those perceptions, in the ventral stream, radiating into the temporal lobe (Milner & Goodale,

2006). Various lines of research have pointed to prisms specifically effecting dorsal areas. Danckert et al. (2008) and Clower and colleagues 1996 have both demonstrated dorsal stream activation during prism adaptation, with fMRI and PET respectively. Both studies found activation in the intraparietal sulcus. Danckert et al. (2008) also found anterior cingulate and cerebellar activation, but neither study identified activation in ventral stream areas.

Luaute and colleagues 2006 found that several areas correlated with the effectiveness of prisms at remediating neglect symptoms using PET. They found an extensive cluster of areas, which included posterior parietal cortex (Luauté et al., 2006). An examination of task-evoked brain activity during recovery from neglect corroborates this notion. Participants performing a covert orienting task while undergoing fMRI exhibited significantly attenuated activity in undamaged areas of visual cortex, posterior parietal cortex (particularly the intraparietal sulcus and superior parietal lobule), and dorsolateral prefrontal cortex (Corbetta et al., 2005).

Thus the effects of prisms appear to be highly specific to the dorsal stream and to spatial attention deficits in neglect, and yet, as highlighted in the previous chapter, there are significant deficits that can be characterized as primarily involving perception and hence the ventral visual system. For example, visual and spatial working memory (Ch.2.; Wojciulik et al., 2001; Striemer et al., 2013), perceptual judgments of spatial extent (Dijkerman et al., 2003; Striemer & Danckert, 2010a), or emotional expression (Ferber et al., 2003; Sarri et al., 2006), among others, are not altered following prism adaptation. This chapter explores the influence of prisms on two functions shown to be impaired in neglect — spatial working memory and temporal perception (Wojciulik et al., 2001; Striemer et al.,

2013; Danckert et al., 2007). These two domains were chosen because they demonstrate impairments in a neglect patient's ability to maintain accurate perceptual representations of his or her environment. Both spatial working memory and temporal perception are likely to be supported by mechanisms primarily located in the ventral stream. As such, we expected to find neglect patients would continue to demonstrate deficits in these two tasks even after prism adaptation. More precisely, we expect prisms would remediate dorsal stream tasks, such as the clinical line-bisection measure, but not perception-dominant tasks, such as spatial working memory or temporal perception.

3.1 Method

3.1.1 Participants

Eight patients with right parietal damage who had shown clinical symptoms of neglect in previous testing were recruited from the Neurological Patient Database (funded through the Heart and Stroke Foundation of Ontario, https://uwaterloo.ca/neurological-patient-database). Two patients were unable to return for the second phase of the experiment because of extenuating circumstances. As can be seen in Table 3.1, the remaining six patients demonstrated a wide range of performance on the clinical tasks at time of testing, including two who were no longer demonstrating neglect symptoms by our criteria (Patients 27, and 97). One participant was not able to perform the spatial working memory task (giving a single response to all trials), and was therefore removed from that component of the analysis. The study was approved by the University of Waterloo's Office of Research Ethics, and the Tri-Hospital

Research Ethics board. All patients were tested at least 19 months post-stroke.

3.1.2 Apparatus and Procedure

Patients participated in at least two sessions. The two sessions were intended to differ only in the presence or absence of prism adaptation. During prism adaptation, patients alternately pointed to targets on a table-top to the left and right of body mid-line every 2–3 seconds for 5 minutes. Prism glasses were worn that shifted vision 10° to the right and visibility of hand movement was not artificially occluded (concurrent visual feedback).

As in the previous chapter, patients were tested for symptoms of neglect using four standard clinical measures. These were line bisection, figure copying, and two cancellation tasks: "stars" and "bells" (Wilson et al., 1987). The four tasks were completed at the beginning of every session. Line bisection was also performed twice during sessions involving prisms, before and after adaptation as a measure of the after-effects of the procedure. Coding and analysis of the tasks were performed in the same way as in Experiment 1. The results of the clinical measures are depicted in Table 3.1. One patient had to leave early during their first session, so repeated it on another day. The duplicated data is included in this chapter's figures for transparency.

Spatial Working Memory Task

The spatial working memory task is a similar, simpler relative of the visual working memory task that was used in the last chapter (Ferber & Danckert, 2006). Patients were seated at a viewing distance of approximately 60 cm, with their head and body axis aligned (no

	Age	Sex	Handedness	Star(pre)	Star(post)	Bell(pre)	Bell(post)	Copy(pre)	Copy(post)
10	68	M	Right	93	87	100	89	+	+
27	43	M	Right	0	7	6	0	-	-
95	70	M	Right	7	0	33	39	+	+
163	68	F	Left	30	7	6	29	+	+
97	66	M	Right	0	0	0	0	-	-
171	71	F	Left	0	0	6	6	+	-

	LB(pre)	LB(post)	TE(pre)	TE(post)	SWM(pre)	SWM(post)
10	-0.80	-9.90	0.40	0.40		
27	-0.80	1.20	0.80	1.00	83.00	87.00
95	0.30	-3.80	0.40	0.30	32.00	35.00
163	0.90	4.90	0.40	0.40	23.00	45.00
97	1.90	-1.60	0.60	0.60	43.00	52.00
171	3.80	1.40	0.40	0.50	43.00	68.00

Table 3.1: Table (a), above, includes demographic information for the patients, as well as performance on star cancellation, bell cancellation, and figure copying, all before and after prism adaptation (See Results for analysis). For star and bell cancellation, values indicate the percentage of left-sided targets omitted. For figure copying, a "+" indicates the presence of neglect. Table (b), below, includes performance on the line bisection (LB), temporal estimation (TE), and spatial working memory (SWM) tasks. Line bisection is recorded as percentage of line length, with positive values indicating rightward bias. TE values represent the slope of a linear model of the log-log transformed real and estimated time intervals. A value of 1 indicates would indicate estimates that increase in proportion to actual time intervals. SWM values indicate accuracy based on hits minus false alarms.

chin-rest was used, optical angles presented below are therefore approximate). The task was programmed in Visual Basic Version 6.0 (Microsoft Inc.). The task was the same as described in Ferber and Danckert (2006). At the beginning of each trial, patients fixated a red central cross. Once fixated, the experimenter began the trial by depressing a key and the cross turned green. After 1 second, three targets were presented 2° to the right of fixation, vertically aligned. The targets were squares subtending 1.5°, and could appear in any of 16 different locations, however, targets were always separated from one-another by at least 2°.

The targets remained on-screen for 2 seconds which was followed by a delay of 3 seconds. Following the delay a probe stimulus (a circle of the same size as the target squares) was presented at one of the 16 possible locations. The probe remained on the screen until a response was entered via the keyboard (Figure 3.1). The patients were asked to remember the locations of the target squares across the delay interval and then verbally report to the experimenter whether or not the probe appeared in one of the locations previously occupied by a target. A total of 120 trials constituted a single session. In 50% of trials, the circle appeared in the same position as one of the preceding squares.

Temporal Estimation Task

The temporal estimation task was displayed on the same computer as the spatial working memory task, but was programmed in E-Prime (Psychology Software Tools). As with the spatial working memory task, patients gave verbal responses, and the experimenter entered those responses and controlled the task via the keyboard. The task was identical to that

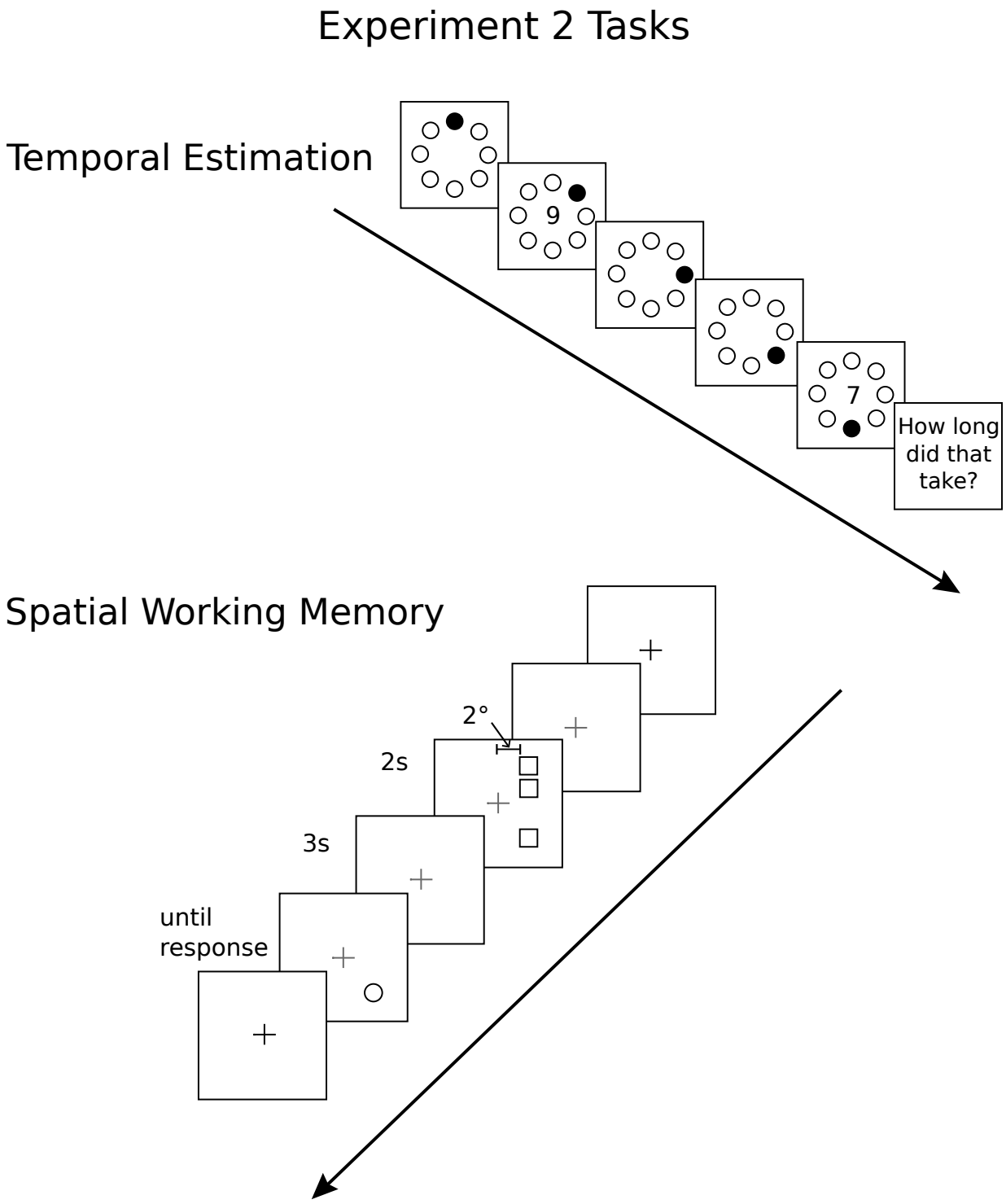


Figure 3.1: Figure upper panel (a) depicts one trial of the temporal estimation task. The numbers were randomly selected and displayed at random times (though, not at the very beginning or end of the trial). The lower panel (b) depicts the spatial working memory task. The trial depicted is a valid trial, as the probe (circle) is in the same location as one of the initial three targets (squares).

described in Danckert et al. (2007). In order to provide a stimulus for the participant to attend to, an illusory motion stimulus was presented that consisted of eight open circles (each subtending 3.5°), arranged in a larger circle around the centre of the screen (radius of 8°), with each circle being filled, sequentially, one at a time, in a clockwise direction (Figure 3.1). This created the illusion of a filled-circle moving around the outer circle. Rather than a fixation, the centre of the screen periodically displayed a number (numbers 1-9, presented for 300ms, 1.5° in size), which the participant was asked to verbally report as they appeared. This effectively maintained central fixation for the patients and provided a check that participants were attending to the task. In addition, this component prevented participants from sub-audibly counting out the interval duration.

To avoid problems with responses, certain constraints were placed on the appearance of the numbers. They could not appear less than 500ms from the beginning or end of the trial, or another number. The interval between numbers was also never more than 1500ms. At the conclusion of the trial, the circles disappeared and the participant was asked to indicate, verbally, the duration of the interval in whole seconds. The intervals were randomly chosen from 5, 15, 30, and 60 seconds with 5 trials per duration.

3.1.3 Data Analysis

As in Experiment 1, line bisection bias was coded as a percentage of line-length, and star- and bell-cancellation tasks, based on the percentage of left-sided target omissions. All measures were computed for pre and post prisms. Where multiple sessions were performed, values were averaged (Table 3.1).

For the spatial working memory task, there were two trial types; those where the probe appeared in the same location as one of the targets, and those in which probes appeared in a non-target location. Based on the two trial types, responses were categorized as true- and false-positives, and true- and false-negatives (positive and negative indicating the responses, and true and false indicating whether the response was correct). A single sensitivity metric was calculated for each patient, pre- and post-prisms, by subtracting false-positives from true-positives (i.e., "hits" - "false alarms"). Normative performance in healthy individuals from pre-existing research with this task was used to provide context to these values (Ferber & Danckert, 2006).

The temporal estimation task analyzed the time interval estimates the patients reported. For each patient, a mean of reported times was calculated for each time interval, both for pre and post prisms data. Individual linear models were also computed to provide a measure of the relationship between true trial durations and reported durations.

3.2 Results

3.2.1 Spatial Working Memory Task

Replicating previous research using this spatial working memory task (Ferber & Danckert, 2006; Striemer et al., 2013), most of the patients performed very poorly. Figure 3.2 plots the patient mean accuracy along with expected normal range, based on the performance of two non-neglecting groups tested on the identical task by Ferber and Danckert (2006). While one patient performed similarly to the non-neglecting group (Patient 27, one of the

two patients no longer demonstrating neglect on clinical tasks), the remaining patients baseline performance was at least 3 standard deviations outside what was observed in either group.

As a group, SWM performance does statistically improve when a one-sided test is used (presuming prisms would not decrease performance, $t(4) = 2.67$, $p < 0.05$). When consulting Figure 3.2, it becomes obvious, however, that the change is small relative to the size of the deficit. All four patients showing clinical signs of neglect at the time of testing still demonstrated large deficits post-prisms, compared with the performance of non-neglecting right brain damaged patients previously examined on this test (z-scores between 3.4 and 7.2). When compared with performance of the more variable, right-brain damaged population (the lighter region in Figure 3.2), Patient 171 does cross into a region statistically indistinguishable from normative performance ($z = 1.2$), but the others remain well outside this range ($3.1 < z < 5.0$).

3.2.2 Temporal Estimation Task

As can be seen in Figure 3.3, the five patients who showed clinical signs of neglect massively underestimated the time intervals. Again, Patient 27, one of two patients no longer demonstrating neglect on clinical tasks, underestimated to only a minor degree pre-prisms, and responded very accurately post-prisms (Figure 3.3). As a result, analysis was done both with and without including Patient 27, and results did not differ. What is presented here is the data excluding Patient 27. An analysis of covariance was performed, with prism condition as a fixed factor and trial duration as a random covariate, and there was no

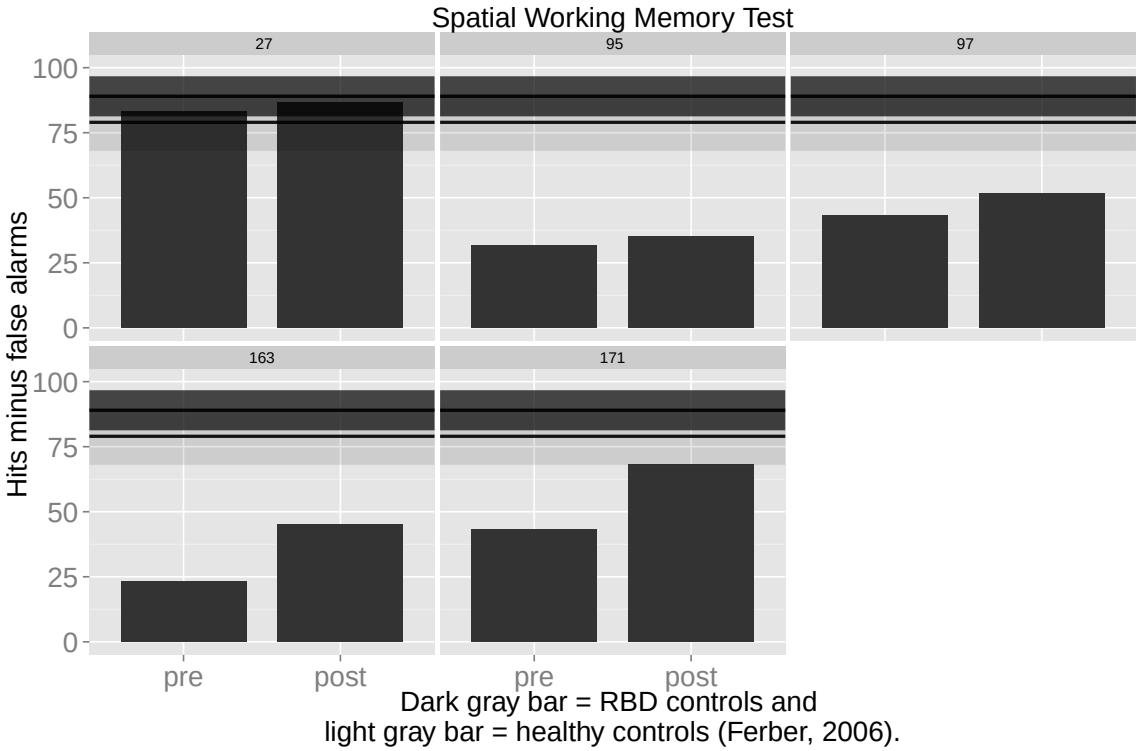


Figure 3.2: Figure depicts pre and post-prism SWM performance for all participants. In order to depict performance expected from non-neglecting individuals, means and bands of ± 2 standard deviations from non-neglecting right brain damaged (dark band, $n = 4$, one female, ages: 55, 55, 68, and 78. All > 3 months post stroke) and neurologically intact controls (light band, $n = 10$, age matched) from @Ferber2006 are overlaid the participant data.

indication of an influence of prisms on time interval estimation ($F(1,4) = 0.79$, p $= 0.4$).

For each participant and condition, a linear model was computed in order to yield a measure of the relationship (slope) between time intervals and estimations. As can be seen in Figure 3.3, the relationship was not recti-linear (first order), so linear models were computed based on log-transformed time. When this was done, linear models fit very well (13 models, one for each participant session, r^2: first quartile = 0.80, median = 0.87, third quartile = 0.92). The worst case model was, nevertheless, still significant ($F(1,14) = 12.4$, p < 0.01, $r^2 = 0.47$), indicating that despite their poor performance, patients' responses were, in fact, reliably influenced by the true trial intervals.

3.2.3 Line bisection

As a group, the neglecting patients showed a significant change in line bisection bias after prism adaptation in the direction traditionally seen in the research when a one-sided test was used (Patient 27 removed, $t(4) = 2.6$, p $= 0.03$). Individual t-tests on the sets of line bisections for each patient, with a bonferonni adjusted criteria ($\alpha = 0.008$), demonstrated a relatively consistent effect across individuals. As can be seen in Figure 3.4, the changes were nearly-universally leftward excepting Patient 27. Patient's 95, 97, and 171 demonstrated significant leftward shifts in bias post-prisms ($t(16) = 3.3$, p < 0.008, $t(17) = 4.1$, p < 0.001, $t(18) = 3.2$, p < 0.008, respectively). Patient 27 demonstrates a direction of change opposite to what is expected, and what the rest of the participants show, but this change is non-significant with the bonferonni adjusted criteria ($\alpha = 0.008$, $t(18) = -2.70$, p $= 0.015$). Patient 408 produced the largest average difference in bias, but was also highly variable,

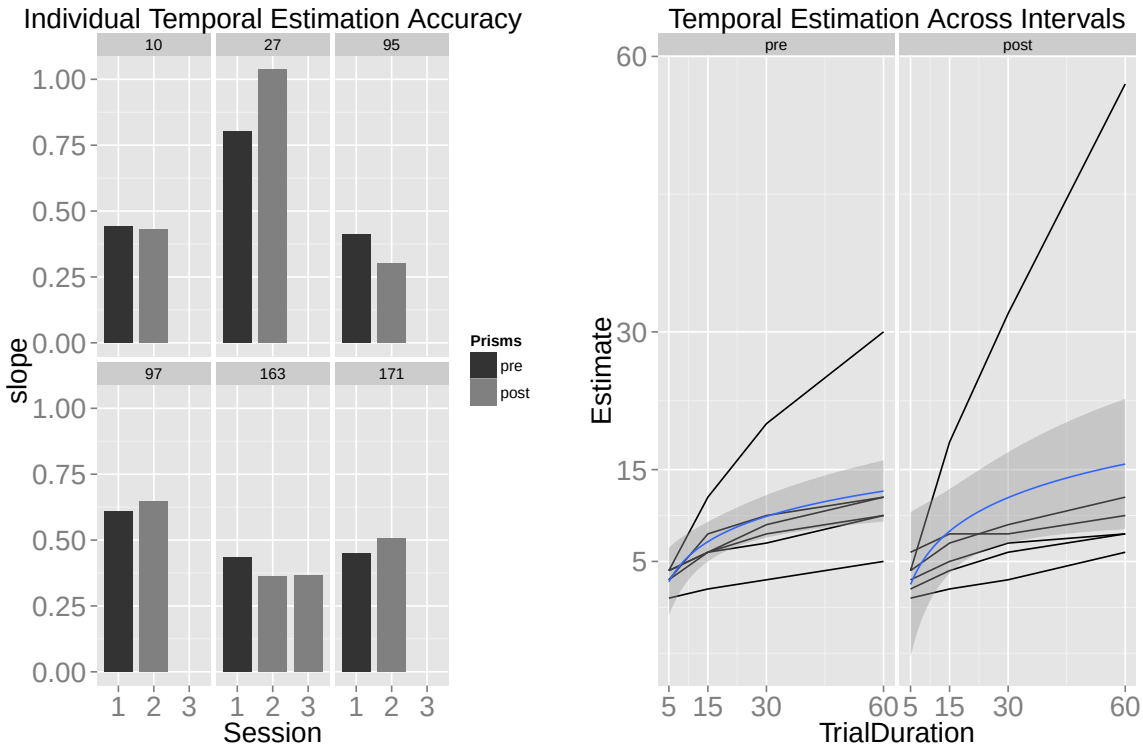


Figure 3.3: Figure depicts both line-plots of reported interval vs. true interval (right), and barplots that depict performance change pre- and post-prisms, calculated as the slope of a linear model of estimated and actual time intervals. One patient repeated the post-adaptation task, and both results are included here. Patient 27, the patient that did not show clinical signs of neglect at time of testing, can be seen to exhibit a slope of near 1 (left), indicating that estimated time intervals increase in proportion to actual intervals, and this can be seen at right, as a nearly diagonal line.

and as a result, did not demonstrate statistically significant change ($t(12) = 1.9$, p = 0.08). Patient 163 clearly did not show measurable change post-prisms ($t(10) = 1.2$, p = 0.3).

As a group, the neglecting patients did not improve on either bells ($t(4) = 0.6$, p = 0.5), or star cancellation ($t(4) = 1.7$, p = 0.2), and, as can be seen in Table 3.1, only one patient showed improvement on figure copying (Patient 171).

3.3 Discussion

As discussed above, prisms have repeatedly been found to influence deficits putatively associated with dorsal visual stream processing. Here, we replicate past findings that prisms effect the bias present when neglect patients perform the line bisection task (Rossetti et al., 1998; Striemer & Danckert, 2010a), a task that involves a motoric reporting of centre and is associated with dorsal brain activation (Foxe, McCourt & Javitt, 2003; Weiss et al., 2000; Çiçek, 2009). While the perception of the line itself, it could be argued, may also involve some ventral stream perceptual processing, past research involving a related perceptual task, the landmark task, suggests that the neglect-induced bias observed in line bisection probably represents a relatively clear indicator of a dorsal deficit within the disorder (Striemer & Danckert, 2010a). The findings here suggest that, in at least some of the neglecting patients, prisms did appear to bring about a shift in bisection toward previously neglected space, replicating previous research, and confirming the prism-induced shift of visual-motor bias in the patients.

The spatial working memory task, despite being spatial in nature, is designed to primar-

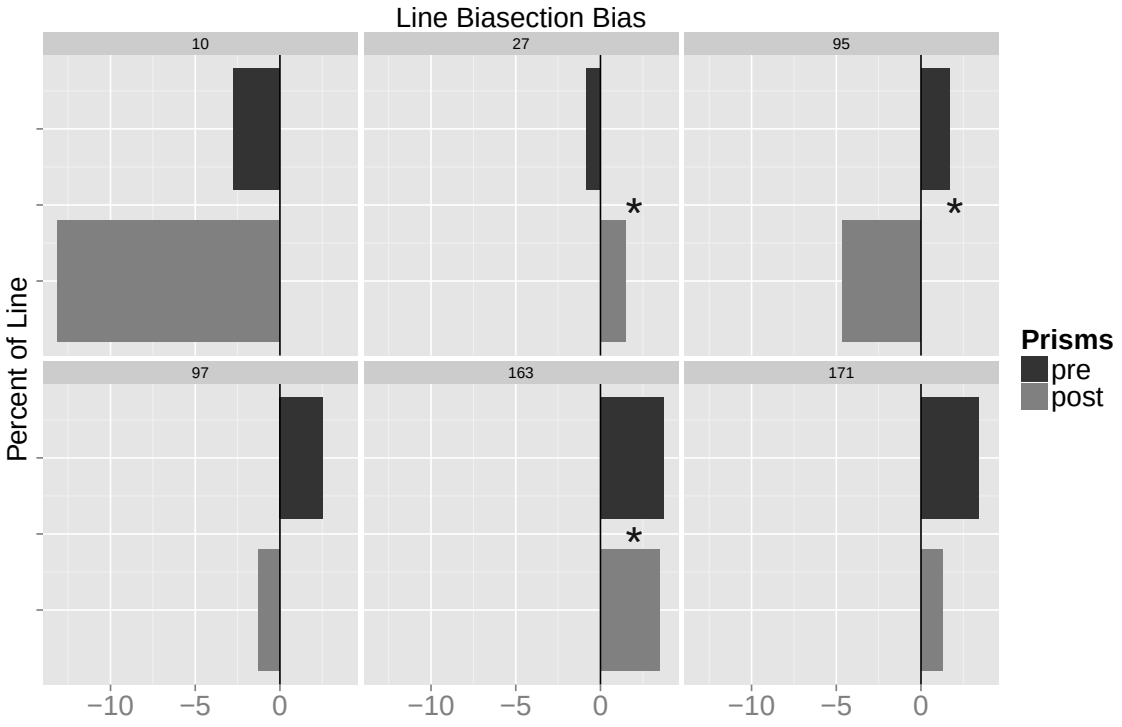


Figure 3.4: Figure depicts each individual's average line bisection performance pre- and post-prisms. Bars indicate the direction of bias, with values encoded as percentage of line length.

ily test for ventrally-oriented working memory deficits, and relies on stimuli in central and right space, rather than left space, where the spatial attention defects associated with neglect predominate. The locations of the targets need to not only be perceived, but recalled again after a delay, and that delay putatively causes the task to rely heavily on ventral, working memory systems (Ferber & Danckert, 2006; Milner & Goodale, 2006). While the patients did show statistically significant improvement as a group on the spatial working memory task after prism adaptation, the change left all four neglecting patients with apparent deficits. Post prisms, three out of four performed well outside of what would be expected in a previously studied control population.

Even more prominently than the spatial working memory results, neglect patients displayed severe deficits on the temporal estimation task. While responses did seem to be influenced by the actual trial duration (i.e., larger estimates were made for longer actual interval durations), the patients underestimated the durations both before and after prisms. In this case, prisms failed to produce any measurable effect on the deficit.

Neglect is a disorder arising from naturally varied brain lesions, and which produces heterogeneous deficits that can range from mild to severe and can recover over time in less than predictable degrees. As a result, there are going to be limitations to what can be inferred from treatment-effect studies like this when sample sizes are necessarily small. However, this chapter demonstrated that prisms can produce significant and relatively reliable change the the line bisection performance, while at the same time, failing to meaningfully ameliorate performance on the other domains that putatively rely on, ventral stream processing. This lack of meaningful improvement fits the prediction that prisms — a treatment demonstrated in the past to influence primarily dorsal brain regions — would

have minimal effects on the deficits of working memory and time perception because they rely on ventral networks. These findings lend support to the hypothesis presented earlier, that neglect is a disorder impacting two independent systems, and that remediation of only dorsal functioning will have minimal effect on the ventral deficits. More effective treatments, therefore, will necessarily need to produce changes in the behaviours attributable to ventral perceptual system function.

Chapter 4

Can saccadic adaptation improve both action and perception?

The previous chapter failed to demonstrate the effectiveness of prism adaptation for improving both spatial working memory and temporal estimation. This can be explained by the dorsal-ventral disassociation, as these tasks were chosen because of their perceptual nature. If prisms influence dorsal stream functioning, and these tasks are predominantly tests of ventral stream functioning, then it follows that these specially chosen perceptual tasks will not be substantially remediated by prisms (Striemer & Danckert, 2010b).

4.0.1 Issues with Prism Adaptation and an Alternative

Prism adaptation, by design, influences both visual and proprioceptive frames of reference (Redding, Rossetti & Wallace, 2005). In fact, depending on the specifics of the adaptation

protocol, the bulk of the influence of prisms can be exclusively in the proprioceptive reference frame (Redding et al., 2005). The protocol used in the previous chapter employed concurrent visual feedback, where the participant is not prevented from seeing his hand throughout the movement. This is likely to have led to a predominantly proprioceptive reference frame realignment. However, regardless of the type of feedback, prism adaptation leads to a mix of proprioceptive and visual, or perceptual, effects, and the degree to which each of these is present is contentious (Redding et al., 2005; Herlihey, Black & Ferber, 2012).

Another visuomotor adaptation procedure, called saccadic adaptation, – a task that changes saccade length by jumping targets forward or backward as a saccade is initiated, inducing an artificial dysmetria (McLaughlin, 1967) – offers a potential alternative approach to overcome some of the shortcomings of prism adaptation. That is, saccadic adaptation exclusively influences visual reference frames, and as a result, may be more likely to induce changes to perceptual processes. In fact, saccades straddle the perceptual and motor systems in a highly unique way. Saccadic adaptation is a form of sensory adaptation, because it changes input to the visual system. At the same time saccadic adaptation is also motor adaptation, as it is fundamentally the parameters of motor action execution, not sensitivity, that is adapted. Unlike prisms, which shift the ocular position of "straight ahead," realigning both visuomotor and limb-proprioceptive reference frames, saccadic adaptation changes the saccade motor plan, directly biasing eye movements, and thus providing a different, and perhaps more direct way of influencing visual perceptual representations.

There are other differences between the two tasks that may also make saccadic adapt-

ation more useful in the eventual study of perceptual bias in neglect. For example; unlike other adaptive systems, saccades are unable to make corrections in-flight due to the lack of useful visual feedback throughout the duration of the action (Dodge, 1900; Mackay, 1970; Campbell & Wurtz, 1978; Volkmann, Riggs, White & Moore, 1978; Matin, 1982). Therefore, they are, by nature, ballistic, relying on error signals after each event to maintain highly accurate motor plans. This may be valuable in neglect as patients tend toward slow, laborious, pointing gestures, and prism adaptation benefits from faster, more fluid movement (Redding et al., 2005)

4.0.2 Saccadic Adaptation

Because of the limitations of vision during eye movements, the saccadic system must rely on errors to maintain precision (Wong & Shelhamer, 2010). As a result, saccade accuracy can be maintained in the face of a wide range of perturbations, from ocular muscle paresis or injury (Kommerell, Olivier & Theopold, 1976), weakness due to aging (Kommerell et al., 1976), or the wearing of magnifying glasses on one or both eyes (Kommerell et al., 1976). There exists a rich, half-century of investigation into the saccadic adaptation system, most of it relying on a behavioural saccadic adaptation paradigm, developed by McLaughlin (1967), that utilizes target perturbations presented during saccades.

Saccadic adaptation involves the systemic perturbation of targets while the participant is making eye movements. If perturbations are configured such that saccades seem to over-shoot their target, then adapted saccades will become shorter over time (McLaughlin, 1967). The same can be done to lengthen saccades, though the mechanisms may be

somewhat different (Catz, Dicke & Thier, 2008; Golla et al., 2008; Hernandez, Levitan, Banks & Schor, 2008; Panouillères et al., 2009; Panouillères et al., 2012; Hopp & Fuchs, 2004).

Saccadic adaptation operates in a retinocentric reference frame. That is to say, the starting eye position is irrelevant, with only the vector direction of the eye movement being important (Catz et al., 2008; Golla et al., 2008; Hernandez et al., 2008; Panouillères et al., 2009; Panouillères et al., 2012). For example, if rightward saccades of 10° are reduced by saccadic adaptation, other similar rightward saccades will be hypometric, regardless of the eye or head position. Congruent with a retinocentric vector-based representation, adaptation of saccades of a given length will continue to affect similar but not drastically different length saccades (Miller, Anstis & Templeton, 1981; Frens & Opstal, 1994; Albano, 1996; Straube, Fuchs, Usher & Robinson, 1997), and horizontal and vertical adaptation are also independent of one-another (Watanabe, Ogino, Nakamura & Koizuka, 2003). Perhaps most indicative of a purely retinotopic reference frame, adaptation of saccades of one direction does not influence saccades of the opposite direction, regardless of spatial overlap (Frens & Opstal, 1994; Albano, 1996). Inducing changes in a retinocentric frame of reference could potentially influence a broader range of behaviours important for both attention and the accurate construction of perceptual representations.

There are also several lines of research that indicate that saccadic adaptation influences perception. For example; Mack, Fendrich and Pleune (1978) found that when a vertical gain was added to horizontal saccades by perturbing targets upward, participants became desensitized to upward motion and sensitized to downward motion. In other words, their threshold for detecting upward motion was increased, while thresholds for detecting down-

ward motion, decreased (Mack et al., 1978). Perception of the spatial location of targets presented before or during saccades can be biased by saccadic adaptation (Awater, Burr, Lappe, Morrone & Goldberg, 2005; Georg & Lappe, 2008; Bruno & Morrone, 2007; Zimmermann & Lappe, 2009), and the pre-saccadic attentional shift can also be influenced (Doré-Mazars & Collins, 2005; Collins & Doré-Mazars, 2006). It could be claimed that the perceptual effects above occur only near saccades, but saccadic adaptation can also induce biases in the perception of spatial extent in the absence of eye movements (Garaas & Pomplun, 2011), providing a good set of converging evidence that saccadic adaptation can influence perception.

The current chapter sets out to examine the potential for saccadic adaptation as a tool for examining the types of perceptual bias observed in neglect, and as a first step toward assessing it as an alternative to prism adaptation for the rehabilitation of the disorder. Despite it's relatively long history of use in psychophysics, the application of saccadic adaptation in clinical research has not been well established, and where it has, it has almost exclusively been with disorders involving cerebellar degeneration, and not cortical disorders like neglect. In one notable exception, saccadic adaptation was used to improve reading speed and performance on a serial visual search task in hemianopic patients (Lvy-Bencheton et al., 2012). It has also been successfully used to improve reading ability in an elderly patient with an acquired oculomotor apraxia and other degenerative disorders that caused gaze abnormalities (Desestret et al., 2013).

Because of the dearth of research, the clinical application of saccadic adaptation on disorders like neglect is unknown. The current chapter examined the influence of saccadic adaptation on perception and action by using landmark and line bisection tasks.

4.1 Method

4.1.1 Participants

A total of 46 individuals, were recruited from the University of Waterloo undergraduate student body through the Research Experiences Group, of which, 37 were able to be successfully calibrated with the equipment to provide reliable eye movement tracking (23 female, 3 left hand dominant, age cohorts: 16-18y = 4, 18-20y = 25, 21-25y = 8). Participants were compensated for participation with course credit, and the experiment was approved by the University of Waterloo Office of Research Ethics

4.1.2 Apparatus and Procedure

Participants were seated with their head fixed in a chin-rest at a distance of 42cm from a touch-screen computer monitor (ViewSonic 17“, Mass Multimedia”Surface Acoustic Wave Touchscreen“; refresh rate 120Hz). The participant was permitted to adjust the height of the chin-rest for comfort. The Eyelink II (SR Research) head-mounted eye-tracker was used to monitor eye movements. During calibration, targets appeared at nine different locations forming a grid that covered the full screen and the participants were instructed to saccade to them as they appeared. The eye-tracker sampled at 500Hz (single eye) and raw eye-position data was saved for later processing. All three computer tasks were programmed using Python and Psychopy (Peirce, 2007).

After eye-tracker calibration, the touchscreen was also calibrated using the manufacturer's calibration task, during which targets appeared at various points on the screen and

the participant was instructed to point to them as they appeared. The landmark and line bisection tasks (described in detail below) were performed first, to measure baseline performance, and then up to four blocks of the three tasks (saccadic adaptation, bisection, and landmark), each beginning with saccadic adaptation, were performed (10 participants opted to end the experiment after 3 blocks due to time constraints). The order that the landmark and line-bisection tasks were presented was randomized from one participant to the next, but remained consistent from block to block.

Landmark and Line Bisection Tasks

Each trial of the line bisection task began with a black screen. The participant was asked to place their finger on the keyboard space-bar. While the key was depressed, after a jittered time interval (on average 0.5 seconds), a horizontal 25° (20cm) by 0.3° white bar appeared on the screen. The line was always centred, but was vertically jittered from trial to trial by up to 6.6°. When the line appeared, the participant was instructed touch the bar where they perceived the centre-most point was, as "quickly as possible." However, the line remained on screen for 1700ms, or until a touch-response was registered on the screen. In practice, this was more than sufficient time for even the most careful participants. A blank screen replaced the target line and the participant was required to return their finger to the space-bar in order to proceed to the next trial. A block of the line bisection task consisted of 10 trials.

Each trial of the landmark task began with a red fixation mark 1.3° tall by 0.3° that appeared near the centre of the screen (jittered vertically by 6.6° from trial to trial). After

0.5 seconds, a horizontal, white bar of the same dimensions as used with the line bisection task appeared behind the red mark and remained on-screen for 1700ms. The red mark was still clearly visible, and the participant was asked to indicate with the computer arrow-keys whether the mark was to the right or left of the centre of the white bar. The following trial, the tick mark would fall slightly further from the end previously reported, and would change in progressively smaller steps from trial to trial (i.e., a staircase procedure). This allowed a precise estimation of the subjective point of equality via a staircase method using up to 20 trials (less if the staircase settled on a stable response earlier). Again, the stimuli remained on screen until a response was registered (Figure 4.1).

Saccadic Adaptation

To the participant, saccadic adaptation appeared to involve visually following a 0.1° black square as it appeared at various places around the grey screen for a period of time (black-on-grey was chosen instead of the white-on-black as used for the other two tasks because of the lingering phosphorescence of the CRT screen when a white-on-black target disappears). Their instructions were simply to follow the dots with their eyes. Underlying this, however, were 100 trials involving central fixation (250ms), followed by a target in the left half of the screen (100ms, jittered by 50ms), then a target 16° (±1.6°) to the right of the previous one. When an eye-movement away from the first target and toward the second was detected (by passing a threshold of distance between the two), the target was perturbed back toward the first target by 30% (5.4°), simulating an overshoot, and intended to reduce saccade amplitude over time (i.e., hypometria; see Figure 4.2 for an overview). One in five trials were "test trials," where the target was not perturbed, but simply disappeared. These trials

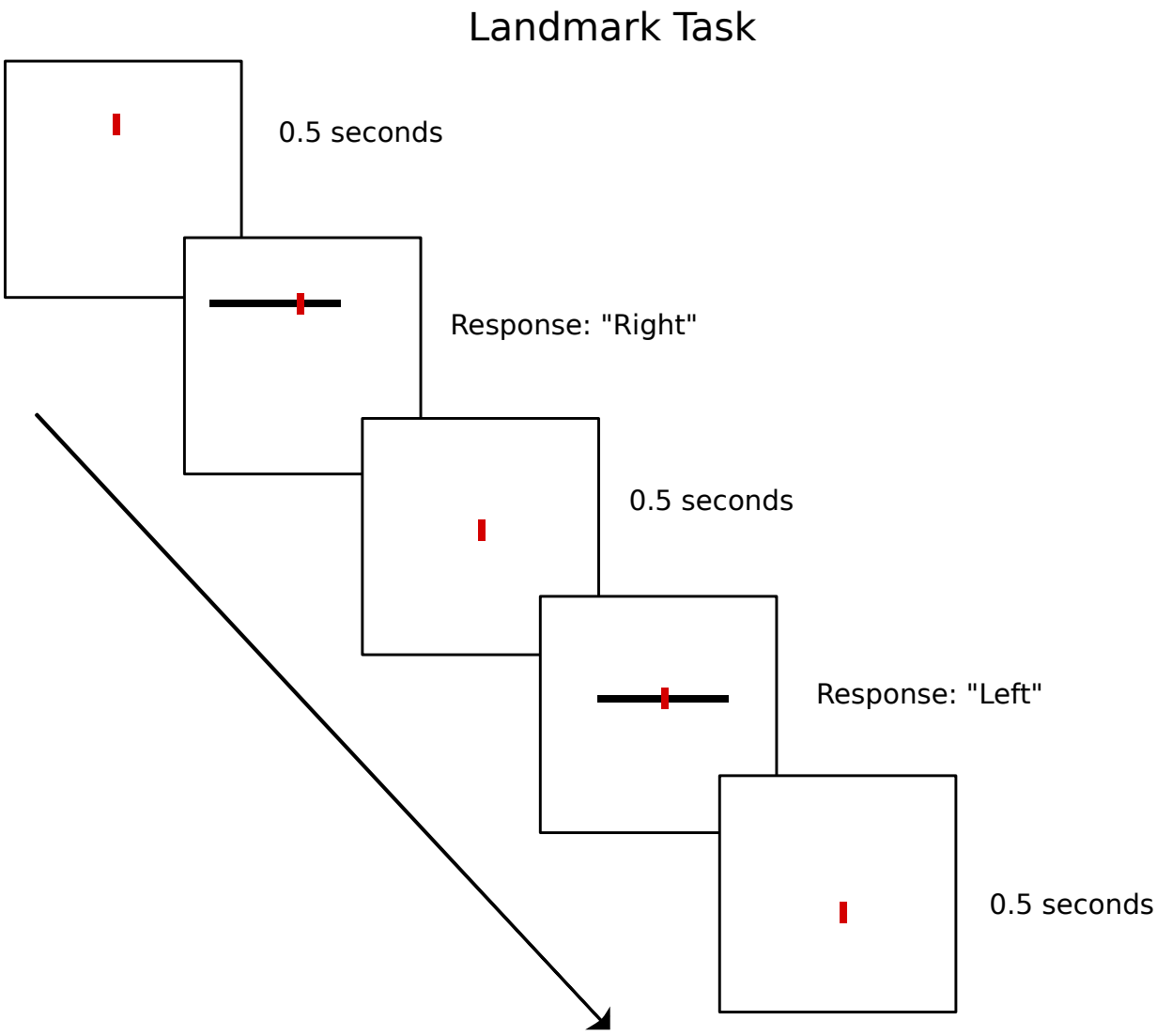


Figure 4.1: Figure depicts two trials of the landmark task. Initial trials have obvious bias, and the participant responds by indicating whether the mark was right or left of centre. The stimuli bias was adjusted with a staircase method to identify the location at which the participant is unable to judge the bias and guesses randomly.

were intended to allow analysis of changes to the saccade length induced by adaptation without the potential that the saccade was somehow updated mid-flight to the new location.

4.1.3 Data Analysis

Landmark and Line Bisection Tasks

For line bisection trials, lateral bias of the touch-responses were recorded with positive values indicating responses to the right of true-centre. For each block, the first trial was removed to allow acclimatization to the task, and the median value of the remaining nine responses was used in the analysis. For the landmark task, the position of the red mark relative to the centre of the line for each trial was recorded, and the mean of the final 5 positions was used in the analysis.

To investigate the potential effect of saccadic adaptation on landmark and line bisection, change scores were computed from the initial, pre-adaptation sessions of the two tasks (i.e., baseline), to the remaining post-adaptation blocks.

Saccadic Adaptation

After the first target of a saccadic adaptation trial was fixated, it disappeared and the second target appeared. At this point, eye position samples from the eye-tracker were recorded until the end of the trial (approximately 2s). This allowed off-line analysis of the initial saccade toward the second target, and any corrective saccades to the perturbed location afterwards. Rather than rely on the real-time saccade detection algorithm executed

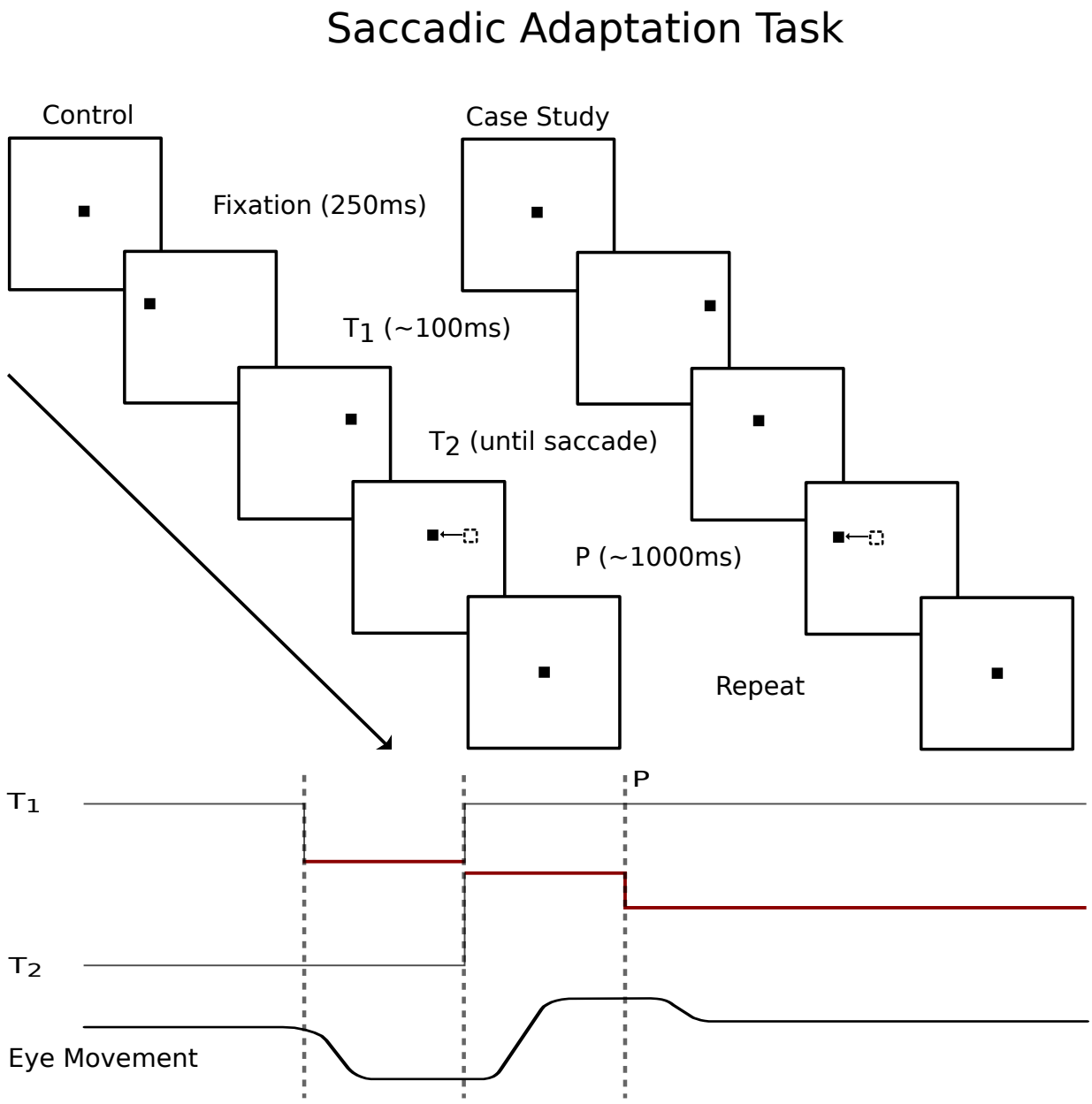


Figure 4.2: Figure depicts saccadic adaptation trials for both experiments. The upper portion depicts the on-screen stimuli presented during an individual trial, while the lower portion depicts expected eye movement relative to target onset and perturbations. The case study (described later) utilized the same timing, but involved different initial target direction, saccade direction, and involved saccadic augmentation, rather than reduction.

by Eyelink's own program, saccades were detected by smoothing and velocity thresholding the data after the experiment was complete (Using SciPy (Jones, Oliphant, Peterson et al., 2001–)). This allowed parameters to be chosen that matched human performance when viewing the eye-position data graphically and manually identifying the precise start and finish of each saccade, permitting accurate saccade length estimates.

Speed data (unsigned horizontal velocity) was smoothed by convolution with a "hanning" window and then a "rolling maximum" of window size of 20ms. A hanning window resembles a Gaussian distribution, but lacks long tails, so makes an effective smoothing filter, emphasizing local characteristics, $w(n) = 0.5\ \left(1 - \cos\left(\frac{2\pi n}{N-1}\right)\right)$). A rolling maximum accentuates sudden bursts of speed, eliminating long rise times, therefore making saccade onset and duration detection easier and more consistent from saccade to saccade. Saccades were detected based on a speed threshold of $57^c irc$/second faster than the median trial speed (empirically determined by visual verification). The analysis of an example trial is presented graphically in Figure 4.3.

Only trials with sufficiently clear initial saccade and at most one corrective saccade were used to calculate eye movement results, and were included based on the following criteria: Trials were required to include more total displacement during identified saccades than fixations (eliminating trials with large drift during fixations). They were also required to contain at least one and at most two saccades in the short window of a trial (3 or more saccades in a single trial usually indicated erratic eye movement recording –often due to partial pupil occlusion). Trials with temporal gaps in samples, which occur during blinks or large head movements, were not included. This stringent criteria resulted in an inclusion rate of approximately half (56%), but provides input for further analysis free from potential

bias by equipment or behavioural artifacts unrelated to the adaptation procedure (Example included and excluded trials are plotted in Appendix A).

The blocks were split up into approximate thirds (30 trials), with the first third of the first block considered as a pseudo-baseline, to be compared with the final third of each of the subsequent blocks (i.e., $Effect_N = \overline{N}_b - \overline{1}_a$). For the first block, this is simply a measure of the change from the beginning to end of the block of adaptation, whereas for the third block, the difference represents the cumulative effect of three blocks of adaptation.

4.2 Results

4.2.1 Saccadic Adaptation

Adaptation was Effective

In order to determine whether the saccadic adaptation procedure successfully changed saccade length from baseline, one-sample t-tests for each block were computed (Figure 4.4a). A participant experienced 6 test trials for each of the block thirds used in this calculation, so each test was run only with participants where the median first saccade length could be based on at least two accepted trials. Blocks 1, 3, and 4 produced significant group change in saccade length ($n = 31$, $t(30) = -2.53$, $p < 0.05$, $n = 20$, $t(19) = -2.58$, $p < 0.05$, and $n = 22$, $t(21) = -3.07$, $p < 0.01$, respectively), while block 2 did not reach significance ($n = 25$, $t(24) = -1.8$, $p = 0.084$). A correction for family-wise error was not applied, as the blocks should be considered a type of replication. While the likelihood of

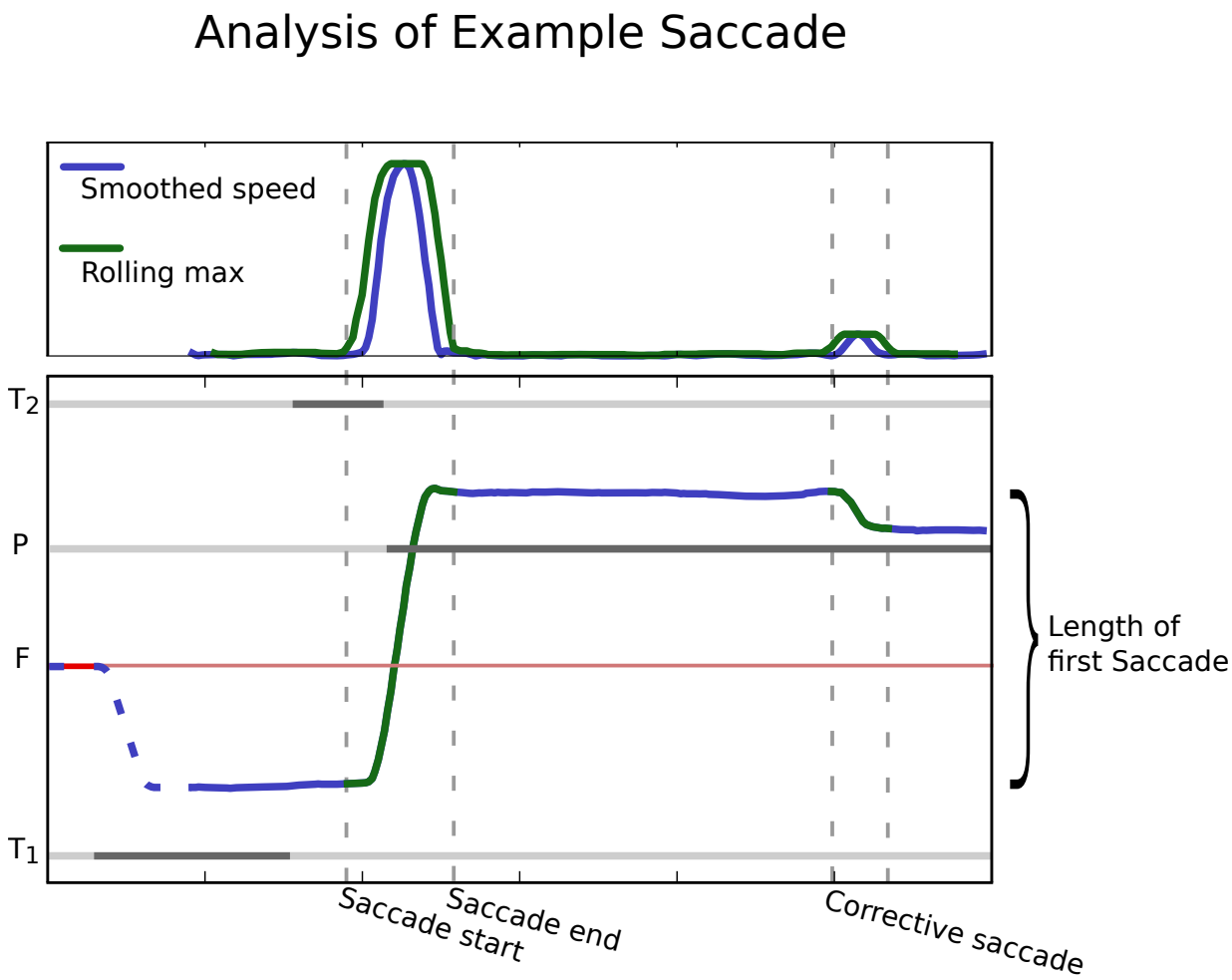


Figure 4.3: Figure depicts typical eye movements over a single trial. Top panel depicts eye movement speed over the course of the trial, while the bottom panel depicts horizontal position relative to the target positions. The rolling maximum broadens the speed curve for a saccade so that a threshold function reliably captures the complete displacement of the saccade. This trial shows partial adaptation, as the initial saccade falls short of the target, but still far enough that a corrective saccade is required to bring the eyes to the perturbed location.

one of the four test-trial tests producing an erroneously significant result, by chance, would be 0.2, the likelihood of 3 erroneous in 4 tests results, as above, is 0.0001.

Magnitude of Adaptation

The test-trials demonstrate significant change post-adaptation free of potential bias by perturbed targets, but the lack of individual trial replication results in large individual variability. The 95% confidence interval for the magnitude of adaptation ranges from 23% to 330%, where 0% would represent no change and 100% would indicate eye movements directly to the perturbed location (i.e., complete adaptation). Thus, adaptation of 330% would indicate severe overcompensation. To gain a more precise estimate of adaptation, the analysis was repeated with all trials. In this case all four blocks demonstrated significant adaptation ($n = 37$, $t(36) = -4.62$, $p < 0.001$, $n = 36$, $t(35) = -6.17$, $p < 0.001$, $n = 35$, $t(34) = -6.76$, $p < 0.001$, and $n = 28$, $t(27) = -5.88$, $p < 0.001$, respectively). Overall, this results in an average adaptation magnitude of 60% (95% CI: 43%–73% adaptation), which is in line with the typical effect size that has been found in the literature (Hopp & Fuchs, 2004).

4.2.2 Landmark and Line bisection

Participants did not show any significant bias when responding on the line bisection task pre-adaptation ($t(36) = 0.57$, $p = 0.575$). In contrast, performance on the landmark task indicated a rightward bias such that participants placed the mark 0.24° (0.18cm) to the right of true centre ($t(36) = 5.23$, $p < 0.001$). Such a rightward bias indicated that

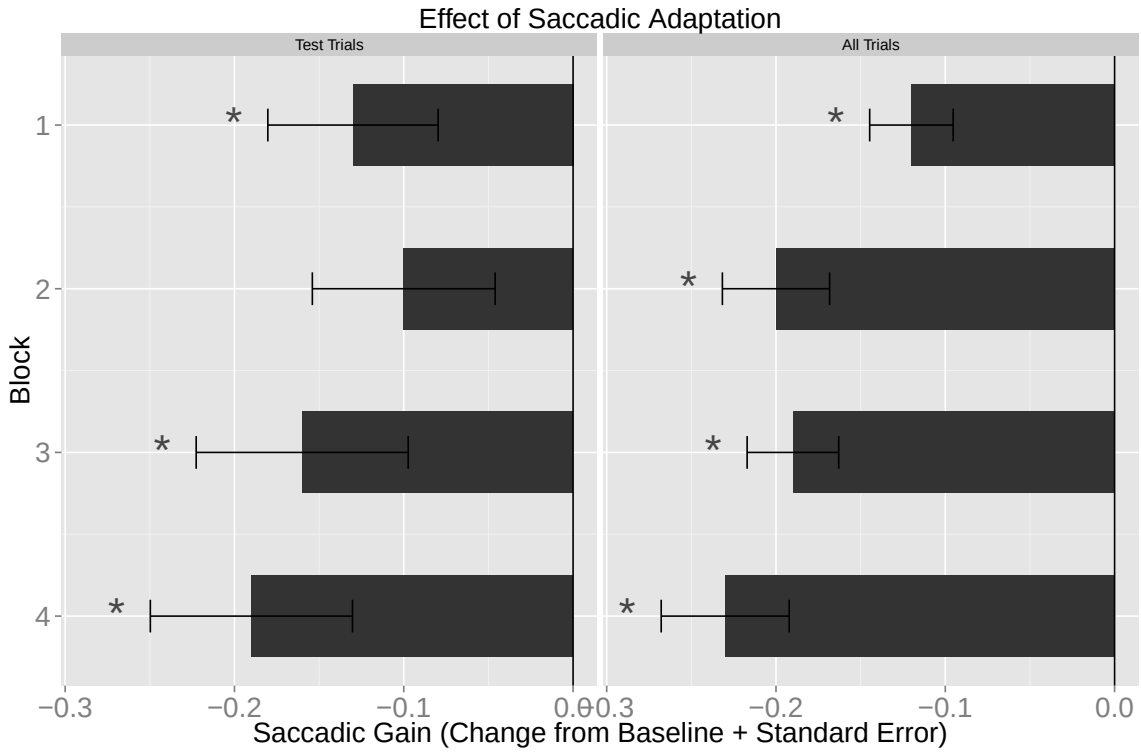


Figure 4.4: Figure depicts the mean degree of adaptation observed in each block. Panel (a) is based on only test trials (i.e., those trials where no target perturbation is displayed), while panel (b) is calculated from all available trials, including non-test trials.

participants perceived the left half of the line to be larger, as has been shown in prior work (Pseudo-neglect; Bowers & Heilman, 1980). Interestingly, all participants performed very accurately on these two tasks, with the worst performance still less than a centimetre from true centre (0.8° and 1.0° for line bisection and landmark, respectively.) Performance on the two tasks was not significantly correlated ($r = -0.3$, $t(35) = -1.71$, p = 0.1).

After the first block, one participant switched to pointing to the end of the line, rather than to the centre, and was excluded from this portion of the line bisection analysis. When the post adaptation change scores were averaged across blocks, neither line bisection, nor landmark task performance showed evidence of a shift ($t(35) = -0.55$, p = 0.583, and $t(36) = -0.88$, p = 0.384, respectively). Based on the sample variance and sample size, a power analysis revealed that the experiment would have had a 95% chance of detecting a post-adaptation change in the landmark task as small as 0.1° (0.08cm, $n = 37$, $sd = 0.15$), less than half the pre-existing bias and a change of 0.12° (0.09cm, $n = 36$, $sd = 0.14$) in line bisection.

The degree of adaptation varied from participant to participant, with a few participants exhibiting mean saccadic change very close to zero. To examine the possible influence of saccadic adaptation further, the above analysis was repeated with only those participants who demonstrated a strong saccadic adaptation effect (i.e., median saccadic gain of -16%, was chosen as the cut off). Again, landmark and line bisection change scores were non-significant ($t(17) = -1.89$, p = 0.076, and $t(17) = -0.36$, p = 0.726, respectively). Note that while this may appear to hint at the possibility of an effect of adaptation on landmark performance, the near-criteria p-value seems to be contingent on the precise cut-off for selecting the participants, so should not be considered reliable.

Examination of the correlation between degree of adaptation and landmark and line-bisection change post-prisms was also non-significant, though landmark performance did approach significance ($r = 0.29$, $t(35) = 1.84$, p = 0.07, and $r = -0.06$, $t(34) = -0.39$, p = 0.7, respectively)

4.3 Discussion

In order to assess the impact of saccadic adaptation on landmark and line bisection performance, it was critical to establish that participants are, in fact, adapting saccade magnitudes. Performance on the first third of the first session was used as a pseudo-baseline, as very little, if any adaptation is expected in the first 30 trials of saccadic adaptation (Hopp & Fuchs, 2004). If this assumption is incorrect, this would only make identifying an effect more difficult.

The test trial data provides a clear indication that saccades decreased in magnitude over the adaptation blocks, but was not able to provide a reliable estimate of the magnitude of that change. By using saccade lengths from all trials, the larger sample sizes produced much less individual variability, and thus provides a relatively precise estimate, which coincides with what has been found in the literature in the past (Hopp & Fuchs, 2004). Because non-test trials included the perturbed target, it is possible that the target influenced the duration of the initial saccade, biasing the adaptation effect calculation, though this should be relatively uniform across participants and blocks, and thus fail to influence the results.

The strict trial inclusion criteria was chosen to ensure confidence that the resulting

metrics were not influenced by artifacts unrelated to the adaptation, however this results in nearly half the trials being removed from the analysis, which magnifies the imprecision of estimates based on the test trials. Future research should consider combining higher frequency test trials and more liberal inclusion criteria. This approach may allow an entire analysis based on test trials, eliminating the possibility of introducing bias.

Performance on the landmark and line bisection tasks was precise, and the experiment was sensitive enough to detect the small pseudo-neglect observed in healthy individuals in previous research (Bowers & Heilman, 1980; Bradshaw, Bradshaw, Nathan, Nettleton & Wilson, 1986; Scarisbrick, Tweedy & Kuslansky, 1987). Saccadic adaptation, however, did not produce a measurable change in landmark or line bisection performance, even though the experiment had sufficient statistical power to detect very small changes.

Chapter 5

General Discussion

The inability to orient spatial attention to left visual space has long been considered the hallmark deficit of unilateral neglect (Danckert & Ferber, 2006). As outlined earlier, research has increasingly questioned the notion that this particular deficit characterizes the primary, or even cardinal characteristic of the disorder. The damage that often leads to neglect happens to straddle the border between the two visual systems as they differentiate dorsally and ventrally (Striemer & Danckert, 2010b). It is therefore perfectly placed to not only interfere with both systems, but potentially corrupt late-stage communication between the dorsal and ventral streams, producing deficits that cannot be accounted for by simplistic single-system, or single-domain, models.

In Experiment 1, patients with neglect demonstrated complex deficits in visual working memory. Namely, when compared with controls, they failed to successfully recall and report the colour of stimuli after a delay (Figure 2.4). They also mis-reported colours when

asked to recall stimuli from a given location, instead reporting colours of stimuli from other, competing, locations (Figure 2.5). While the first deficit appears to demonstrate a simple problem of visual working memory, the latter probably represents a somewhat more complex problem of binding visual information (colour and location) in working memory. The experiment also supports the notion that these working memory deficits are not likely to be down-stream effects of more basic spatial attention deficits. The severity of the visual working memory deficits from one patient to the next did not correlate with the magnitude of deficits observed on covert orienting, but appeared to be relatively independent.

The choice of colour as the characteristic to be remembered was made in response to a possible challenge to previous findings of spatial working memory deficits in neglect. Namely, that such deficits may result from an inability to access attentional resources for rehearsal of spatial locations (Awh & Jonides, 2001). In the single square condition, if rehearsal was utilized, it would primarily involve rehearsal of information such as colour, rather than involving spatial attention. Despite this, the working memory deficit was, indeed, evident. As a result, the findings support the notion that working memory deficits observed in neglect are not a direct consequence of attention deficits, and are likely independently caused.

Thus far, one of the most promising treatments for rehabilitating neglect has been prism adaptation (Luauté et al., 2006). The reason prism adaptation has appeared to be so successful, however, may have been a result of the fact that much of the research has been restricted to tests that effectively measure deficits of spatial attention. Besides the popular covert orienting task, researchers have often used clinical paper-and-pencil tests such as object cancellation, figure drawing or copying (Wilson et al., 1987), tasks that

are, by their very nature, sensitive to an inability to orient to the left. Experiment 2 investigated whether or not prism adaptation would produce a measurable effect on tasks thought to measure ventral-stream dependant processing using spatial working memory and temporal estimations tasks that would presumably not be improved by remediation of spatial attention in the dorsal stream, the apparent target of prisms (Danckert et al., 2008; Clower et al., 1996). The experiment replicated findings that prisms produced a change in line bisection performance, a deficit that is likely driven, at least in part, by an inability to orient leftward, though the effect was far from clear-cut. However, when examining the deficits of spatial working memory in right space, and temporal estimation, two tasks presumably un-affected by deficits of leftward orienting, prisms appeared to lack any significant rehabilitative function. Patients demonstrated extreme deficits on these two tasks both before and after prism adaptation (Figure 3.2 and 3.3).

It was speculated that saccadic adaptation may represent a viable alternative to prism adaptation in the study and treatment of neglect. Although the task is not that different from prism adaptation, it has been demonstrated to produce subtle changes in perception for healthy individuals (Mack et al., 1978; Awater et al., 2005; Georg & Lappe, 2008; Bruno & Morrone, 2007; Zimmermann & Lappe, 2009; Doré-Mazars & Collins, 2005; Collins & Doré-Mazars, 2006; Garaas & Pomplun, 2011). Experiment 3 examined performance of healthy individuals on the landmark and line bisection tasks after sessions of saccadic adaptation. The two tasks comprise largely similar perceptual properties but appear to rely on distinct visual systems (Striemer & Danckert, 2010a). Healthy participants typically demonstrate very small biases, compared with neglect patients, on these tasks. It was therefore suspected that if saccadic adaptation produced changes in perception of

spatial extent and spatial attention, it may show up as small changes on the landmark and line bisection tasks, respectively. Unfortunately, though the participants demonstrated adequate saccadic adaptation, the effect did not appear to influence either task.

The results of the first two experiments involved small groups of patients with unilateral neglect. As with any research examining such restricted population sizes, this limits the confidence that can be placed on the external validity of the results. It cannot be realistically assumed that such a small sample can exactly represent the population as a whole. Further, the heterogeneity of unilateral neglect, both in terms of the extent of brain damage, and in terms of the particular type and severity of deficits, makes extrapolating from a small group problematic. Further research with larger groups of patients are required to verify the reliability and validity of the conclusions made here.

Saccadic adaptation failed to produce a measurable change in landmark and line bisection results, but there are avenues left unexplored in examining the possible reasons for this. First, most of the perceptual after-effects that have been demonstrated post-saccadic adaptation have been restricted to spatial illusions immediately before or after saccades similar to those which were adapted (Awater et al., 2005; Collins & Doré-Mazars, 2006).

Longer lasting effects appear to be possible, but it may require highly specific design elements empirically chosen to maximize them. The types of parameters used are likely to be important, as research has demonstrated that the type of saccade (Schraa-Tam et al., 2009; Johnston & Everling, 2008; Müri & Nyffeler, 2008), or even the magnitude of the adaptation direction (i.e., ±gain; Catz et al., 2008; Golla et al., 2008; Panouillères et al., 2012) can result in very different patterns of brain activation. There are also paradigms

that utilize self-paced, voluntary saccades rather than the reflexive saccades used here, and there is evidence that adaptation of voluntary saccades may rely more heavily on cortical as opposed to cerebellar, circuits (Schraa-Tam et al., 2009; Müri & Nyffeler, 2008), which may prove promising for the rehabilitation of unilateral neglect. Garaas and Pomplun (2011) were able to identify long-lasting perceptual effects of saccadic adaptation, but this involved developing a new, whole-field adaptation protocol. Future attempts to change perceptual biases with saccadic adaptation should consider these parameters and designs, especially the potential use of whole-field adaptation (Garaas & Pomplun, 2011).

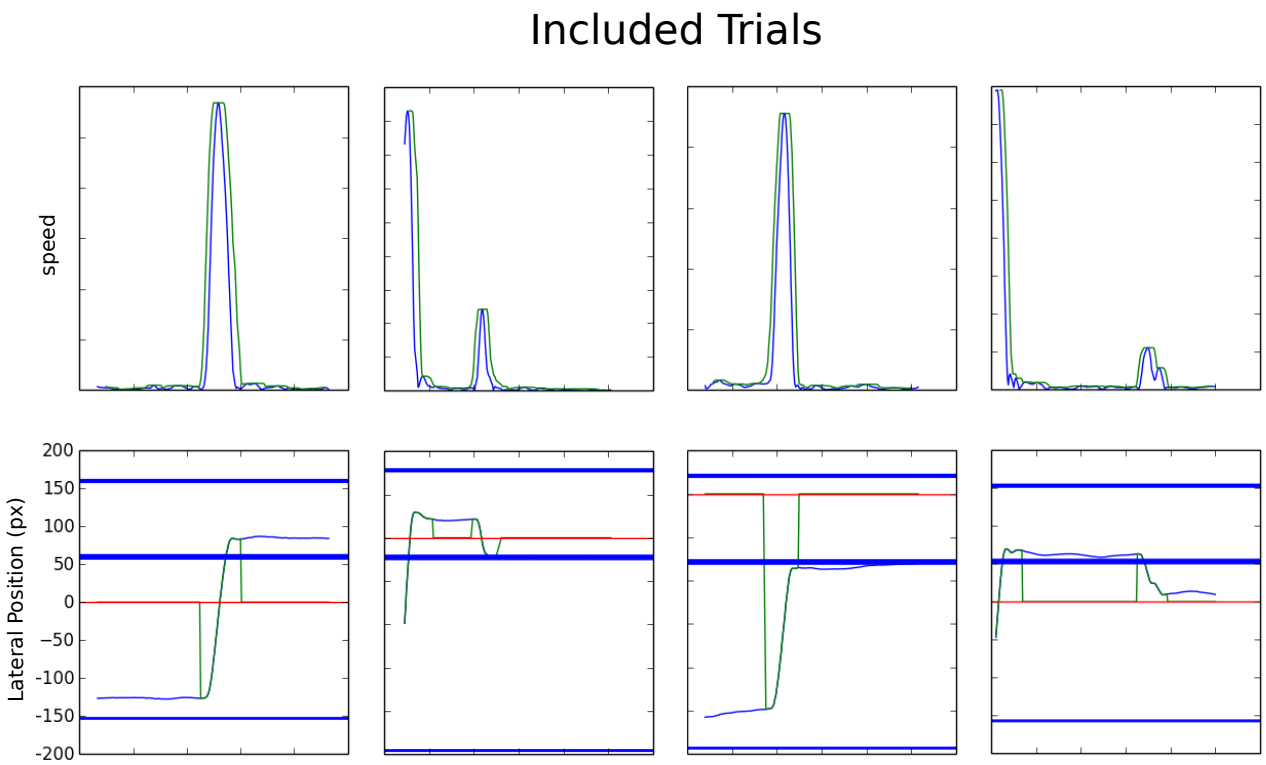
Beyond the type of adaptation used, it is possible that the landmark and line bisection tasks were insufficiently sensitive to reliably measure any effect of the adaptation procedure. Introducing a horizontal jitter to the bisection stimuli may remove the participant's ability to rely on the body mid-line as a reference point and may increase task difficulty, and thus the sensitivity to any subtle biases of healthy individuals. It may also prove fruitful to calibrate the length of the line to maximize sensitivity to the participant's own spatial bias established at baseline. Utilization of a control group or condition, or a positive control, where saccades are lengthened, may also prove effective for identifying subtle changes in the two tasks without the confound of practice effects or fatigue.

Future research should remain considerate of the limitations of prism adaptation, and the particular domains where they do and do-not appear to be effective. Research should concentrate on combining other techniques with prisms to more completely rehabilitate the disorder. For example, the working memory results presented here demonstrate severely degraded abilities. Considering the importance of working memory in self-care and everyday functioning, it seems imperative that prism adaptation be supplemented with some

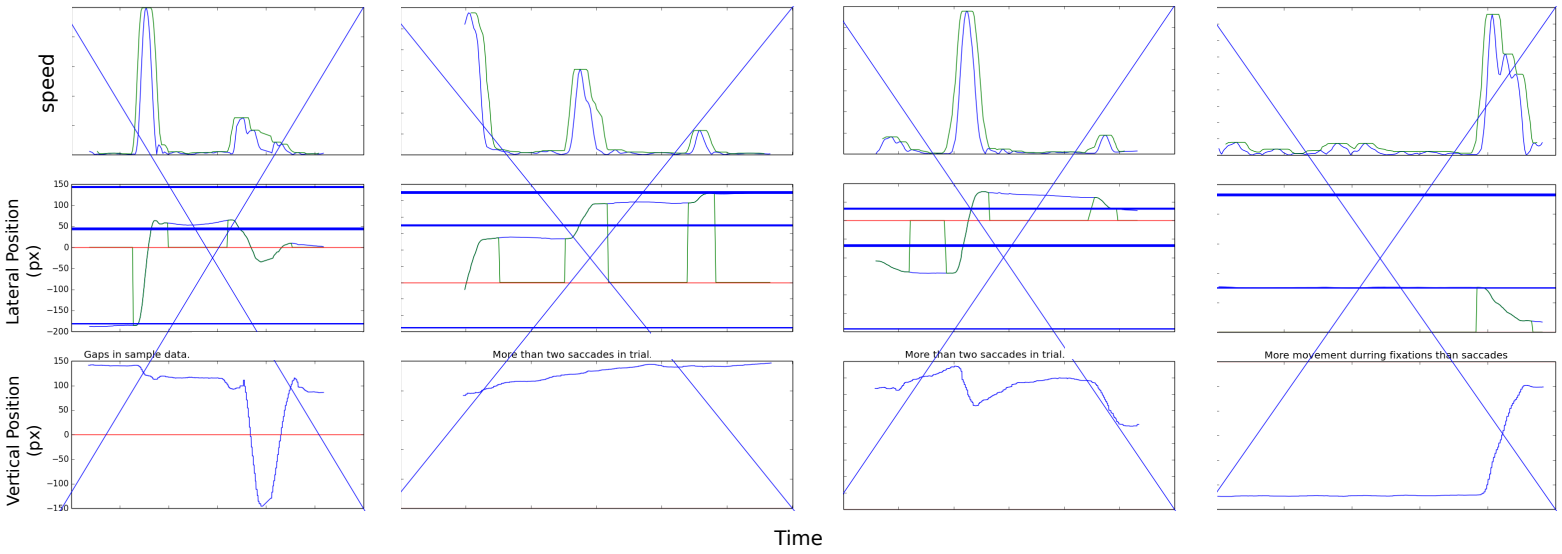
form of working memory training to maximize recovery.

Appendix A

Example Included and Excluded Trials


Included Trials
speed
Lateral Position (px)
200
150
100
50
0
−50
-100
-150
-200

Excluded Trials



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