## Introduction

Unilateral spatial neglect is a disorder commonly resulting from damage to the right inferior parietal or superior temporal cortex [tk]. Hereafter, specifically referred to simply as "neglect," the disorder causes a heterogeneous collection of deficits that can be generally categorized as an inability to respond to information on the contralesional side of space. People with the disorder are spatially biased away from contralesional space in their search behaviour [tk], grooming and eating [tk], drawing [tk], posture [tk], and perceptual judgments of spatial extent [e.g., line bisection]. The disorder is, as can be expected from the list of symptoms, debilitating, and is associated with poor rehabilitative outcome. Less than half of patents show improvements in the weeks after a neglect inducing stroke, and a small minority fully recover [Farnè2004@].

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 [@DriverMattingley1998 ,@HalliganVallar2003,@HeilmanValenstein1993] , or a general loss of environmental awareness that can at its most extreme, cause a person to act as if the entire contralesional half of their world has ceased to exist [@Mesulam1981 ]. 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 the visual search task) and figure copying (a free-hand drawing task) are believably influenced by the patient’s ability to deploy attention across the page. Where attention cannot be directed, mistakes or omissions are made. Even for something like 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 an endpoint is a plausible explanation for impaired performance [i.e., typically marks are placed a long way to the right of true centre; @tk].

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. The so-called ‘disengage deficit’ was first posited as an explanation of the related phenomenon of extinction – the failure to report a contralesional stimulus when presented simultaneously with an ipsilesional stimulus [@tk]. @Posner1984 examined this further using 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; @Posner1980]. 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 the cue when presented in right space [see @BartolomeoChokron2002 and @LosierKlein2001 for reviews]. Similarly, in a visual search task, performance in contralateral space is driven by the number of ipsilesional distractors [@EglinKnight1989]. 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 the current focus and reorient toward a new, salient location [for a review, see @CorbettaShulman2002 ].

Given the debilitating nature of the disorder a broad range of rehabilitation protocols have been attempted [tk]. Perhaps because of the heterogeneity of the symptom profile in neglect, most rehabilitation strategies have met with varied success [@Danckert2006] . 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; @AdairHeilman2003 ,@KarnathHartje1993,@KarnathDichgans1996,@Rubens1985]. 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 recently been shown to have broader, and more lasting effects in neglect [@Rossetti1998; RossiKheyfetsReding1990]. When patients with neglect are adapted to a rightward visual shift and the glasses removed, the after-effects on several behavioural measures are profound, and last considerably longer than the adaptation time [@FarnèRossetti2002 ,@Frassinetti2002,@Pisella2002,@Rossetti1998]. Judgment of straight-ahead and line bisection become closer to true centre [@Danckert2006], object cancellation, and figure copying improves [@Rosetti1998 ], exploratory eye movements demonstrate a reduction in rightward bias [@Danckert2006,@Ferber2003,,], visual imagery [@Rode2001 ,@Rode1998], and posture [@Tilikete2001 ].

Despite the long list of behaviours prisms have been shown to ameliorate, more recent randomized controlled trials have failed to show prisms as an efficacious rehabilitation treatment [@Nys2008 ,@Turton2009]. 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 [@Striemer2007,Nijboer2008], and extinction [@Serino2007], while other, perhaps more realistic measures of attention, such as a serial visual search task, have failed to show an effect [@Morris2004]. 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 as before [@Dijkerman2003 ,@Ferber2003]. This appears to be demonstrating a dissociation between occulomotor "looking" and perceptual "seeing," with prisms restoring the former but not the latter [@Danckert2010].

The dissociation between after effects that influence actions and those that influence perception invokes the dual visual pathways hypothesis of Goodale and Milner [@tk]. 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; tk]. Prisms have been shown to primarily influence processing within the dorsal stream [tk fMRI refs; neglect recovery refs of Luaute et al and Corbetta and gang; Clower 1996 PET paper and 2000’s retroviral tracing in monkeys]. In this framework, prisms will primarily influence behaviours supported by the 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 [@Danckert2010]. In the same respect, the damage limits the ability of a rehabilitative technique such as prisms, that operates primarily on the dorsal stream,from influencing areas in the ventral system responsible for higher level perceptual judgments. This thesis outlines three experiments and a case study chosen to examine this duality between the reactive, motor action system, and perceptual representation/awareness in neglect.

Chapter 1 explores the relationship between visual working memory and spatial attention. It examines the hypothesis that these two domains represent separate, but interacting deficits in patients with neglect. Chapter 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. Chapter 3 develops a procedure for using saccadic adaptation to explore the possibility that modifying eye position sense would lead to more generalized improvements in both action and perception. This preliminary work was conducted in healthy controls. Chapter 4 presents data from a single case study of a neglect patient undergoing the saccadic adaptation procedure. The failure to adapt in this patient points to future directions of research to address both volitional and reactive saccadic eye movements.

The evidence presented in this thesis supports the notion that neglect is not *just* a disorder of attention, but can be characterized by a failure to build accurate perceptual representations of the world. Prisms appear to have an effect on the spatial action systems, having such a strong effect in part *because* of the lack of awareness [@Danckert2010]; however, they do not seem to change the deficits of perceptual representation. Deficits of perceptual representation, as well as being central to the disorder, also represent a major contributor to the debilitating nature of neglect. Concentrating on deficits of perceptual representation has the potential of making substantial steps forward in understanding the disorder and producing more effective rehabilitation efforts.

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

As discussed, 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 right-space stimuli [Posner1984], an attentional ‘stickiness’ that results from disruption to inferior parietal cortex – a region known to be important for effective attentional disengagement and re-orienting [@Corbetta2002]. This anchoring of neglect as an attentional disorder, however, colours performance deficits observed with other tasks – tasks which 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 behavior (i.e., re-cancelling old targets as if they were ‘new’), commonly observed on the non-neglected, "good" side [@Husain2001,@Patron2006], suggest that 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 behavior on the task [@Mark2012].

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 [@Robertson1995], even when operating in a non-spatial modality [@Roberson1997]. 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 between targets in order to identify both correctly [@Husain1997]. 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 [@Husain2001,@Danckert2006,@Malhotra2005,@Striemer2013].

Non-lateralized selective attention and sustained attention are strongly correlated with both neglect severity, and recovery over time [@Husain2003]. Further, remediation of these non-spatial deficits can improve spatial neglect symptoms [@Robertson1995]. 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 [@Husain2003]. 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 [tk]. Unfortunately, while prism adaptation produces striking changes in spatial attention [tk], there is a small, but increasing set of neglect deficits that are not improved [tk]. Many of these findings make use of perceptual tasks, such as the landmark [tk], and chimaeric faces tasks [tk]. 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 in "non-neglected," right or central space [tk]. 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 [@Awh2001]. Specifically, in healthy people, mechanisms of spatial attention provide a rehearsal-like function to maintain information held in working memory [@Awh2001].

This arguably creates three possible causes of working memory problems in neglect. First, they could be a direct result of spatial attention 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 WM. If this was the case, though, we might expect perceptual deficits to improve along with attention deficits and this does not appear to be the case [tk]. Second, the ability to utilize spatial attention for rehearsal may be disrupted in neglect via disconnection of the dorsal and ventral streams arising from the neglect-inducing lesion. This would imply that ventral processing may not be directly impaired in neglect, but that the spatial working memory deficit comes from the ventral system's inability to recruit attentional mechanisms to support rehearsal processes [tk Awh]. Third, working memory deficits may be fully independent of spatial attention deficits.

To test this possibility, 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 the spatial locations of targets, memory for target colour was tested. Placing the primary requirement of the task on colour processing dramatically reduced reliance on spatial attention and placed any rehearsal mechanism requirements within the ventral stream, eliminating the likelihood that the measured deficits would be the result of the hypothesized disconnection 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.

## Method

### Participants

We had patients and controls perform a standard covert orienting task and a visual working memory task (both described below). The covert orienting task was performed by two groups, a group of eight neurological patients who showed symptoms of neglect in pre-testing (3 male, 2 left handed, mean age of 66, see table [tbl:VWM] for more details), and a healthy older control group (3 male, handedness untested, mean age of 74). The study was approved by all relevant hospital and institutional ethics review boards. The two groups were not strictly age-matched, but did not significantly differ with respect to age (, ). All patients were tested at least tk months post-stroke. The visual working memory task was performed by these same two groups plus an additional control group of 9 healthy young adults (tk female, mean age of tk).

FIXME: Recruitment pool(s)?

Patients were also tested for signs of neglect using three standard clinical tests: line bisection, star cancellation, and figure copying [@Wilson1987]. 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 (see table [tbl:VWM]). Only one did not show neglect on any task.

TODO: Table [tbl:VWM] goes about here. Demographic, clinical, VWM, and COVAT summary results of the neurological patient group.

### Apparatus and Procedure

#### Visual Working Memory Task

The visual working memory task was a modification of the one used by @Emrich2012. 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 targets and a colour wheel surrounding central fixation, the colour wheel was replaced with a vertical colour bar and it, as well as the targets, always appeared to the right of centre in order to minimize the impact of spatial attention deficits on WM performance (see Figure [fig:CH1-task]).

A trial sequence for the VWM task was as follows: a fixation cross was presented for 500ms, followed by a target array which consisted of either 1, 2, or 3 targets of different colours presented vertically aligned on the right side for 500ms. Targets could appear in one of 16 different locations in the vertical column. Following target presentation there was a delay of 1000ms, followed by the appearance of the vertical colour bar and probe stimuli. The probes occupied *the same locations* occupied by the targets but were unfilled (i.e., probes did not contain any colour information; Figure [fig:CH1-task]). One of the probes was highlighted by a bolded outline, and participants were asked to indicate, by external mouse input, the colour of the target indicated by the bolded probe location (Figure [fig:Ch1-task). 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 target colour. Note that in the single target condition, there would only be one outline, and the task was essentially to remember the colour of the target. In the two and three target 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 [fig:Ch1-task]).

TODO: Figure [fig:Ch1-task] goes about here. Figure depicts both VWM and COVAT tasks diagrammatically. Task makes clear that there may be 1, 2 or 3 targets on the VWM task.

#### Covert Orienting of Attention Task

The covert orienting task (Posner, 1978, 1980) was identical in design to that of @Striemer2007 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, outlined in figure [fig:CH1-task]. A single trial sequence consisted of a fixation cross with peripheral landmarks (empty green circles 12º to right and left of centre, each subtending 2º). 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 the cued location (valid trials) or at the opposite location (invalid trials; Figure [fig:Ch1-task). Cues were non-informative (i.e., 50% of cued trials were valid and 50% were invalid trials). There were also no-cue trials in which the target appeared without any preceding cue. 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.

### Data Analysis

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 target colour (), one of the distractor target colours (, in the two and three target conditions), or simply represented a random guess (), was calculated with the probabilistic model described in @Emrich2012 and @Bayes2009 (see figure [fig:Emrich2012]).

For each trial, these measures were calculated based on the physical location of the participant's response relative to the true target colours. First, a probability that the participant indicated the correct target colour, , by 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 the response to a non-target, , is calculated in the same way. Lastly, the probability the patient guessed randomly is based on a flat distribution, but the above distributions were chosen so that this was effectively the remainder (i.e., . To compute an estimate of the precision of target responses, the 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 target colour (i.e., and ).

TODO: Figure [fig:Emrich2012] goes about here. If we use this, we need permission to reprint it (right half of figure in @Emrich2012). Figure graphically depicts the three probability distributions used to calculate the three values. I'll combine this with an image of the target and colour bar I also have.

For the covert orienting task, response times were recorded and means were calculated for each trial category for each participant. Cue-effect sizes (CES) – the difference in RT between valid and invalid trials – for leftward and rightward shifts of attention for each participant at each level of SOA were calculated. For leftward shifts, RTs to validly cued right targets were subtracted from invalidly cued left targets (i.e., in both cases, the cue is on the right, and the magnitude of the difference comes from the extra time taken re-orienting to the left invalid target). The rightward CES was calculated in the inverse way – RTs to validly cued left targets were subtracted from invalidly cued right targets.

FIXME: Chris wrote the following in his 2007 paper, is that what was done here? "For controls, RTs were discarded if they were <150 ms or more than two SDs above the participant’s overall mean. For patients, RTs were discarded if they were <150 ms or >1000 ms." Since means were calculated, cutoffs should probably be stated.

Significance was defined as throughout the thesis. Where independent samples -tests are used, unless otherwise specified, the Welch approximation of the degrees of freedom for unequal variance was used.

## Results

### Visual Working Memory

#### Single Target Condition

The single target condition of the VWM task was analyzed separately as it represents an arguably distinct challenge to participants, and the outcome variables are different (i.e., it lacks a measure) when compared with the two and three target conditions. Unlike those conditions, the single target does not require the participant to encode spatial location, or any binding of colour and spatial location. It is more purely a measure of the person's ability to precisely encode and recall a target colour.

Response precision for the single target condition was compared between the three groups using a one-way ANOVA. There were no significant differences between the group means, despite an apparent advantage for the young controls (one way: , ). Both older groups contain extreme examples that, by themselves, significantly increase mean precision for the groups. However, while removing one or both extreme examples from the two older groups may result in a significant group effect, the procedure would only increase the homogeneity of the two older groups, implying an effect of age rather than neglect on precision. It is also worth noting that all of the patients responded within the range of performance observed in the two control groups.

FIXME: No, this is just based on the single target condition. This test is only here to rule out the possibility that effects of neglect, found later, are *not* the simple result of a lost motoric ability to point accurately. I suspect that a mixed effects Anova would be a less robust way to answer this question, due to the increased assumptions. I'll run the mixed model later so it can be slipped in if needed.

Because the single target condition has no non-targets, and therefore no (i.e., ), there is effectively only one dependent variable and the choice of which probability to use for analysis is arbitrary. For convenience, is used here as the dependant variable. As can be seen in figure [fig:VWM\_1Target], the two healthy groups perform nearly perfectly by this metric. A one-way ANOVA containing all three group means was significant (, ). Tukey HSD tests were performed to compare the means, and the two healthy groups, who appear to have been performing at ceiling, are not shown to be different (, ). However, both young adults and the older control group were significantly different from patients (, , and , , , respectively).

TODO: Figure [fig:VWM\_1Target] goes about here. Figure depicts the guessing probability for the three groups, with the two healthy groups obviously at ceiling.

#### Two and Three Target Conditions

In the multi-target conditions, three outcome probability estimates were produced. As was the case for the one target 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, , and the probability of indicating a non-target ()). 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 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.

Guessing measures the tendency to indicate a colour that was not represented in any of the target distributions (see Figure a). The restricted range of probability scores, and high frequency of near-zero outcomes produced a highly skewed and non-normal distribution that even with data transformations, was not sufficiently normal for parametric analysis to be appropriate. The means of the three groups and two target conditions can be seen in figure [fig:VWM\_MTarget\_G]. As an attempt to analyze the data, the two target conditions were collapsed to produce means for a more generic "multi-target" performance metric.

TODO: [fig:VWM\_MTarget\_G] goes about here.

The Kruskal-Wallis rank sum test was used for the non-parametric omnibus model of , and it did not indicate differences (, ). Non-parametric relative effects using Tukey contrasts were performed in a "one-sided" fashion, assuming age and injury would only impair performance. The Patients did not significantly differ from either the young adults (, ), or older controls (, ). Additionally, the two healthy groups did not differ from one another (, ). [Footnote: Parametric tests were also performed using a square-root transform of the data and yielded the same results.]

As was the case for the , the data is highly non-normal and transformations are ineffective in correcting for the nature of the data. Figure [fig:VWM\_MTarget\_NT] presents the means for the two multi-target conditions (2- and 3-targets). As was done for the guessing data, analysis was performed on the collapsed means of the two conditions. Here, however, the Kruskal-Wallis test was significant (, ). Multiple comparison tests yielded significant differences between the patients and the two healthy groups (, , , for older controls, and , , , for young adults). The two healthy groups did not significantly differ from one another (, ).

TODO: Figure [fig:VWM\_MTarget\_NT] goes about here. Figure depicts non-target probability means for the three groups. Might include visual indication of the two conditions that contribute to each mean.

### Covert Orienting Task

Analysis of the covert orienting data was extremely limited given that 3 of the 8 patients failed to respond to any left-sided targets. Not only does this prevent any measure of leftward orienting deficits in almost half the sample, but those three participants also exhibited the strongest symptoms of neglect on the clinical measures. This means that not only is the statistical power of any analysis substantially reduced, but that analysis will necessarily be performed only on moderately neglecting participants.

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 (, , for the patients, and , 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 (, ), while SOA and the interaction were non-significant (, , and , ).

Figure [fig:COVAT] depicts the CES of the 5 neglect participants over the range of performance observed in the healthy controls. As can be seen in the figure, three of the patients performed well within the range of healthy controls. In contrast, the final two patients demonstrated leftward CESs that were well outside the range of the healthy 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 only weakly 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 stars test. It also should be noted that Patient 171 did not show similarly large rightward CE sizes, so it cannot be said that the result was a deficit of general covert re-orienting, but, indeed, a lateralized deficit ( of -22 and 11 for 50 and 150ms SOA respectively). For Patient 454, it was less clear ( of -263 and -21 for 50 and 150ms SOA respectively; negative values indicate faster invalid trials).

FIXME: I don't like the above paragraph, but am not sure what to do with it. It seems muddled to me.

TODO: Figure [fig:COVAT] goes about here. Depicts left CES of each of the 5 patients. I'd include right CES as contrast, but don't think it makes sense as right invalid trials would include a left cue that was (probably) missed.

### Comparing TE and SWM

The reduced group size, as a result of the inability of three patients to orient to leftward targets, prevents reliable statistical analysis of the relationship between the covert orienting and visual working memory tasks. The two patients that performed well outside the range of healthy performance on the covert orienting task did not stand out with extreme performance deficits on the visual working memory task. When compared with the rest of the neglecting group, as can be observed in table [tbl:VWM], Patient 454 performed slightly worse than the median on both visual working memory measures, while Patient 171, who, incidentally was the only one in the group to score negatively on all three clinical measures of neglect, was actually the most accurate participant, again, on both measures. This lack of reliably similar performance between the two tasks hints at the decoupled nature of the two domains suggested earlier.

## Discussion

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 two control groups, demonstrating that basic perceptual representations were intact, and that they are able to perform the motor response as effectively as controls when they are able to recall the correct visual information. In contrast, when examining the apparent reliability of patient's recollections, the data appears to indicate that neglect patients fail to recall the colour of targets and respond in a way that indicates more prevalent guessing.

When participants were asked to perform the same VWM task in the presence of distractors, two things change: there is an increase in memory load, as patients are asked to remember more items, and some of that information must be associated, as patients must now bind colours and locations. 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 distractors as belonging to the indicated spatial position (incorrect target response).

Interestingly, in contrast to the single target condition, the patient group does not appear to guess more frequently than the other groups when presented with multiple targets. This may reflect a limited sensitivity in this task variant, as in the multi-target condition, binding errors appear to be the overwhelming source of failures. While the single-target condition is effectively tuned to detect guessing (as that is the only type of error possible), the multi-target conditions simply provides less opportunity to detect guessing, both in terms of space on the colour bar that results in coding a response as a guess, and in terms of response frequency, given the three possible outcome probabilities.

Additionally, it should not be automatically discounted that a difference in the healthy control groups might account for the failure to identify group differences in guessing in the multi-target condition. The control groups perform almost perfectly on the single target condition, but fell away from this "ceiling" somewhat on the multi-target condition. The difference between neglect and healthy performance may simply be more accentuated when the task is calibrated such that healthy performance is near perfect and not highly variable.

Patients were more likely to select non-targets in multi-target conditions. There are many potential explanations for this, the most obvious being an increase in binding failures (tk Binding errors citation: Treisman, Behrmann or Humphreys and Riddoch). When more than one target is presented, colour information must be explicitly associated with spatial location in memory. 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 50% of the time in the two-target condition, and 66% 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 all of the stimuli colours. If the target colour cannot be recalled, it is possible the participant may be inclined to select one of the distractor colours, or something close to it, by strategy or cognitive anchoring. This experiment is not able to clearly disambiguate the two causes. However, if the large deficit observed here was 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 increase in this condition, binding errors are the more likely culprit.

The data also brings to light some difficulties with the covert orienting task in the study of neglect. Neglect is often defined in terms of attention, but in this case, for three patients, leftward re-orienting of attention appeared to be less sensitive a measure of neglect than the paper and pencil standard clinical measures. As used here, it appears to suffer from a restriction of range problem. While several of the most severely neglecting participants could not complete the task at all, several others, whom still exhibited signs of neglect on at least one clinical measure, performed well inside normal parameters. The apparent failure of the task to capture either subtle or strong deficits indicates that the task, as it was used here, may not be very effective for capturing the range of attention deficits in neglect, or useful for the comparison of attention and other deficits in neglect.

While a reliable statistical comparison of the two tasks was made impossible by the inability of several participants to complete the task, there is some information that may be gleaned from what remains, and provide hints toward further research. The two patients with strikingly poor ability to re-orient leftward did not stand out as being particularly degraded on either visual working memory or clinical measures of neglect. In fact, one of them did not show clinical neglect at all. This should serve as a cautionary note, hinting that it may be possible for some individuals to exhibit strong leftward covert orienting biases in the absence of symptoms on clinical measures of neglect, or visual working memory deficits.

Despite the fact that 8 patients with neglect were recruited for this study, as can be seen from the results, there are several issues with making strong claims about group differences. Most notably, neglect patients are a highly heterogeneous group, with widely varying degrees of deficits, and different relationships between the deficits. Clinical measures such as those used here may not be sensitive enough, or cover enough domains of performance, to detect deficits still present in the individual. Further research, would benefit from within-subject designs, such as before-and-after certain treatments, or longitudinally, as patients recover. Such designs would avoid some of the problems inherent in group-wise comparisons hamstrung by the heterogeneity of the disorder. The clinical symptoms, covert orienting deficits, and visual working memory deficits examined here may emerge from damage to un-related or weakly-linked domains of the neglect disorder, but further research with larger sample sizes, preferably making use of repeated measures designs, are needed to explore this further.

Most rehabilitation techniques implemented in neglect focus on remediating the attention deficits. If these attention deficits are indeed distinct from the working memory impairments discussed here and elsewhere (tk), 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.

# 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 specific to spatial working memory, and therefore cannot be reduced to a simple consequence of spatial attention. This working memory deficit joins several perceptual deficits discovered in neglect to highlight an independent, subtle but debilitating, set of deficits 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 [tk]. Much of the research into prism adaptation has focused on the striking changes in spatial attention, demonstrating a shift from completely ignoring stimuli left of centre, to attending almost equally to leftward as rightward stimuli [one or more of Striemer & Danckert, 2007; Nijboer et al., Schindler et al., 2008]. Interestingly, at least one prism adaptation study failed to demonstrate what seems consistent and reliable elsewhere. While most of the research investigating the effects of prism adaptation on spatial attention utilize tasks such as covert orienting or tk, @Morristk used a visual search paradigm, and was unable to demonstrate any benefits of prism adaptation [@Morristk].

Serial visual search involves successive steps that make use of more than a single system. There is the perceptual judgment of stimulus identity that determines progress in the search, for instance. 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 fixate but fail to identify targets occasionally [tk], so reduced perceptual judgment could play a role in diminished performance. That 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. Further, the revisiting behaviour observed when neglect patients perform object cancellation tasks [tk] suggests that their search patterns may be indicative of impaired working memory (refs).

The reliable effect of prisms on remediating spatial attention deficits, with their simultaneous lack of obvious efficacy on more perceptually demanding tasks and visual search, a working memory loaded task, indicate that their effect may be primarily on 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 much of the parietal lobe [tk]. Conversely, it places perception, and working memory of those perceptions, in the ventral stream, radiating into the temporal lobe [sametk]. Various lines of research have pointed to prisms specifically effecting dorsal areas. @Danckert2008 and @Clower1996 have both demonstrated "dorsal stream" activation during prism adaptation, with fMRI and PET respectively. Both studies found activation in the intraparietal sulcus. @Danckert2008 also found anterior cingulate and cerebellar activation, but neither study identified activation in ventral stream areas.

Some research into the specific neural correlates of prisms in neglect. @Luatei2006 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 [@Luate2006]. 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 [@Corbetta2005].

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 loading the ventral visual system in neglect (i.e., visual and spatial working memory [Ch.1., tk], perceptual judgments of spatial extent [tk], or emotional expression [tk], among others). This chapter explores the influence of prisms on two functions shown to be impaired in neglect, and chosen because they demonstrate impairments in a neglect patient's ability to maintain accurate perceptual representations of his or her environment. The effect of prisms on spatial working memory and temporal perception were examined. Both spatial working memory and temporal perception are predominantly tasks of perception, and 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 expected to show prisms simultaneously benefit dorsal stream tasks, such as the clinical line-bisection measure, but not perception-dominant tasks, such as spatial working memory or temporal perception.

## Method

### Participants

Nine 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). Two patients were unable to return for the second phase of the experiment because of extenuating circumstances, and a third participant was removed from the study because of extensive cerebellar damage. The remaining six, (tk male, tk female) patients completed the task. The group had a mean age of tk (), and tk were right handed. The study was approved by the relevant hospital and institutional ethics review boards. All patients were tested at least tk months post-stroke. 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.

TODO: [tbl:Prisms] goes about here. Table includes demographics, stroke info, clinical measures, pre- and post-prisms z-scores on the two tasks.

### 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. One patient discontinued their first session due to fatigue but was able to complete testing in a second session.

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" [@Wilson1987]. 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. Coding and analysis of the tasks were performed in the same way as in Chapter 1. The results of the clinical measures are depicted in table [tbl:Prisms].

#### Spatial Working Memory Task

The spatial working memory (SWM) task is a similar, simpler relative of the visual working memory task that was used in the last chapter [@Ferber2006]. Patients were seated at a viewing distance of approximately 60 cm, with their head and body axes aligned (no chin-rest was used, optical angles presented below are therefore approximate). The task was programmed in Visual Basic Version 6.0 (Microsoft Inc.), and displayed on a tk computer with a tk inch display. The task was the same as described in @Ferber2006. 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 2º to the right of fixation, vertically aligned. The targets were squares subtending 1.5º, and could appear in any of 16 different locations, however, targets were always separated from one-another by at least 2º.

The targets remained on-screen for 2 seconds which was followed by a delay of 3 seconds. A probe stimulus (a circle of the same size as the target squares) appeared at one of the 16 possible locations. The probe remained on the screen until a response was entered via the keyboard (figure [fig:Prisms]). 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.

TODO: Figure [fig:Prisms] goes about here. Diagrammatic outline of the SWM and TE tasks.

#### Temporal Estimation Task

The Temporal Estimation (TE) task was displayed on the same computer as the SWM task, but was programmed in E-Prime (Psychology Software Tools). As with the SWM task, patients gave verbal responses, and the experimenter entered those responses and controlled the task via the keyboard. The task was the same as @Danckert2007. When a trial was initiated by the experimenter, an illusory motion stimulus was presented that consisted of eight open circles (each subtending 3.5º), arranged in a larger circle around the centre of the screen (radius of 8º), with each circle being filled, sequentially one at a time, in a clockwise direction (figure [fig:Prisms]). 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, 1.5º 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.

### Data Analysis

As in chapter one, 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 pre- and post-prisms, and where multiple sessions were performed, values were averaged (Table [tbl:Prisms]).

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 [@Ferber2006].

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.

## Results

### Spatial Working Memory Task

Replicating previous research using this spatial working memory task [@Ferber2006, @Striemer2013], all of the patients who were showing clinical signs of neglect performed very poorly. Figure [fig:SWM] plots the patient mean accuracy along with expected range (2 standard deviations from the means) of the neurologically intact and non-neglecting right brain damaged participants from @Ferber2006. While the patient who did not demonstrate neglect on the clinical tasks at time of testing (27) performed similarly to the non-neglecting group, the remaining patients baseline performance was at least 3 standard deviations outside what was observed in either group.

TODO: Figure [fig:SWM] goes about here. Depicts pre and post-prism SWM performance for all participants, with normative regions.

As a group, SWM performance does statistically improve when a one-sided test is used (presuming prisms would not decrease performance, , ). When consulting figure [fig:SWM], it becomes obvious, however, that there is not a consistently large improvement across all patients, and even those who did improve did not demonstrate performance in the range expected from healthy individuals (figure [fig:SWM]). All four patients showing clinical signs of neglect still showed 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, neurologically intact right-brain damaged individuals (the lighter region in figure [fig:SWM]), patient 171 does cross into a region statistically indistinguishable from normative performance (), but the others remain well outside ().

### Temporal Estimation Task

As can be observed in figure [fig:TE], the five patients who showed clinical signs of neglect massively underestimated the time intervals (Patient 27 underestimated to some degree pre-prisms, and responded very accurately post-prisms). 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 indication of an influence of prisms on time interval reporting (, ).

For each participant and condition, a linear model (least squares) was computed in order to yield a measure of the relationship (slope) between time intervals and reports. As can be seen in figure [fig:TE], 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, : first quartile =0.80, median =0.87, third quartile =0.92). The worst case model was, nevertheless, still significant (, , ), indicating that despite their poor performance, patients' responses were, in fact, reliably influenced by the true trial intervals.

TODO: Figure [fig:TE] goes about here. Figure depicts both line-plots of reported interval vs. true interval, and barplots that more clearly depict performance change pre- to post prisms (slope of log-time).

### 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, , ). Individual t tests on the sets of line bisections for each patient demonstrated a relatively consistent effect across individuals. As can be seen in figure [fig:LB\_Prisms], the changes were nearly-universally leftward excepting Patient 27, the non-neglecting patient.

TODO: Figure [fig:LB\_Prisms] goes about here. Figure caption will include all of the individual t-tests and differences on the plot will be indicated with stars. All patients showed significant change post prisms except 163 and 408 (with the latter not quite reaching significance due to extreme trial-to-trial variability).

As a group, the neglecting patients did not improve on either bells (, ), or star cancellation (, ), and, as can be seen in table [tbl:Prisms], only one patient showed improvement on figure copying (Patient 171).

## 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 [tk], a task that involves a motoric reporting of centre and is associated with dorsal brain activation [tk]. 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 [tklandmarklinebisectiondanckert]. The findings here strongly suggest that, in at least some of the neglecting patients, prisms did appear to bring about a shift in bisection toward the neglected field. Due to the characteristics of the treatment and sample-size limitations, an experimental design that would have eliminated possible practice-effects was not possible. However, keeping in mind that limitation, it is the pattern of response between this "dorsal" task and the other, more perceptual, tasks that is most informative.

The spatial working memory task, despite being spatial in nature, is designed to test for the more ventrally-oriented working memory deficits, and relies on stimuli in central and right space, rather than left space, where spatial attention defects 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 [tk]. When the patients performed the spatial working memory task after prism adaptation, they did show statistically significant improvement as a group, but that improvement, for the most part, would not be considered clinically significant. That is to say that the change left all four neglecting patients with large deficits relative to typical control performance, with three of those four performing well outside of what would be expected to be observed in the control population.

Like 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 made for longer interval durations), the five patients who showed clinical signs of neglect massively underestimated the durations both before and after prisms. In this case, it appears prisms had no 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, here data are presented where prisms produced significant and relatively reliable change in individuals with neglect, and this data is paired with two other tasks which putatively rely on different, ventral stream processing. These other two tasks demonstrate continued deficits post prisms. This lack of clinically relevant improvement fits the prediction that prisms, a task demonstrated in the past to influence primarily dorsal brain regions, would have minimal effects on the deficits of working memory and time perception observed in neglect because they rely on putatively ventral functions. The disassociation between these two sets of results lends credence to the hypothesis presented earlier that neglect is a disorder involving two independent systems, and that remediation of only one system will have minimal effect on the deficits arising from the other. More effective treatments will then necessarily need to induce changes in the ventral perceptual system.

# Can saccadic adaptation improve both action and perception?

The previous chapter demonstrates that prism adaptation fails to improve performance on both spatial working memory and temporal estimation tasks. This can be explained by the dorsal-ventral disassociation. These tasks were chosen because of their perceptual nature. If prisms influence dorsal stream functioning, and these tasks are dominantly tests of ventral stream functioning, then it follows that these specially chosen perceptual tasks will not be substantially remediated by prisms [@Striemer2010].

Prism adaptation, by design, influences both visual and proprioceptive frames of reference [@Redding2005]. 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 [@Redding2005]. 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. 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 [@Redding2005, @Herlihey2012].

Another visuomotor adaptation procedure, called saccadic adaptation, offers a potential alternative approach to rehabilitating neglect that may overcome some of the shortcomings of prism adaptation. This is because 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 make saccadic adaptation more useful as a rehabilitation tool 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 [@Matin1982]. 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 [@Redding2005]

Because of the limitations of vision during eye movements, the saccadic system must rely on errors to maintain precision [@Wong2010]. As a result, saccade accuracy can be maintained in the face of a wide range of perturbations, from ocular muscle paresis or injury [@Kommerell1976] , weakness due to aging [@Kommerell1976], or the wearing of magnifying glasses on one or both eyes [@Kommerell1976]. 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 @mclaughlin1967, 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 [@mclaughlin1967]. The same can be done to lengthen saccades, though the mechanisms may be somewhat different [@Catz2008, @Golla2008, @Hernandez2008, @Panouillères2009, @Panouillères2012].

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 [@Catz2008, @Golla2008, @Hernandez2008, @Panouillères2009, @Panouillères2012]. For example, if rightward saccades of 10º 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 [@Miller1981; @Frens1994; @Albano1996; @Straube1997], and horizontal and vertical adaptation are also independent of one-another [@Watanabe2003]. 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 [@Deubel1986; @Frens1994; @Albano1996]. 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 can influence perception. For example, @Mack1978 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 downward motion decreased [@Mack1978]. Perception of the spatial location of targets presented before or during saccades can be biased by saccadic adaptation [@Awater2005, @Georg2008, @Bruno2007, @Zimmermann2009], and the pre-saccadic attentional shift can also be influenced [@Dore-Mazars2005, @Collins2006]. 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 [@Garaas2008], 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 rehabilitative tool for neglect. However, the application of saccadic adaptation in clinical research has not been well established. 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-Bencheton2012]. 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 [@Desestret2013]. Despite the dearth of research, the clinical application of saccadic adaptation on disorders like neglect is under-examined.

# Method

### Participants

A total of 46 individuals (33 female, 3 left hand dominant, age: , ), were recruited from the University of Waterloo undergraduate student body through the Research Experiences Group.

### 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, both eyes were monitored, but afterwards only one eye was monitored during the task. The eye-tracker sampled at 500Hz and raw eye-position data was saved for later processing. All three computer tasks were programmed using Python and Psychopy [@Peirce2006].

After eye-tracker calibration, the touchscreen was 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 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 (approximately 0.5 seconds), a horizontal 25º (20cm) by 0.3º white bar appeared on the screen. The line was always centred, but was vertically jittered from trial to trial by up to 6.6º. 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 line bisection consisted of 10 trials.

Each trial of the landmark task began with a red fixation mark 1.3º tall by 0.3º that appeared near the centre of the screen (jittered vertically by 6.6º 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 (see figure [fig:Landmark]).

TODO: Figure [fig:Landmark] goes about here. Diagrammatic depiction of trial progression and full experimental sequence (two-panel).

#### Saccadic Adaptation

To the participant, saccadic adaptation appeared to involve visually following a 2º 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 300 (+-30)º to the right of the previous one. When an eye-movement toward the second target was detected (by passing a threshold of distance between the two), the target was perturbed back toward the initial target by 30% (100º), simulating an overshoot, and intended to reduce saccade amplitude over time (i.e., hypometria; see figure [fig:SA] for an overview). One in 5 trials were "test trials," where the target was not perturbed, but simply disappeared. These trials 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.

TODO: Figure [fig:SA] goes about here. Diagrammatic depiction of saccadic adaptation trial.

### 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.

#### Saccadic Adaptation

After the first target of a saccadic adaptation trial was fixated, it disappeared and the second target appeared. At this point, 500hz eye position samples from the eye-tracker were recorded until the end of the trial (approximately 2s). This allowed later 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 by Eyelink's own program, an algorithm was developed that matched human performance when viewing the eye-position data graphically and manually identifying the precise start and finish of each saccade. The eye position data contained a large amount of noise, so determining the precise start and end of a saccade, which are needed to produce reliable estimates of saccade length, and thus adaptive gain effects, was critical to robust analysis.

Duplicate samples were removed and eye movement speed was then calculated as the sample-to-sample position change (unsigned). This speed data was smoothed by convolution with a "hanning" window (a hanning window resembles a Gaussian distribution, but lacks the long tails, so makes a good smoothing filter, ). Saccades were detected by first convolving a "rolling maximum," with a window of 10 speed samples. A rolling maximum was chosen instead of the more commonly used average, as it accentuates sudden bursts of speed, therefore making saccade detection easier and more reliable. A saccade was defined as regions where the rolling maximum met a threshold greater than the median trial speed plus an experimentally determined parameter (1500º/second). The analysis of a typical trial is presented graphically in figure [fig:Saccade\_detection].

TODO: Figure [fig:Saccade\_detection] goes about here. Depicts the three stages of detecting the saccades from a trial in panes.

Individual trials were then removed from the analysis if the data was not of sufficient quality to calculate a reliable first-saccade length. These criteria and parameters were determined by plotting randomly selected trials from the data-set and comparing the algorithm's selections with manual judgment. Trials were removed if there was more total displacement during fixations than identified saccades (which occurred when large but slow velocity drifts occurred during fixations). They were also removed when there were more than two saccades in the short window of a trial (3 or more saccades in a single trial usually indicated erratic eye movements). Trials were also dropped if they appeared to contain no saccades, or if a lack of eye position data from the tracker resulted in large gaps or a low overall number of samples (which can result from blinking). As a result, approximately half (56%) of trials proved usable in the analysis.

The blocks were split up into approximate thirds, 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. Five participants were removed from the analysis because they lacked a sufficient number of acceptable trials per third (10) to make reliable calculations, on two or more of the four blocks.

### Case Study

As a pilot experiment to examine the practical considerations and potential viability of saccadic adaptation in unilateral neglect, a single participant who had demonstrated symptoms of neglect was recruited from the Neurological Patient Database (University of Waterloo). The parameters of the task were eased in anticipation of the needs of the participant. For the saccadic adaptation, the target was larger (6x6º). The initial target was always to a target in the right half of the screen (100 to 300º right of mid-line, 300º above or below the horizon), rather than left as in the normative sample above. It was followed, by a second target 300º left of this initial position. When a leftward saccade was detected, this target was perturbed further leftward, with the intent of simulating an undershoot, with the intent of augmenting saccade length over time. A leftward increase in saccadic gain was chosen based on the hypothesis that inducing a leftward saccadic bias may reduce the rightward attentional bias inherent in the disorder. During the landmark task, the patient reported verbally rather than by keyboard and, for both tasks, the stimuli remained on-screen as long as required for a response.

## Results

### Saccadic Adaptation

The median saccade length of the test trials belonging to the first third of the first black of adaptation trials (i.e., what is being used here as a baseline measure) were subtracted from the medians of each block's final third test trials. Because so many trials were removed for poor data quality, many participant's had individual blocks lacking sufficient test-trial data to perform this calculation. Out of the 41 participants, between 11 and 22 of them did not have at least 2 acceptable test trials (out of a maximum of 6) from which to calculate adaptation. Nevertheless, one-sample t-tests of the remaining participant blocks were used to determine whether the adaptation paradigm had successfully shortened saccades, and 3 of 4 blocks showed significant change from baseline (see table [tbl:Adaptation]).

While test trials provide a measure of the degree of adaptation in the absence of any responses to target perturbations mid-flight, the sparsity of data when using only these trials limits the potential power and reliability of further statistical analysis. Further, the average change in saccadic length (including all all blocks) was -69%, which is more than double the actual target perturbation (30%), and includes an exceptionally large 95% confidence interval ranging from -100% to -7%. Alternatively, if all trials are included instead of just test-trials, the overall mean saccadic change is -18% (95% CI of (-0.22, -0.13)). This change represents 60% of the perturbation distance, which is in line with the typical effect size that has been found in the literature [tk]. Given this, the results based on all trials, rather than just test trials, are taken to provide a more reasonable measure of the effect, and is used in the remainder of this analysis.

TODO: [tbl:Adaptation] goes about here. Data below:

### Landmark and Line bisection

Participants did not show any significant bias when responding on the line bisection task pre-adaptation (, ). In contrast, performance on the landmark task indicated a rightward bias such that participants placed the mark 0.24º (0.18cm) to the right of true centre (, ). Such a rightward bias indicated that participants perceived the left half of the line to be larger, as has been shown in prior work [tk pseudo neglect ref]. Interestingly, all participants performed very accurately on these two tasks, with the worst performance still less than a centimetre from centre (0.8º and 1.0º for line bisection and landmark, respectively.) Performance on the two tasks was not significantly correlated (, , ).

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, to the remaining post-adaptation sessions. One participant was excluded from line bisection task as they pointed to the end of the line, rather than centre, after the first block. When the change scores were averaged across blocks, neither line bisection, nor landmark task performance showed evidence of change post-adaptation ( , , and , 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 0.1º (0.08cm, , ), less than half the pre-existing bias and a change of 0.12º (0.09cm, , ) 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 influence of saccadic adaptation further, the above analysis was repeated with only those participants demonstrating a strong saccadic adaptation effect (The median saccadic gain, of -16%, was chosen as the cut off). Again, landmark and line bisection change scores were non-significant ( , , and , 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 ( , , , and , , respectively )

### Case Study

The neglect patient made saccades normally to the first target in the adaptation task (rightward), however, he was never able to acquire the second, leftward target. After the first target disappeared, the patient always returned to the centre of the screen, anticipating the central fixation which would begin the next trial. The trial would time-out and the fixation would then appear. After several unsuccessful attempts to verbally and manually cue the patient to the second target in the sequence, the experiment was discontinued.

## 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 [tk]. If this assumption is incorrect, this would only make identifying an effect more difficult.

The sparsity of test-trials in the saccadic adaptation paradigm raises questions about the reliability of results derived from them. However, regardless of whether just test-trials or all trials were used, participants appeared to reliably shorten their saccades in each block (table [tbl:Adaptation]). While the test-trial data set provides a clear indication that adaptation was successful, it is not able to provide a reliable estimate of magnitude, necessitating calculations based on all trials. When this was done, adaptation magnitude was typical of that found in the literature.

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 [tk]. 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.

The case study made clear that special experimental considerations, beyond what is typically made for prism adaptation, need to be made with saccadic adaptation for the task to work with neglect patients. The design of the stimuli used here was either insufficient in saliency, or involved too large a leftward saccade, to effectively elicit a leftward saccade to acquire the second target. Further research attempting saccadic adaptation may require either a new experimental configuration, or locating a patient who is only showing weak signs of neglect. These potential constraints on saccadic adaptation highlight the relative ease with which patients are able to perform prism adaptation. For practical reasons, saccadic adaptation may not be suitable for rehabilitation of neglect.

# General Discussion

The inability to orient spatial attention to left visual space has long been considered the hallmark deficit of unilateral neglect [@Danckert2006]. 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 [@Danckert2010]. 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 chapter 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. They also mis-reported colours when asked to recall stimuli from a given location, instead reporting colours of stimuli from other, competing, locations (figure [fig:tk]). 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.

Thus far, one of the most promising treatments for rehabilitating neglect has been prism adaptation [tk]. 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 [@Wilson1987, tkmodernreview], tasks that are, by their very nature, sensitive to an inability to orient to the left. Chapter 2 investigated whether or not prism adaptation would produce a measurable effect on tasks thought to measure ventral-stream dependant processing: 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 [@Danckert2008, @Clower1996]. 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 [fig:tk]).

It was speculated that saccadic adaptation may represent a viable alternative 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 [@tk]. Chapter 3 began with an examination of healthy performance on the landmark and line bisection tasks. The two tasks have been used before in neglect research as they comprise largely similar perceptual properties but likely rely heavily on distinct visual systems [@tk]. 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. At the same time, a single case study attempting saccadic adaptation in a neglect patient was unsuccessful because the task demands proved too difficult.

The results of the first two chapters 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 [@Awater2005, @Collins2006]. 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-Tam2009,@Johnston2008,@Müri2008], or even the magnitude of the adaptation direction [i.e., +- gain, @Catz2008, @Golla2008, @Panouillères2012] can result in very different patterns of brain activation. @Garaas2008 was 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, especially the potential use of whole-field adaptation [@Garaas2008].

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, where they exist. 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.

The saccadic adaptation case study demonstrated that the task demands of visually following a rapidly perturbed target on a screen may be too difficult to be a useful tool in rehabilitating patients suffering from neglect. However, the parameters used here placed the second target somewhat to the left of centre. Placing all targets completely in right space may improve a patient's chance of successfully performing the task. Further, increasing the salience of the targets, by, for example, increasing their size, brightness, or flashing them at onset, may improve the patient's ability to orient and saccade toward them. 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-Tam2009, @Müri2008], which may prove promising for the rehabilitation of unilateral neglect. Finally the durations that targets remain on the screen should be carefully calibrated to the particular abilities of the patient, again maximizing their chances of completing the task and adapting to the direction and magnitude of shift desired.

It remains possible that improved methodologies may enable neglect patients to successfully undergo saccadic adaptation. However, the results presented here do not, in any strong way, suggest that saccadic adaptation appears to be a strong contender to replace prism adaptation in the remediation of neglect. In practice, it appears that prism adaptation more closely accommodates the abilities of neglect patients, and the existing body of positive research makes turning away from prisms appear to be a poor choice. Instead, 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.