EXPLORING THE LINK BETWEEN INPUT-OUTPUT SUBTYPES OF SPATIAL NEGLECT AND PRISM ADAPTATION MECHANISM

by

Jasmine R. Aziz

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Dalhousie University is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq.
We are all Treaty People.

DEDICATION PAGE

I dedicate this thesis to the generations of my family who came before me. It was their compassion, industriousness, and integrity that inspired me to follow my intellectual passions and that afforded me the privilege to undertake this body of work.

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ABSTRACT

Spatial neglect is a complex neurocognitive syndrome predicting greater chronic disability after stroke and other acquired brain injuries. The heterogeneity of neglect symptomatology poses challenges for assessment and treatment. These challenges are exemplified by research on prism adaptation (PA), a sensorimotor learning task that can reduce neglect symptoms but has shown inconsistent effects in clinical trials. Prism adaptation's therapeutic effects may vary due to differences in neglect subtypes. The Input-Output neglect subtyping dimension describes neglect symptoms as arising at different stages of information processing, yielding symptoms at the input stage (perceptual or Input neglect), and/or the output stage (premotor or Output neglect). Some research suggests that PA mainly acts on Output neglect symptoms. However, variability in the conceptualization and measurement of Input-Output neglect makes it challenging to connect this subtyping concept to PA's therapeutic mechanisms. This thesis aimed to: 1) explore the Input-Output neglect subtyping dimension, and 2) evaluate how PA impacts different stages of information processing by testing whether PA can induce temporary Output biases in healthy adults. Chapter 1 provides historical and theoretical foundations for the subsequent body of work. Chapter 2 presents a systematic scoping review summarizing the terminology, measurement tools, and neural theories/correlates of Input-Output neglect. Conclusions were drawn from review results in the areas of: 1) terminology and conceptual models; 2) methodological issues of dissociating Input and Output subtypes; 3) updating neural theories; and 4) connecting mechanisms underlying assessment and treatment. These scoping review conclusions informed the design of two behavioural experiments recruiting healthy adults. In the first experiment, left-shifting PA induced an Output bias on a speeded reach task in right-handers (Chapter 3), but not in left-handers (Chapter 3A). In the second experiment, PA did not impact Input-Output biases measured by a horizontal line judgment task (Landmark task; Chapter 4). Chapter 5 interprets these differential PA effects through the lens of the scoping review conclusions. Overall, this thesis concludes that future research on the link between Input-Output neglect and PA effects should recruit persons with neglect and consider the integration of Input and Output processing in addition to their dissociation.

LIST OF ABBREVIATIONS USED

ANOVA	Analysis of Variance
BIT	Behavioural Inattention Test
d	Cohen's *d* Effect Size
CBS	Catherine Bergego Scale
DAN	Dorsal Attention Network
ERP	Event-Related Potential
FEF	Frontal Eye Field
FIM	Functional Independence Measure
(f)MRI	(Functional) Magnetic Resonance Imaging
I/MFG	Inferior and Middle Frontal Gyri
IPL	Inferior Parietal Lobule
IPS	Intraparietal Sulcus
iRT	Reach Initiation Time
LAT	Limb Activation Training
LPA	Left-Shifting Prism Adaptation
M	Mean Proportion of 'Default' Responses
N	Sample Size (total)
n	Sample Size (subset of total)
NIBS	Non-Invasive Brain Stimulation
PET	Positron Emission Tomography
PwN	Persons with (Spatial) Neglect
PA	Prism Adaptation
PB	Perceptual Bias on the Landmark Task
PLATO	Portable Liquid crystal Apparatus for Tachistoscopic Occlusion
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses, Extension for Scoping Reviews
PSE	Point of Subjective Equality
RB	Response Bias on the Landmark Task
RPA	Right-shifting Prism Adaptation
rTMS	Repetitive Transcranial Magnetic Stimulation
SHD-VAS	Shift in Hemispheric Dominance Within the Ventral Attentional System
SPL	Superior Parietal Lobule
STG	Superior Temporal Gyrus
TPJ	Temporo-Parietal Junction
VAN	Ventral Attention Network
VFC	Ventral Frontal Cortex
VR	Virtual Reality
VST	Visual Scanning Training

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CHAPTER 1 GENERAL INTRODUCTION

Stroke is one of the leading causes of adult death and disability worldwide. With the world's aging population, the global burden of stroke sequelae on survivors, their families and caregivers, and the overall healthcare system is expected to increase, especially for low-income countries (Feigin et al., 2021). One significant source of post-stroke disability is deficits in cognitive functioning, which can limit a person's independence and quality of life (Rost et al., 2022). The assessment and management of cognitive deficits is widely recognized as an essential component of stroke rehabilitation (Lanctôt et al., 2020). The present thesis focuses on the underlying mechanisms of spatial neglect, a common and disabling neurocognitive disorder after stroke, and prism adaptation (PA), a sensorimotor learning task that shows promise as a neglect treatment.

1.1 An Introduction to Spatial Neglect and Associated Disability

The complex constellation of symptoms described as spatial neglect has intrigued researchers and clinicians for many decades. Early work described neglect as "visual disorientation" in the left visual field observed after right-hemisphere lesions not adequately explained by a primary sensory impairment (Brain 1941; Riddoch 1935, as cited in Heilman & Valenstein, 1979). A later and more widely referenced definition comes from Heilman (1979), who defined neglect as the failure to report, respond, or orient to novel or meaningful stimuli presented in a specific location, when this failure cannot be attributed to either sensory or motor deficits. Neglect typically arises from acquired brain injury, and while stroke is the prevailing etiology in research and clinical practice, neglect can also occur after other forms of acquired brain injury such as tumors (Stone et al., 2011), traumatic brain injuries (Chen et al., 2016), or even neurodegenerative disorders (Andrade et al., 2010). In essence, persons with neglect (PwN) are observed to 'neglect' the side of space or their body that is contralateral to their brain injury. Some examples of the more obvious clinical manifestations of neglect include not shaving one side of the face, not acknowledging someone approaching from one side of space, not eating food on one side of a plate, or not noticing and thus repeatedly bumping into objects on one side of space. In addition to these negative symptoms, PwN may also display positive symptoms, such as perseveration on or difficulty disengaging attention from ipsilesional stimuli (Posner et al., 1984; Vallar & Calzolari, 2018). Approximately 40-65 % of PwN show limited awareness of their deficits (i.e., anosognosia, Appelros et al., 2007; Azouvi et al., 1996; Grattan et al., 2018). As described by Mesulam (1981), "in severe cases, [PwN] may behave almost as if that half of the universe had abruptly ceased to exist" (p. 309).

Spatial neglect is associated with poorer stroke outcomes. Although many PwN show reductions in neglect symptoms by six months post-stroke, a subset of individuals experience more long-term neglect-related deficits (Cassidy et al., 1998; Demeyere & Gillebert, 2019). Furthermore, the presence of neglect during the acute and subacute phases post-stroke predicts greater chronic disability and functional dependence (Buxbaum et al., 2004; Farnè et al., 2004; Katz, Hartman-mae, et al., 1999; Oh-Park et al., 2014). Persons with neglect also tend to display reduced engagement in inpatient rehabilitation activities and increased length of stay in hospital (Barer, 1990; Barrett & Muzaffar, 2014; Spaccavento et al., 2017). Caregivers of PwN report greater caregiver stress and burden than the caregivers of stroke survivors without neglect (Chen et al., 2017). Overall, advancements in the assessment and treatment of neglect have potential to improve the outcomes of many persons living with the effects of stroke, while also reducing impacts on caregivers and the healthcare system. However, one significant obstacle to advancing the clinical management of neglect is the heterogeneity of neglect symptom presentation, which complicates both assessment and treatment. The next section elaborates upon this point by reviewing the spatial and non-spatial aspects of neglect.

1.2 Heterogeneity of Neglect: Spatial and Non-Spatial Aspects

While the spatial deficits of neglect are more observable, more widely studied, and form the namesake of this disorder, non-spatial deficits have long been described in PwN and are considered a core feature of the neglect syndrome (Corbetta & Shulman, 2011; Robertson, 2001; Van Vleet & DeGutis, 2013). For instance, PwN after right-hemisphere stroke are more likely to show deficits in sustained attention than persons with right-hemisphere stroke without neglect (Robertson et al., 1997). These non-spatial sustained attention deficits may cause spatial deficits to fluctuate over the course of a testing session

(Robertson & Manly, 2002). Persons with neglect may also show deficits in arousal, evidenced by an amelioration of spatial deficits when non-spatial phasic alerting cues are provided (Robertson, Mattingley, et al., 1998). Other key non-spatial symptoms of neglect include: reduced attentional capacity, evidenced by performance decrements in dual-task paradigms (Robertson & Frasca, 1992); weaknesses in spatial working memory, even for vertically oriented stimuli on the ipsilesional (less affected) side of space (Ferber & Danckert, 2006; Husain et al., 2001; Wojciulik et al., 2001); and dysfunctional temporal perception (Danckert et al., 2007; Husain et al., 1997). While these non-spatial aspects must be acknowledged, the present thesis largely focuses on the spatial aspects of neglect.

A core feature of spatial neglect is a pathological egocentric bias toward the ipsilesional side of space (Corbetta & Shulman, 2011). This spatial bias is complex and may manifest in many different ways depending on the individual. Several neuro-behavioural subtypes of spatial neglect have been proposed to help explain this symptom heterogeneity (for reviews, see Buxbaum et al., 2004 or Williams et al., 2021). One subtyping dimension describes symptoms across different spatial sectors: personal neglect of one side of the body, peri-personal neglect of (near) space within reaching distance, and extra-personal neglect of (far) space beyond reaching distance (Beschin & Robertson, 1997). A related subtyping dimension is axis of space (i.e., horizontal, vertical, or radial neglect; Mark & Heilman, 1998). Neglect symptoms may also be described in different reference frames, with egocentric neglect for stimuli on one side of the body midline, and allocentric neglect for one side of stimuli regardless of their position relative to the midline (Farah et al., 1990). Another subtyping dimension describes symptoms at different stages of information processing, yielding Input (perceptual) neglect or Output (premotor) neglect subtypes (Bisiach et al., 1990; Harvey, 2004; Heilman & Valenstein, 1979). With respect to Input neglect, while neglect symptoms have been classically studied in the visual modality (Riddoch, 1935; Brain, 1941), tactile and auditory neglect have also been described (Gainotti, 2010), though they are less well-studied than visual neglect. Representational neglect has also been described, whereby individuals neglect the contralesional side of mental representations (Bisiach et al., 1979; Bisiach & Luzzatti, 1978). Overall, given this symptom heterogeneity, it is not surprising that there are many methods of neglect assessment and treatment, with no single ‘gold standard’ approach (Teasell et al., 2020).

1.3 Prevalence and Laterality of Neglect

The heterogeneity of symptomatology and associated assessment methods makes it difficult to establish precise prevalence statistics for neglect, but it is clearly a common consequence of stroke. Across various studies, neglect is reported to affect approximately 30-85% of stroke survivors, with variable prevalence rates depending on assessment tools and sample characteristics (Azouvi et al., 2002; Esposito et al., 2021; Hammerbeck et al., 2019; Hepworth et al., 2016). Spatial neglect is generally more common and severe after right-hemisphere damage compared to left-hemisphere damage (Heilman, 1998; Ten Brink et al., 2017). However, it is worth noting that right-sided neglect after left-hemisphere stroke may be underdiagnosed due to interference of language deficits on cognitive testing (Hreha et al., 2017). While spatial deficits are typically less severe in right-sided neglect, associated functional impairment may be comparable to left-sided neglect (Ten Brink et al., 2017). Furthermore, ipsilesional neglect may occur either in isolation or as an extension of contralesional neglect, with estimated prevalence rates of 10-20% after right-hemisphere stroke (Kim et al., 1999; Sacchetti et al., 2015). Given the overall higher prevalence and larger body of research, the present thesis will focus on left-sided neglect after right-hemisphere stroke.

1.4 Neuro-anatomical Theories of Neglect

Neglect research has significantly advanced our understanding of the neural mechanisms of attention, spatial cognition, and the nature of consciousness. As well-stated by Karnath, Milner, and Vallar (2002):

> The phenomena of neglect may greatly help our understanding of the normal mechanisms of directing and maintaining spatial attention, and of the anatomo-functional characteristics of representations of space. Furthermore, research in this field is highly relevant to the contemporary search for the cerebral correlates of conscious experience and voluntary action, and may ultimately offer a fuller

understanding of the very nature of the integrated self and of personal identity (Preface).

In a demonstration of these valuable contributions to cognitive neuroscience, this section describes the lesion locations that typically cause neglect, followed by a brief history of prominent neural theories of neglect.

The classic lesion location associated with neglect is the posterior parietal cortex, particularly the right inferior parietal lobule (IPL, Vallar, 2001; Vallar & Perani, 1986). However, many other key locations have been reported, such as the superior temporal gyrus (Karnath et al., 2001), the ventral frontal cortex (Heilman & Valenstein, 1972; Husain & Kennard, 1997), and subcortical regions (Karnath et al., 2002). The anatomical heterogeneity of neglect parallels its symptom heterogeneity, but differences in sample characteristics or imaging analysis methods can also contribute to variability in neural correlates (discussed in Moore et al., 2023). A review of some prominent neural theories of neglect may shed light on why such a range of lesion locations can produce neglect behaviour.

One influential neural theory of neglect was Kinsbourne's hemispheric rivalry hypothesis (Kinsbourne, 1970, 1977). This theory asserted that each cerebral hemisphere inhibits or 'rivals' the other hemisphere through interhemispheric connections, competing for influence on brainstem output mechanisms (e.g., superior colliculi) that allow for orienting to the contralateral side of space. When one hemisphere is damaged, the other hemisphere is released from inhibition and becomes hyper-active, creating an imbalance between hemispheres that biases attention toward the ipsilesional side of space. Kinsbourne (1970) further reasoned that neglect is more common after right-hemisphere damage because verbal processing governed by the intact, (usually) dominant left hemisphere would heighten the interhemispheric imbalance. Kinsbourne's hemispheric rivalry hypothesis was consistent with cat lesion studies that demonstrated that lesioning the superior colliculus contralateral to an occipito-temporal cortex lesion (or lesioning the intercollicular commissure) alleviates visual neglect symptoms by releasing the ipsilesional superior colliculus from inhibition (the 'Sprague effect'; Sprague, 1966). More recent support for an interhemispheric rivalry model of neglect comes from neurostimulation studies suggesting that stimulating the ipsilesional hemisphere or inhibiting the contralesional hemisphere via non-invasive brain stimulation (NIBS) can reduce neglect symptoms in humans (Zebhauser et al., 2019). Another theory from the 1970's that built upon Kinsbourne's (1970, 1977) theory was the attention-arousal hypothesis, which asserted that neglect arises from unilateral damage to the corticolimbic-reticular loop, which causes the lesioned hemisphere to become hypo-active (Heilman & Valenstein, 1972; Reeves & Hagamen, 1971; Watson et al., 1973, 1974). This decreased arousal reduces the lesioned hemisphere's ability to both process incoming stimuli from the contralesional side of space and plan movements toward said stimuli (Heilman & Watson, 1977). Overall, these early theories identified interhemispheric inhibition, lateralized processing of contralateral space, and cortical-subcortical connections as important factors in understanding the predominantly hemi-spatial presentation of neglect after unilateral brain injury.

The next two theories by Mesulam (1981) and Corbetta and Shulman (2002, 2011) both describe neglect as resulting from disruptions in a distributed cortical network. Mesulam's (1981) cortical network theory identified four nodes that contribute to the neural control of directed attention in extrapersonal space: a posterior parietal component that forms an internal sensory map of the external environment; a frontal component that coordinates motor programs for exploratory behaviour; a cingulate component that contributes to a motivational salience map; and a reticular component that coordinates basic arousal. Mesulam (1981) reasoned that lesions in different nodes of this network may produce different combinations of neglect symptoms. With advances in neuroimaging, Corbetta and Shulman (2002, 2011) developed a theory of spatial attention networks that describes a right-lateralized ventral attention network (VAN) extending from the temporoparietal junction (TPJ, including the IPL and the superior temporal gyrus, STG) to the ventral frontal cortex (VFC, including the inferior and middle frontal gyri, I/MFG) that subserves orienting to salient and/or unexpected events, and a bilateral dorsal attention network (DAN) extending from the superior parietal lobule (SPL) and intraparietal sulcus (IPS) to the frontal eye field (FEF) that subserves voluntary attention and exploratory behaviours. This theory asserts that structural damage to the right VAN results in a functional asymmetry between left and right DAN activity that biases attention and visuomotor exploration toward the right side of space. In support of this proposal, neglect symptoms (at least in the visual modality) most often arise from damage to the right VAN and its white-matter connections to the DAN (Lunven & Bartolomeo, 2017), and neglect recovery is linked to balancing of DAN activity (Corbetta et al., 2005; He et al., 2007).

In summary, while numerous neural theories of neglect have been proposed, they all generally recognize the right-hemisphere lateralization and distributed neural networks that give rise to visuo-spatial functions. These network-based theories can account for the observation that many different lesion locations can cause neglect. Indeed, neglect is now broadly accepted to be a 'disconnection syndrome' with white matter tract dysfunction contributing significantly to its manifestation (Bartolomeo et al., 2007; Corbetta & Shulman, 2011; Doricchi et al., 2008; Lunven & Bartolomeo, 2017). Furthermore, neuroimaging is emerging as a method of assessing neglect by identifying neuro-anatomical subtypes (Brodtmann & Loetscher, 2022). However, it has also been acknowledged that clearly defining different behavioural subtypes of neglect is essential to understanding the condition's neuro-anatomical heterogeneity (Moore et al., 2023; Vuilleumier, 2013). With the neuroanatomy of neglect as a backdrop, the next section will cover behavioural measures of neglect.

1.5 Overview of Neglect Assessment

Many behavioural measures have been developed to assess for spatial neglect. Assessment methods can be broadly categorized into conventional and functional measures. Conventional measures are traditionally administered in peri-personal space (i.e., within reaching distance) and use a pencil and paper (but computerized versions are becoming more prevalent, e.g., Vaes et al., 2015). Cancellation tasks involve crossing out targets such as lines or shapes, with or without the presence of distractors (Albert, 1973; Bickerton et al., 2011; Ferber & Karnath, 2001; Gauthier et al., 1989). The manual line bisection task involves marking the midpoint of a horizontal line (Schenkenberg et al., 1980). Figure copying tasks and representational drawing tasks involve reproducing a line drawing either from a reference picture or from memory, respectively (Gainotti et al., 1972). Overall, these conventional measures test for lateralized impairments in egocentric space, with contralesional omissions (e.g., not drawing left side of an object) or size distortions (e.g., marking a horizontal line to the right of centre) as indicative of neglect. One well-known neglect assessment battery that includes all the above conventional measures is the Behavioural Inattention Test-Conventional (BIT-C; Wilson et al., 1987). On the other hand, functional measures test the PwN's ability to complete basic and instrumental activities of daily living (Azouvi, 2017). Like conventional measures, functional measures test for contralesional omissions or space distortions, but on functional tasks. For example, the BIT has a Behavioural version (BIT-B) that requires the PwN to complete tasks such as reading a menu or using a telephone, which are scored in terms of number omitted words/numbers on the contralesional side of the stimulus card (Wilson et al., 1987). Another prominent functional measure is the Catherine Bergego Scale (CBS), an observational measure that requires a clinician to rate the severity the PwN's symptoms across various functional behaviours, such as eating, grooming, and wheelchair navigation (Azouvi et al., 1996, 2003; for a standardized procedure for administering the CBS, see Chen et al., 2012). With respect to common usage, an international survey of clinicians' neglect assessment methods found that the most used conventional measure was line cancellation (Albert, 1973), and the most used functional measures were clinical observation, interviews, and the Functional Independence Measure (FIM), a measure of post-stroke functional outcome that is not specific to neglect (Checketts et al., 2021). Importantly, conventional neglect measures vary considerably in their sensitivity, and no single test is pathognomonic of neglect (Azouvi et al., 2002); as a result, a battery approach is typically recommended (Lezak, 2012). While functional measures are typically more sensitive and ecologically valid than conventional pencil-and-paper measures (Azouvi, 2017; Azouvi et al., 2006; Esposito et al., 2021), these strengths may come at the cost of reduced specificity in terms of what is causing the functional impairment.

One significant challenge when selecting and interpreting neglect assessment measures is the heterogeneity of neglect symptom presentation. As noted previously, several neglect subtyping dimensions have been proposed to fully capture this complex disorder, and numerous measures have been developed for each subtyping dimension (Williams et al., 2021). Since conventional pencil-and-paper measures are not typically designed to measure these subtypes (or non-spatial deficits), it is not surprising that they have variable sensitivity. Moving beyond conventional measures and assessing subtypes of neglect is valuable because these subtypes may arise from distinct functional neuro-anatomical mechanisms (Baldassarre et al., 2016; Sapir et al., 2007; Vaessen et al., 2016), show different recovery patterns (Goedert et al., 2012; Moore et al., 2021; Rengachary et al., 2011), and may require different interventions (Barrett & Burkholder, 2006; Gammeri et al., 2023; Goedert et al., 2014). The present thesis aims to further this third line of research that seeks to understand the interface between neglect subtype assessment and treatment mechanisms, by focusing on the Input-Output neglect subtyping dimension and prism adaptation (PA) therapy. I will first provide some historical context for the concept of Input-Output neglect, followed by my rationale for focusing on this subtyping dimension in the present thesis.

1.6 Input and Output Neglect Subtypes

The Input-Output approach to modelling behaviour is a very old idea. For instance, in the 17th century, René Descartes theorized that the human body contained animal spirits that transmitted information from the sense organs (e.g., eyes, ears) to the muscles that produce movement, via the pineal gland that he considered to be the seat of the human soul (Descartes, 1649). Among the pioneers of measuring this information transmission empirically was von Helmholtz, who measured the speed of nerve impulses in frogs in the mid-19th century; Donders and de Jaager applied von Helmholtz's nerve conduction experiments to the more complex mental processes of human beings, demonstrating through reaction time experiments that 'thinking takes time' and thus founding the area of mental chronometry (reviewed in Schmidgen, 2002). The concept of mental chronometry was foundational to the field of experimental psychology, with just a couple influential applications being Sternberg's (1969) observations of linear increases in response time based on stimulus set size, or Posner's (1978) application of mental chronometry in his famous spatial cueing paradigm. One general assumption of these methods is that the efficiency of cognitive operations can be indirectly measured by subtracting the time that elapses between the presentation of a stimulus and the initiation of a motor response across tasks with differing cognitive demands.

Two other historical movements that help frame the concept of Input-Output neglect are behaviourism and the cognitive revolution. In brief, Pavlov pioneered stimulus-response theory with his famous experiments in dogs, demonstrating that stimulus-response pairings can be learned through classical conditioning; Pavlov, amongst other behaviourists (e.g., Watson, Skinner, etc.), developed these ideas into the field of behaviourism in the early 20th century (reviewed in Moore, 1987). The general sentiment of behaviourism was to emphasize the importance of behaviour in the study of psychology and downplay the importance of cognition (Watrin & Darwich, 2012). However, the rise of computationalism in mid-20th century provided a clearer framework for the conceptualization of cognition, as the brain was likened to a computer handling 'inputs' (i.e., stimuli from environment), performing operations (i.e., cognition) and producing 'outputs' (i.e., observable behaviour; McCulloch & Pitts, 1943; Turing, 1950; Watrin & Darwich, 2012). Within the context of this 'cognitive revolution,' staged models of human information processing became more prominent, such as Broadbent's (1958) filter model of attention, or Treisman and Gelade's (1980) feature integration theory. Staged information processing models continue to be used in the multidisciplinary study of human behaviour (e.g., for clinical neuropsychology, see Cohen et al., 2014; for engineering psychology and human performance, see Wickens et al., 2021).

With this general historical context, the next logical question is: how have these information processing concepts been applied to spatial neglect? Heilman and Valenstein (1979) summarized three key hypotheses for neglect behaviour in a manner consistent with the aforementioned concept of staged human information processing. The first hypothesis was that neglect results from "deafferentation," or a lack of sufficient sensory input. This hypothesis was one of the earliest in the neglect literature (Battersby et al., 1956, as cited in Heilman, 1979), but was refuted by electrophysiological experiments in monkeys demonstrating that the event-related potentials disrupted in neglect were the later components of 'higher-level' cognitive operations, whereas earlier sensory components were unaffected (Watson et al., 1977). Moreover, it was noted that neglect could arise from lesions outside of primary sensory brain regions (Heilman, 1979). The second hypothesis mentioned by Heilman and Valenstein (1979) was that neglect results from "sensory inattention," meaning that PwN may receive sensory input from the left side of space but have difficulty attending to it. The third hypothesis was that neglect arises from "hemispatial hypokinesia," which they described as slowed or absent initiation of movement towards the neglected hemi-space not adequately explained by a primary motor impairment such as hemiparesis (for original proposal, see Watson et al., 1978). When taken together, the latter two hypotheses provide a foundation for the Input-Output distinction under study in this thesis[1]. Another past conceptualization of neglect that maps perhaps even more directly onto the Input-Output neglect concept are the ideas put forth by Jeannerod and Biguer (1987), who described neglect as a deficit in the transformation of sensory input maps to motor output responses across body-centered reference coordinates.

There are three main reasons why the present thesis focuses on the Input-Output subtyping dimension of neglect as opposed to other subtyping dimensions. The first reason is that the Input-Output neglect concept has the potential to encompass other subtyping dimensions. For instance, Williams et al.'s (2021) review of neglect subtypes describes neglect in different sensory modalities (i.e., visual, auditory, tactile) as a subcategory of the broader approach of subtyping by information processing stage (i.e., perceptual, representational, motor). In addition, Input-Output processes can be examined across different spatial sectors (e.g., personal, peri-personal, extra-personal) or reference frames (e.g., egocentric, allocentric). A second reason is that the distinction between Input and Output neglect subtypes seems less clearly delineated than distinctions between spatial sectors or reference frames, and thus the concept would benefit from a more thorough examination (as is done in Chapter 2 of the present thesis). Finally, my initial motivation for studying the Input-Output neglect concept was that it has been previously linked to the therapeutic mechanisms of PA, a link that is also examined in the present thesis (see Chapters 3 and 4). Before describing PA and its potential link to Input-Output neglect, I

[1]Heilman (1979) also described a fourth hypothesis for neglect behaviour not covered in Heilman and Valentein (1979), which was the hemispatial memory hypothesis.

will provide context with a brief overview of neglect treatment.

1.7 Overview of Neglect Treatment

Robertson and Manly (2002) described the relationship between neglect rehabilitation research and advancements in cognitive neuroscientific theory as a “unique symbiosis” (p. 365). Indeed, neglect treatments have arisen from neurocognitive understandings of the neglect syndrome and, in turn, the study of neglect treatment effects has contributed to advancements in the understanding of attention and space representation. For example, visual scanning training (VST), which provides PwN with ‘top-down’ strategies to encourage visuomotor exploration (Cottam, 1987; Dundon et al., 2015), was developed in response to the observation that spontaneous recovery in neglect could be partially attributed to the PwN developing strategies to compensate for their spatial deficits in daily life (reviewed in Robertson & Manly, 2002). Another early and influential neglect treatment was limb activation training (LAT), whereby the PwN’s contralesional limb is moved in contralesional space, thus drawing attention to contralesional space and reducing neglect symptoms (Eskes et al., 2003; Robertson et al., 1998; Robertson & Hawkins, 1999). Studies on LAT informed the basic study of spatial attention by demonstrating that attentional and motor functions are tightly interconnected. Robertson and colleagues (1998) also investigated sustained attention training as a potential neglect treatment, in response to the observation that many PwN show non-spatial attentional deficits in arousal and vigilance that interact with spatial deficits over time (Robertson, 2001). Sustained attention training has been combined with LAT as both therapies stimulate arousal networks to encourage and/or compensate for deficits in orienting (Wilson et al., 2000). Another group of therapies, including mirror therapy (Ramachandran et al., 1999; Zhang et al., 2022), monocular patching (Barrett & Burkholder, 2006; Posner & Rafal, 1987), and PA (Jacquin-Courtois et al., 2013; Rossetti et al., 1998) all aim to alleviate neglect symptoms by manipulating characteristics of visual input, and they have helped advance our knowledge about the relationship between sensorimotor and cognitive processes. According to Chen et al. (2018)’s survey of expert clinicians, the four most used behavioural interventions for neglect are VST, limb activation, sustained attention training, and PA. Taken together, a brief review of these therapies demonstrates the strong connection between the development of interventions and neurocognitive accounts of neglect. The present thesis carries on this tradition by discussing the interface between different neglect presentations and mechanisms of PA.

With respect to the efficacy of these various neglect treatments, according to the current Canadian Stroke Best Practice Recommendations, there are no neglect treatments with Level A evidence[2] (Teasell et al., 2020). There are, however, several neglect treatments with Level B evidence[3]; amongst these treatments, the strongest evidence is for the use of VST, and VR and other computer-based interventions, whereas there is weaker and/or conflicting evidence for the use of PA, monocular patching, LAT, mirror therapy, and mirror therapy combined with LAT. There are many possible reasons for the lack of Level A evidence in neglect rehabilitation research (e.g., lack of high-powered randomized controlled trials), but three interconnected reasons that are pertinent to the present thesis' aims are: 1) the heterogeneity neglect symptom presentation; 2) the lack of clarity on specific therapeutic mechanisms; and 3) uncertainty regarding how these mechanisms may interact with different neglect presentations.

Why does the present thesis focus on PA as opposed to another neglect treatment? One clear reason is, as noted previously, PA has been linked to Input-Output neglect subtypes in past research (see Section 1.9 of this Introduction for a review). Another reason is that the longstanding and ongoing use of PA in experimental cognitive studies provides a good knowledge base to draw from when attempting to link its mechanisms to Input-Output neglect subtypes. With respect to its clinical application, PA is non-invasive, relatively low-cost, and feasible to implement in inpatient rehabilitation (Longley et al.,

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[2] The criteria for Level A evidence are defined as "evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or undesirable effects clearly outweigh desirable effects" (Teasell et al., 2020, p. 766).

[3] The criteria for Level B evidence are defined as "evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or undesirable effects outweigh or are closely balanced with desirable effects" (Teasell et al., 2020, p. 766).

2022). Moreover, since PA is a 'bottom-up' therapy (Rode et al., 2003), the anosognosia that often accompanies neglect is not a significant barrier to its use (if anything, PA may show stronger effects when awareness of the visual displacement is reduced, see Jakobson & Goodale, 1989, and Michel et al., 2007). For these reasons, PA could function as an adjunct therapy for clinicians to supplement more 'top-down' strategies like VST. With this rationale made evident, the next section will discuss PA in greater detail.

1.8 Prism Adaptation

Prism adaptation was used in the late 19th century to experimentally investigate human sensorimotor learning mechanisms (von Helmholtz, 1867, 1962). During PA, individuals reach for targets while wearing glasses or goggles fitted with prismatic lenses that refract the incoming light, causing a horizontal displacement of visual input. Initially, the individual makes reaching errors in the direction of the visual displacement (i.e., direct effects). However, reaching accuracy improves with repeated reaching movements as the individual adapts to the displacement. The amount of online visual guidance during this prism exposure period may vary by study: typically, the individual can see either the last ~2/3 of their reaching movement (concurrent exposure), or only the final portion of their reaching movement (terminal exposure; Facchin et al., 2018; Herlihey et al., 2012; Redding et al., 2005). Upon removal of the prism glasses, the individual now makes reaching errors in the direction opposite the visual displacement reflecting the adaptive process (i.e., aftereffects, Prablanc et al., 2020). Redding and Wallace (1996) proposed two learning processes underlying PA: a rapid, strategic correction process that contributes to the immediate reduction of pointing errors early in prism exposure, termed strategic recalibration; and a slower, implicit adjustment of the body's spatial reference frames to resolve the visuo-motor discrepancy, termed spatial realignment. The magnitude of prism aftereffects has been used a proxy for spatial realignment and/or the degree of sensorimotor learning that has taken place (Redding et al., 2005).

The discovery that PA could possibly be used to treat neglect was made just prior to the turn of the 21st century. In their seminal article, Rossetti et al. (1998) first demonstrated that a single session of right-shifting PA (RPA) reduced left-sided neglect symptoms across copying, line bisection, and cancellation tasks administered to PwN both immediately and two hours following the prism exposure period. This finding stimulated a new and exciting field of neglect rehabilitation research, whereby PA has been shown to improve neglect symptoms across a wide range of cognitive and functional measures, such as temporal order judgements (Berberovic et al., 2004), visual search (Saevarsson et al., 2009), postural balance (Nijboer et al., 2014), and wheelchair driving (Watanabe & Amimoto, 2010), to name just a few (for reviews, see Champod et al., 2018; and Jacquin-Courtois et al., 2013). PA therapy also resulted in improvement on broader measures of post-stroke functional outcomes, such as improved FIM scores up to three months post-PA therapy (Mizuno et al., 2011). Furthermore, there seems to be a positive correlation between number of PA sessions administered to PwN and the degree of functional benefits measured by the FIM (Chen et al., 2022). Taken together, these studies suggest that PA has the potential to benefit many aspects of stroke recovery.

Despite these promising findings, other studies have reported null effects of PA (Longley et al., 2022; Rousseaux et al., 2006; ten Brink et al., 2017; Turton et al., 2010; Vilimovsky et al., 2021), or transient benefits that are lost at long-term follow-up (Li et al., 2021; Nys et al., 2008; Vaes et al., 2018). The inconsistent therapeutic benefits of PA are reflected in the current Canadian Stroke Best Practice Recommendations, which state that "there is conflicting evidence on the effectiveness of prism glasses… for improving neglect" (Teasell et al., 2020, p. 782). There are many potential reasons for these inconsistent PA effects. As with any intervention, treatment response variability may arise from inter-study differences in dosage parameters. In the case of PA, such parameters include the number of pointing movements, the prism shift magnitude, the number, duration, and frequency of PA sessions, and initiation time of PA post-neglect onset (Goedert et al., 2015). Another source of inconsistent effects is differences in the specific PA exposure method (Prablanc et al., 2020; Redding et al., 2005). Indeed, some studies have compared different PA paradigms, such as concurrent versus terminal exposure (Facchin et al., 2018; Herlihey et al., 2012), continuous versus intermittent (i.e., alternating blocks of prism and clear glasses) exposure (Scheffels et al., 2021), or the type of motor task completed while wearing the prism goggles (e.g., pointing at visual targets versus more ecological tasks; see Fortis et al., 2013). In addition to differences in the treatment itself, differences in the outcome measures of PA-mediated improvements may yield different effects (e.g., see Li et al., 2021, for a comparison of conventional and functional measures of neglect outcome after PA). While differences in treatment parameters and outcome measures are important factors to consider in PA research, the present thesis largely focuses on a third, critical factor in understanding PA's variable effects, which is the proposal that inconsistent PA treatment response can be attributed, at least in part, to differences in the neuro-behavioural subtype of neglect (Barrett et al., 2012; Striemer & Danckert, 2010b).

Starting with the 'neuro' component of this neuro-behavioural subtype proposal, there are numerous empirical articles suggesting that PA treatment response in PwN appears to differ by lesion location: neglect due to frontal and subcortical lesions has generally been linked to showing greater PA-related benefits, whereas neglect due to post-central cortical lesions, especially in temporo-parietal areas, has been associated with showing reduced benefit (Chen et al., 2014; Goedert et al., 2018; Gossmann et al., 2013; Saj et al., 2019; Scheffels et al., 2022; Serino et al., 2006). Interestingly, Mesulam (1981) predicted this very pattern several decades ago. When describing data from rhesus monkeys supporting the role of the posterior parietal cortex in creating an internal sensory map of the external environment, he reasoned the following:

> It is conceivable that the internal representation of space [in monkeys with unilateral posterior parietal lesions, including the dorsolateral PG] had become skewed in favor of the ipsilateral side and that the motor program for reaching merely reflected this bias, in a fashion somewhat analogous to the behavior of humans subjected to prismatic distortion of visual space.* (footnote: *Humans rapidly adapt to prismatic distortion, perhaps with the assistance of the neural mechanisms in parts of the brain homologous to the dorsolateral PG in the monkey. One would predict that such adaptation is far more difficult in patients with unilateral posterior parietal lesions.) (Mesulam, 1981, p. 314).

Mesulam's (1981) prediction and associated reasoning are consistent with the interpretations shared by some of the authors of the aforementioned empirical articles. For instance, Saj et al. (2019), who found that PwN due to frontal lesions displayed greater post-PA reductions in neglect symptoms than PwN due to parietal lesions, concluded that successful PA relies on intact parieto-cerebellar networks and, in particular, the capacity of the parietal cortex to construct sensorimotor maps of extra-corporeal space in relation to eye-head-body reference frames. Alternatively, Chen et al. (2014) proposed an interactive effect between damaged frontal and intact post-central brain regions, after observing that PwN due to frontal lesions showed greater post-PA functional gains than PwN without frontal lesions, but that the frontal lesion group also had less damage to medial-temporal structures. Chen et al. (2014) suggested that PA rehabilitates the neglect-related motor-intentional 'aiming' deficits that are associated with frontal lesions by recruiting intact posterior brain regions that are more involved in the 'bottom-up' processing of discrepant visual feedback. These views are supported by neuroimaging data identifying parieto-temporo-cerebellar networks as instrumental in spatial realignment (Chapman et al., 2010; Clower et al., 1996; Danckert et al., 2008; Luauté et al., 2009; but see Panico, Fleury, et al., 2020, for importance of M1 in aftereffect retention). Similarly, studies of event-related potentials (ERPs) during PA have identified a more frontal error monitoring system linked to strategic recalibration processes, and a more posterior context-updating component linked to spatial realignment processes (Lazar-Kurz et al., 2023; MacLean et al., 2015; Vocat et al., 2011), with the latter component more critical to the formation of strong prism aftereffects (Aziz et al., 2020).

While neglect lesion studies have established a link between frontal lesions, intact temporo-parietal regions, and PA-mediated neglect recovery (Chen et al., 2014; Goedert et al., 2018; Gossmann et al., 2013; Saj et al., 2019; Scheffels et al., 2022; Serino et al., 2006). the specific mechanisms underlying these relationships require further study. For instance, Scheffels et al. (2022) pointed out that stroke survivors with parietal lesions tend to have worse recovery trajectories in general, so the difference in PA response by lesion site may not be PA-specific (Phan et al., 2013; Rangaraju et al., 2015; Seyedsaadat et al., 2020, as cited in Scheffels et al., 2022). Scheffels et al. (2022) also noted that the field would benefit from a standard method of identifying PA responders and non-responders, in line with other researchers' call to develop knowledge of behavioural presentations of neglect alongside advances in neuroimaging (Moore et al., 2023; Vuilleumier, 2013). Thus, while there is clear value in linking neuro-anatomical regions to differential PA response (e.g., to substantiate neural theories of neglect and PA), the present thesis focuses on linking behavioural measures of neglect subtypes to PA effects, as spatial neglect is, in essence, a clinical syndrome observed through behaviour. Finally, I will now turn to the 'behavioural' component of the proposed link between PA treatment response and neuro-behavioural neglect subtypes, and in particular, the Input-Output neglect subtyping dimension.

1.9 Input-Output Neglect and Prism Adaptation Response

There is a small body of evidence suggesting that PA may differentially impact Input and Output neglect subtypes. These studies have dissociated Input and Output neglect using either a manual line bisection task under congruent or incongruent viewing conditions (Fortis, Chen, et al., 2011; Goedert et al., 2014), or a line bisection task with differing perceptual or motor response demands (Gammeri et al., 2023; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a). I will describe each subtyping method followed by the findings from the PA studies employing that method.

Spatial opposition tasks aim to uncouple Input and Output subtype components by comparing performance on a manual line bisection task across two visual feedback conditions. In the congruent (i.e., direct) viewing condition, visual feedback of the hand's movement is congruent with the hand's actual movement, and thus Input- and Output-related components are additive. In the incongruent (i.e., indirect, reversed) viewing condition, however, visual feedback of the hand's actual movement is left-right reversed using methods such as a video monitoring apparatus, 90-degree wedge mirror, or pulley device, which place visual Input and motor Output components in spatial opposition (Bisiach et al., 1990; Schwartz et al., 1997; Tegnér & Levander, 1991; for more details, see Section 2.3.3.1 of Chapter 2). Fortis, Chen, et al. (2011) asked five PwN to complete this spatial opposition task before and after two sessions of RPA, and they found that PwN's symptoms of Output neglect on the spatial opposition task (described as their "motor-intentional 'aiming' bias") reduced, whereas their symptoms of Input neglect (described as their "perceptual-attentional 'where' bias") were unaffected. Importantly, this study employed a simple pre-post design that could not rule out spontaneous recovery or practice effects. The same research group conducted another study that used the same spatial opposition task to classify 24 PwN into three groups with either an isolated perceptual-attentional “where” bias (n = 7), an isolated motor-intentional “aiming” bias (n = 5), or a combination of both biases (n = 12; Goedert et al., 2014). The authors found that PwN who had either an isolated motor-intentional “aiming” bias or a combination of both biases showed significant functional improvements on the CBS over the course of two weeks of RPA, whereas PwN who had an isolated perceptual-attentional “where” bias did not significantly improve. This pattern remained after statistically controlling for spontaneous recovery rate (measured from two pre-PA screening sessions), age, and baseline CBS score. These findings provide behavioural evidence for the aforementioned suggestion by Chen et al. (2014) of a link between PA’s therapeutic effects and motor-intentional “aiming” deficits in PwN.

The other approach to distinguishing Input and Output neglect symptoms in PA studies has been using variants of the line bisection task that differ in their perceptual or motor response demands. For instance, Striemer and Danckert (2010a) asked three PwN to complete both a manual line bisection task and a ‘perceptual’ version of line bisection that does not require a manual response and instead involves making verbally reported judgements about pre-transected horizontal lines (i.e., the Landmark task; Milner et al., 1993). Striemer and Danckert (2010a) found that a single session of RPA shifted manual line bisection performance leftward but had no impact on Landmark task performance. The authors likened this dissociation to other research suggesting that PA can affect a PwN’s visuomotor behaviours (e.g., eye movements) without affecting perceptual judgements (e.g., chimeric faces; Ferber et al., 2003). Striemer and Danckert (2010b) went on to propose the theory that PA mainly acts on the dorsal (occipito-parietal) visual stream that guides attentional and visuo-motor behaviour and has relatively minimal impacts on the ventral (occipito-temporal) visual stream that coordinates explicit perceptual judgments (for initial descriptions of two-stream visual theory, see Goodale & Milner, 1992). In addition, Striemer and Danckert (2010a) conceptualized neglect as arising from a disconnection between dorsal and ventral streams, which would restrict PA’s effects to the dorsal stream. In line with this theory, Saj et al. (2013) fMRI study found that a single PA session (outside the scanner) improved PwN’s performance on line bisection and visual search tasks (in the scanner), and this improved performance was associated with pre-post

PA increases in bilateral dorsal fronto-parietal brain activity, whereas no such behavioural or neuronal modulations were observed pre-post PA during a visuospatial working memory task. Further behavioural evidence for Striemer and Danckert's (2010b) proposal came from Gutierrez-Herrera et al.'s (2020) study, which tested 19 PwN on a manual line bisection and verbal Landmark task before and after two sessions of RPA, and found that improvements on the manual line bisection task (amongst other neglect measures with high motor involvement) were positively correlated with the PwN's proprioceptive prism aftereffects, whereas no such correlation was seen for the Landmark task. In addition, Gutierrez-Herrera et al.'s (2020) lesion subtraction analysis revealed that the PA-related improvements on tasks with high motor involvement were stronger for PwN who had intact temporo-parietal areas and damaged frontal-subcortical areas, consistent with the other lesion-PA response studies described in the previous section.

The final study I will describe that used a Landmark task to identify PwN's differential responding to PA shows a pattern that appears to refute Striemer and Danckert's (2010b) proposal. Gammeri et al. (2023) sought to compare the effects of PA and VST on the Landmark task (i.e., not compared to manual line bisection) that calculates perceptual and response biases from the same Landmark data set using formulae developed by Bisiach et al. (1998). Contrary to the findings from the aforementioned articles, Gammeri et al. (2023) found that PwN receiving PA displayed greater reductions in their perceptual bias, whereas PwN receiving VST displayed greater reductions in their response bias. Importantly, separating Input and Output neglect by comparing manual line bisection to a verbal Landmark task, compared to calculating biases from only the Landmark task, are very different subtyping methods (Chapter 4 of the present thesis discusses this point in greater detail). Different subtyping methods may tap into different neurocognitive mechanisms, and thus be expected to bear a different relationship to PA effects.

In summary, there is some evidence from studies of PwN that PA affects the Output subtype more than Input subtype, but this relationship may vary by which subtyping task is used. In addition, many of these studies have lacked enough experimental control to confidently rule out the potential contributions of spontaneous recovery and subtyping task practice effects.

1.10 USING PA TO INDUCE INPUT-OUTPUT BIASES IN HEALTHY ADULTS

Another method of probing the relationship between measures of Input-Output neglect and PA's mechanisms is to use PA to induce temporary, neglect-like cognitive biases in adults who have not had a stroke. There are several reasons to use this method, the first being implications for mechanisms of PA-induced reductions in neglect symptoms. Because a core feature of spatial neglect is a pathological egocentric bias toward the ipsilesional side of space (Corbetta & Shulman, 2011), if PA can experimentally induce a 'neglect-like' spatial bias in neurologically intact adults, PA may also be able to reduce these spatial biases in PwN. Overall, studies in healthy adults can enhance our knowledge of PA's effects on spatial cognition, which can inform models of PA's effects in spatial neglect (Clarke et al., 2022; Michel, 2006, 2016). Another reason to study bias induction in healthy controls is that it provides information about normative spatial biases that may influence measures of spatial neglect. It has long been known that small spatial biases exist in the general population, such as the slight leftward perceptual bias (termed "pseudoneglect") that is observed on tasks requiring a judgement of horizontal extent (Bowers & Heilman, 1980; for a seminal review, see Jewell & McCourt, 2000). Such normative biases provide important context for interpreting the pathological biases seen in PwN. Yet another reason to study PA effects in healthy adults is because they can potentially tolerate longer testing sessions, which is conducive to pre-post designs with greater experimental control (e.g., manipulating PA shift direction within-subjects to account for individual variability; longer baseline measurements on subtyping tasks prior to PA to minimize practice effects). Lastly, the study of PA-induced spatial biases is valuable on a broader scale than its application to neglect rehabilitation, as it can advance knowledge of the normative lateralization of spatial attention and related cognitive functions in humans.

Colent et al. (2000) kickstarted the PA bias induction research area by demonstrating that a single session of LPA in healthy adults caused a rightward shift in their verbal Landmark task performance but no significant shift in their manual line bisection performance. Since then, researchers have examined PA's effects across a wide range of cognitive tasks (for a good review of the cognitive effects of PA in absence of stroke, see

Michel, 2016). A subset of this research has examined the effect of PA on Input-Output subtyping tasks, including the spatial opposition task described above (Fortis, Goedert, et al., 2011), Landmark versus line bisection tasks (Gammeri et al., 2020; Herlihey et al., 2012; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Danckert, 2010a) and lateralized reaching tasks (Bracco et al., 2018; Striemer & Borza, 2017). Several of these studies have supported a link between PA effects and measures of Output-related processing (Bracco et al., 2018; Fortis, Goedert, et al., 2011; Gammeri et al., 2020; Striemer et al., 2016). However, other studies have not shown this pattern, such as: Colent et al. (2000), described above; Herlihey et al. (2012), who found opposite effects on perceptual and manual line bisection tasks depending on the PA exposure paradigm; and Striemer and Danckert (2010a), who found that PA induced spatial biases on both the verbal Landmark and line bisection tasks. Overall, much like my listed reasons for the variable effectiveness of PA in PwN (see Section 1.7), the variability in this bias induction literature could be attributed to differences in the PA paradigm, the existence and magnitude of normative biases in spatial attention at baseline, and conceptual and methodological characteristics of the Input-Output subtyping task under study. The present thesis focuses largely on this third factor.

1.11 Summary and Aims

To summarize this introductory material, spatial neglect is a behaviourally and neuro-anatomically heterogeneous condition that is associated with significant post-stroke functional disability and that currently has no 'gold standard' method of assessment or treatment (Teasell et al., 2020; Williams et al., 2021). While PA is a widely studied and promising treatment in the neglect rehabilitation literature, one essential step to advancing PA as a therapy is to clarify why certain PwN benefit from PA while others do not (Barrett et al., 2012; Rossetti et al., 2019). This endeavour requires a combined understanding of the complex clinical presentation of neglect, the underlying mechanisms of PA, and their interface. One initial step toward identifying a potential interface is the proposal that PA primarily impacts the Output stage of information processing, as measured by Input-Output neglect subtyping tasks. Substantiating this claim is challenging given the broad nature of the Input-Output neglect concept. It is also unclear to what extent this concept can be harnessed to advance knowledge of PA's therapeutic mechanisms, but using PA to induce Output biases in healthy adults is an interesting avenue to explore this link.

Given the above rationale, the overarching question of the present thesis was to evaluate the utility of the Input-Output conceptualization of post-stroke spatial neglect in understanding PA's effects on normal spatial cognition. I addressed this question through two thesis aims. The first aim was to explore the Input-Output neglect subtyping dimension. Using a systematic scoping review approach (Tricco et al., 2018), Chapter 2 provides an integrated summary of the subtyping terminology, measurement approaches, neural correlates, and prominent neural theories reported by 110 articles that attempted to: a) measure a distinction between Input and Output neglect in PwN after stroke; or b) induce spatial biases on an Input-Output subtyping task in healthy adults. This scoping review demonstrated the broad scope of the Input-Output neglect concept and resulted in implications for future research on Input-Output neglect subtyping and, arguably, for the study of any neglect subtyping dimension.

The second aim of the present thesis was to experimentally investigate whether PA could be used to simulate Output neglect in healthy adults. To this aim, Chapter 3 and 4 describe two experiments during which participants completed an Input-Output subtyping task before and after a session of either left- or right-shifting PA. I tested for pre-post PA shifts in Input-Output biases in the direction of the prism after-effect. The first experiment (Chapter 3) used a speeded reach task to measure Input-Output biases (Husain et al., 2000; Mattingley et al., 1998), which was chosen for its experimental control and for its focus on mental chronometry as the method of measuring information processing stages that was consistent with our conceptual model of Input-Output neglect (outlined in Chapter 2). Given the potential contribution of postural effects and stimulus-response compatibility on this task, data from both right- (Chapter 3) and left-handed (Chapter 3A) participants were collected. The second experiment (Chapter 4) calculated Input and Output biases using the Landmark task (Bisiach, Ricci, Lualdi, et al., 1998; Toraldo et al., 2004). The Landmark task was chosen because it was identified by the scoping review as the most used subtyping task overall, as well as the most used subtyping task amongst the included articles that investigated PA.

Chapter 5 provides a general discussion that links the results of the two thesis aims together. Specifically, I used the conclusions from the scoping review (Chapter 2) as a means of comparing, contrasting, and critiquing the findings across my two experiments (Chapters 3/3A and 4). Following this discussion, I revisited the proposed link between PA response and Output neglect by discussing evidence for and against this claim, and by connecting the Input-Output neglect concept to other theories of PA mechanism. Ultimately, I arrive at the conclusion that the Input-Output subtyping dimension cannot explain all aspects of the neglect syndrome, but it does provide a useful framework for investigating the parallels between PA's neurocognitive mechanisms and the neglect symptoms being targeted by this treatment. Important limitations of thesis scope and avenues for future research are also discussed.

CHAPTER 2 A SCOPING REVIEW OF INPUT-OUTPUT NEGLECT

This chapter consists of a manuscript in preparation. The authors of this work include Jasmine R. Aziz, Samantha R. Good, Samantha C. Horne, and Gail A. Eskes. My contributions to this project include: conceptualization, review protocol development, project management, article screening and selection, data charting and analysis, interpretation, and write-up.

A poster for this study was presented at the 2023 Advances in Stroke Recovery Conference, and an abstract for this poster was published in Neurorehabilitation & Neural Repair (doi: 10.1177/15459683231163223).

2.1 INTRODUCTION

Spatial neglect is a neurocognitive disorder that occurs after stroke and other acquired brain injuries whereby individuals have difficulty reporting, orienting, and/or responding to the contralesional side of space (Buxbaum et al., 2004; Heilman & Valenstein, 1979). These symptoms cannot only be attributable to primary sensorimotor impairments. Neglect is most common after right-hemisphere stroke, occurring in approximately 30-85% of cases, with variable prevalence rates by measurement approach and sample selection (Azouvi et al., 2002, 2006; Buxbaum et al., 2004; Leibovitch et al., 2012). Persons with neglect (PwN) tend to experience poorer rehabilitation outcomes, increased length of stay in hospital, and greater functional disability (Barrett & Muzaffar, 2014; Katz, Hartman-mae, et al., 1999; Viken et al., 2012). Although addressing neglect symptoms has the potential to benefit many aspects of recovery after stroke, the condition currently lacks any "Evidence Level A" treatments (Teasell et al., 2020). One significant obstacle to establishing effective treatments for neglect is heterogeneity in neglect symptom presentation, which results in diagnostic challenges (Barrett et al., 2012). Because each PwN presents with a different constellation of symptoms, researchers have proposed various subtyping dimensions to better characterize the disorder (Williams et al., 2021). In this review, we focus on the subtyping dimension based on the concept of Input (perceptual) and Output (premotor) neglect, and how their terminology, measurement approaches, and neural correlates have varied across the literature.

Most conventional measures of neglect are not designed to distinguish Input and Output neglect symptoms. For example, the line bisection task is a classic measure of neglect wherein PwN are asked to bisect a horizontal line at its central point (Wilson et al., 1987). When a PwN erroneously marks the line to the right of center, it is unclear whether they failed to perceive the left portion of the line, and/or whether they failed to plan or execute a leftward movement (Coulthard et al., 2006; Heilman & Valenstein, 1979). Researchers have investigated various approaches to isolating Input and Output neglect symptoms, such as: 'perceptual' versions of the line bisection task that involve making judgements of pre-transected horizontal lines (i.e., the Landmark task; Bisiach et al., 1998; Harvey & Milner, 1995; Milner et al., 1993); spatial opposition tasks that place perceptual and motor feedback in opposition (Fortis, Goedert, et al., 2011; Na et al., 1998; Tegnér & Levander, 1991); or reaching tasks that manipulate the reaching direction to peripheral targets by varying the hand's starting position (Husain et al., 2000; Mattingley et al., 1998). Subtyping approaches have varied considerably, and researchers have rarely compared subtype classifications across methods. One study by Harvey et al. (2002) compared the Landmark task and two spatial opposition tasks (the pulley technique and mirror reversal tasks; Bisiach et al., 1990; Tegnér & Levander, 1991). Out of 12 PwN, only one PwN had consistent subtype classifications across all three tasks. Furthermore, the Landmark task was more likely to classify PwN as having Input neglect, whereas the spatial opposition tasks were more likely to classify PwN as having Output neglect. These data indicate that the distinction between Input and Output neglect is inconsistent and likely bound by the measurement tools used to define it (Harvey, 2004; Saevarsson, 2013; Toraldo et al., 2014). Given this lack of clarity, it is not surprising that the neural correlates of Input and Output subtypes have also varied across studies. For example, Output deficits identified by spatial opposition tasks have often been linked to frontal lesions (Bisiach et al., 1995; Goedert et al., 2018; Tegnér & Levander, 1991), whereas Output deficits identified by the Landmark task and directional reaching tasks have been linked to parietal and subcortical regions (Bisiach, Ricci, Lualdi, et al., 1998; Husain et al., 2000; Sapir et al., 2007; Vossel et al., 2010). While not exhaustive, this discussion highlights that the classifications and neural correlates of Input and Output neglect may vary by subtyping approach.

Overall, the concept of Input and Output neglect lacks clarity, as evidenced by the variability in subtyping tasks and neural correlates documented across the literature. This variability poses challenges for the diagnosis and management of neglect symptoms, given that different subtypes may require different interventions (Gammeri et al., 2023). A scoping review is commonly used to define or clarify a concept in the literature (Munn et al., 2018), and thus would be a valuable method for mapping the various terminology, measurement tools, and neural correlates of Input and Output neglect. With respect to relevant prior reviews, Saevarsson (2013) conducted a systematic review of motor response deficits of neglect. However, their review focused on motor neglect (i.e., underuse of the *contralesional* limb despite intact primary sensory and motor function) in addition to premotor neglect (i.e., difficulty initiating or executing movements into the contralesional space with the *ipsilesional* limb), with minimal discussion of perceptual deficits. By contrast, the present scoping review aims to understand methods of distinguishing Input (perceptual) and Output (premotor) neglect. We did not focus on motor neglect studies when they concerned use of the contralesional limb and were conceptually farther from this Input-Output distinction. Another relevant past review was Williams et al. (2021), who conducted a scoping review of neglect assessment tools. However, their review was broader than ours in that it summarized measurement tools for several subtyping dimensions. Our review adds to Williams et al.'s (2021) work by elaborating on the Input-Output neglect subtyping dimension and discussing neural correlates and theories in addition to assessment tools.

The objective of this scoping review was to explore how Input and Output neglect have been measured, and thus conceptualized, across the literature. To this aim, we created a systematic summary of the terminology, measurement approaches, and neural underpinnings of these subtypes. Our research questions were: 1) what terminology has been used to describe the Input and Output subtypes of spatial neglect; 2) what measurement approaches have been used to distinguish these subtypes; and 3) what are the neural correlates and theories of these subtypes, as defined by each measurement approach.

2.2 METHOD

2.2.1 Protocol and Registration

The review protocol for the present scoping review was developed with reference to the scoping review guidelines from the JBI Manual for Evidence Synthesis (Peters et al., 2020), and the PRISMA extension for scoping reviews (PRISMA-ScR; Tricco et al., 2018). The protocol was registered on February 5, 2021 and is accessible via the Open Science Framework (OSF; https://osf.io/tf596). Deviations from this protocol are summarized at the end of this chapter.

2.2.2 Eligibility Criteria

Our eligibility criteria were specified according to the Population, Concept, Context (PCC) framework recommended for scoping reviews (Tricco et al., 2018). **Populations** under study included adults with stroke and a history or current presentation of spatial neglect (defined as indication of neglect on at least one measure[4]), and healthy adults. Given that this review focused on the **concept** of the Input-Output neglect subtyping dimension, the article needed to have a research question or objective that involved the Input-Output neglect subtyping dimension (exact terminology could vary by article) that was measured by at least one task. To limit the analysis to one sensory system and effector, we only included subtyping tasks that focused on visual stimuli and manual responses of the ipsilesional limb (e.g., upper-limb reaching or grasping movements). Tasks that compared performance of ipsilesional and contralesional limbs were included so long as the task was attempting to distinguish Input and Output components and was not intended to measure motor neglect. If the study was interventional, it could meet inclusion criteria so long as the treatment effects and/or sample characteristics were analyzed by Input-Output neglect subtype. Studies of healthy adults without stroke were included if they attempted to induce or manipulate Input or Output biases through methods such as neurostimulation or prism adaptation. Finally, there were no specific restrictions on the **context** of the study (e.g., no limits on country, geographical region, or clinical/research setting).

Exclusion criteria were studies focusing on neurological injuries other than stroke (e.g., traumatic brain injury, spinal cord injury, brain tumours), so that the PwN under study shared a similar etiology. If the study had a mixed or broader sample (e.g., acquired brain injury), the sample needed to consist of at least 50% stroke etiology. In addition, we excluded animal studies, human pediatric studies (< 18 years of age), and articles focused

[4]Our decision not to require neglect diagnosis to be derived from specific measures was made in the interest of representing the diverse body of literature on Input-Output neglect, and was also made based on the work of Azouvi et al. (2002, 2006), who demonstrated notable inconsistency in neglect diagnosis across different conventional and functional measures, precluding the establishment of specific diagnostic criteria.

on clinical conditions other than neglect such as optic ataxia, visual field defects, or visual agnosia. We also excluded studies that measured eye movements or ambulation as the motor response, as well as studies focusing on motor neglect, defined as underuse of the contralesional limb unexplained by sensorimotor deficits (Saevarsson, 2013).

For types of evidence sources, we included peer-reviewed empirical journal articles written in English with full-text available. We also included relevant dissertations and theses. Papers that were only published in languages other than English were excluded for feasibility reasons. Reviews and commentaries were not included in the scoping review, but we searched the reference lists of relevant papers for original research articles of interest.

2.2.3 Information Sources and Search Strategy

The following electronic databases were searched from the database inception to the most recent search date (February 21, 2023): PubMed/MEDLINE, PsycINFO, EMBASE, CINAHL, and ProQuest. JA developed the search strategy by conducting a preliminary search of relevant literature and consolidating keywords and terminology. Appendix A contains the PubMed/MEDLINE search string, which was adapted for the other databases of interest. The search string contained common terms for spatial neglect (e.g., hemispatial neglect, unilateral neglect), including various terms for the neglect subtypes of interest (e.g., input/perceptual neglect, output/premotor neglect, directional hypokinesia). Search limits included English and Humans. The search was applied to the title, abstract, and keywords. Relevant MeSH terms or subject headings were also included.

2.2.4 Selection of Source of Evidence

Selection of sources of evidence was conducted using Covidence online software (https://www.covidence.org/). JA conducted the database searches, and all citations were uploaded into Covidence. After removing duplicates, JA and one other reviewer (SG or SH) independently screened all titles and abstracts. Articles deemed potentially eligible were downloaded as full-texts. All full-texts were screened by JA and one other reviewer

(SG or SH) to confirm that they met the inclusion criteria, at which point they were included in the scoping review. Disagreements during the selection process were resolved by consensus between JA, SG, and SH, and in consultation with a more senior reviewer (GE). Prior to formal screening, we pilot-tested the above procedure on a subset of the search results and ensured at least 80% inter-rater reliability. The research team also hand-searched the reference sections of all included articles as well as the included articles from Saevarsson's (2013) review of response deficits in neglect. Potentially relevant papers underwent the selection process described above. Finally, we contacted one author (Dr. Buxbaum) for additional information about one subtyping task (Buxbaum et al., 2004).

2.2.5 Data Charting and Synthesis of Results

Prior to formal data charting, we pilot-tested the procedure by having JA, SG, and SH chart a sample of included articles (<10) and compare results for agreement (Levac et al., 2010). Discrepancies between reviewers were resolved through discussion and consultation with GE. For the formal process, JA, SG, and SH each performed data-charting on a subset of the articles included in the review. Reviewers then traded data charts and verified each others' work. Appendix B contains the data chart with descriptions of all data items, developed in Excel by JA and GE. In brief, we charted data on: article details (e.g., citation information, country of origin); study characteristics (e.g., objective, study design); participant characteristics (e.g., sample size, demographics, stroke severity); Input-Output measure(s) (e.g., terminology, apparatus, task description, psychometrics); and neural correlates (e.g., imaging type, neural correlates of each bias). First, we conducted a frequency analysis to count the number of included articles by publication date, country of origin, population (i.e., adults with stroke, healthy controls, or both), and study design (e.g., interventional or non-interventional). We also compiled the Input and Output subtyping terminology used in the included articles. Next, subtyping tasks were organized into categories based on methodological approach (see Results for more details). Measurement approaches and neural correlates were summarized for each subtyping category. Data in Tables 2.1-2.5 were completed by JA and verified by one other reviewer, whereas data summaries in Tables 2.6 and 2.7 were completed independently by two reviewers (82% initial agreement, discrepancies resolved through consensus with third reviewer).

2.3 RESULTS

2.3.1 Selection and Characteristics of Sources of Evidence

Figure 2.1 displays the selection of sources of evidence in a flowchart format, consistent with PRISMA guidelines (Page et al., 2021). A total of 110 articles were deemed eligible and were included in the scoping review. In terms of populations, 43 articles studied adults with stroke and neglect (39%), 30 articles studied healthy controls (27%), and 37 articles studied both PwN and healthy control groups (34%). Next, we constructed figures depicting frequency of publication date and country of origin for included studies. Figure 2.2 displays a histogram of all 110 included articles by publication year, which ranged from 1979 to 2023 and peaked in the late 1990s. Figure 2.3 displays a map of included articles in terms of their country of origin; the most prevalent country of origin was the United States (n = 44 articles), followed by the United Kingdom (n = 27), and Italy (n = 22).

2.3.2 Subtyping Terminology (Research Question 1)

Terminology for Input and Output subtypes was first presented in a graphical format using a free online "world cloud" generator software (Zygomatic, 2021). Figure 2.4 depicts the terminology used to describe Input and Output neglect subtypes across all 110 included articles. Terms depicted in a larger font were more commonly used. For the Input subtype (Figure 2.4a), the three most common terms were "perceptual," "attentional," and "perceptual-attentional." For the Output subtype (Figure 2.4b), the three most common terms were "motor," "motor-intentional," and "premotor" (see Appendix C for frequency counts for all recorded terms). "Directional hypokinesia" was a historically relevant term that specifically referred to slowed initiation of reaches toward the contralesional

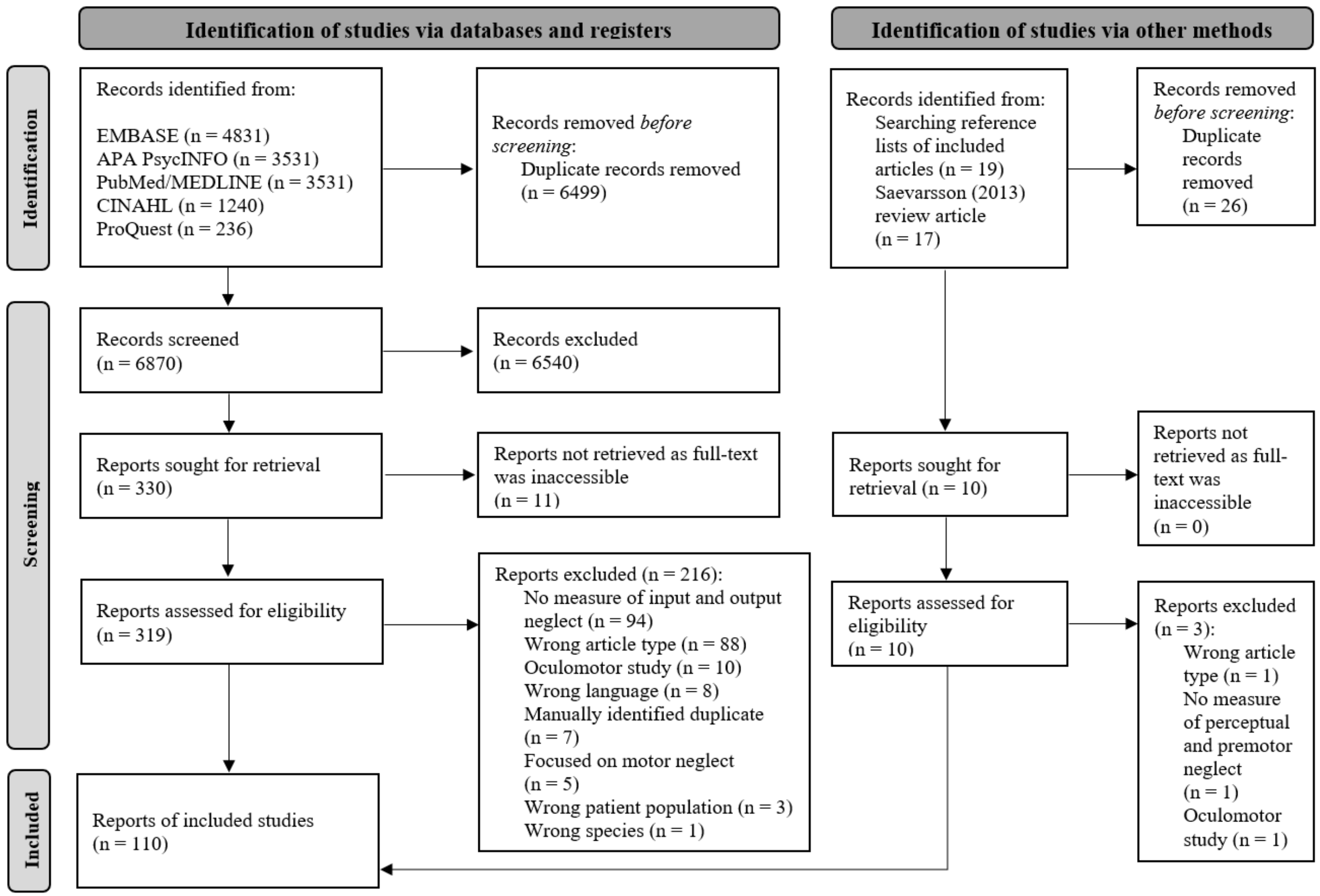


Figure 2.1 PRISMA flow diagram of the selection of sources of evidence.
Note. Based on Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

hemispace with either upper limb (Heilman et al., 1985; Watson et al., 1978). Other related output terms included "directional hypometria," "directional bradykinesia," and "directional akinesia," which referred to shorter movement amplitude, slower movement speed, and an absence of movement, respectively, in the contralesional direction (for a review that further discusses these motor response deficits in neglect, see Saevarsson, 2013).

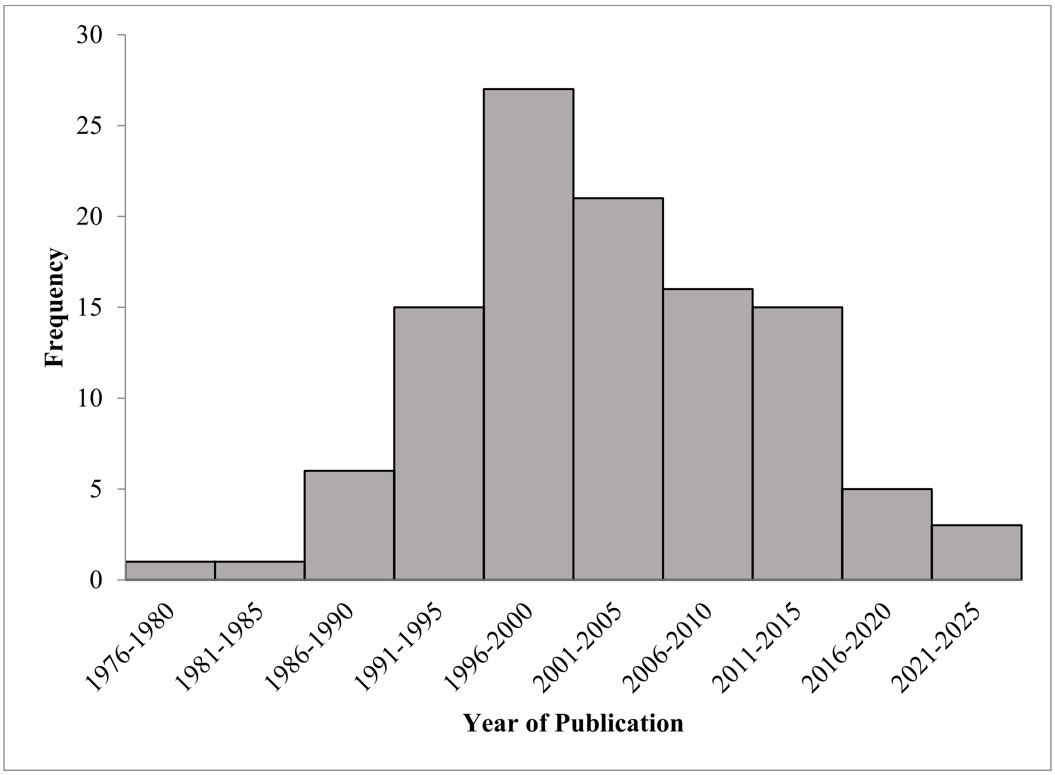


Figure 2.2 Histogram of included articles (*N* = 110) by year of publication.

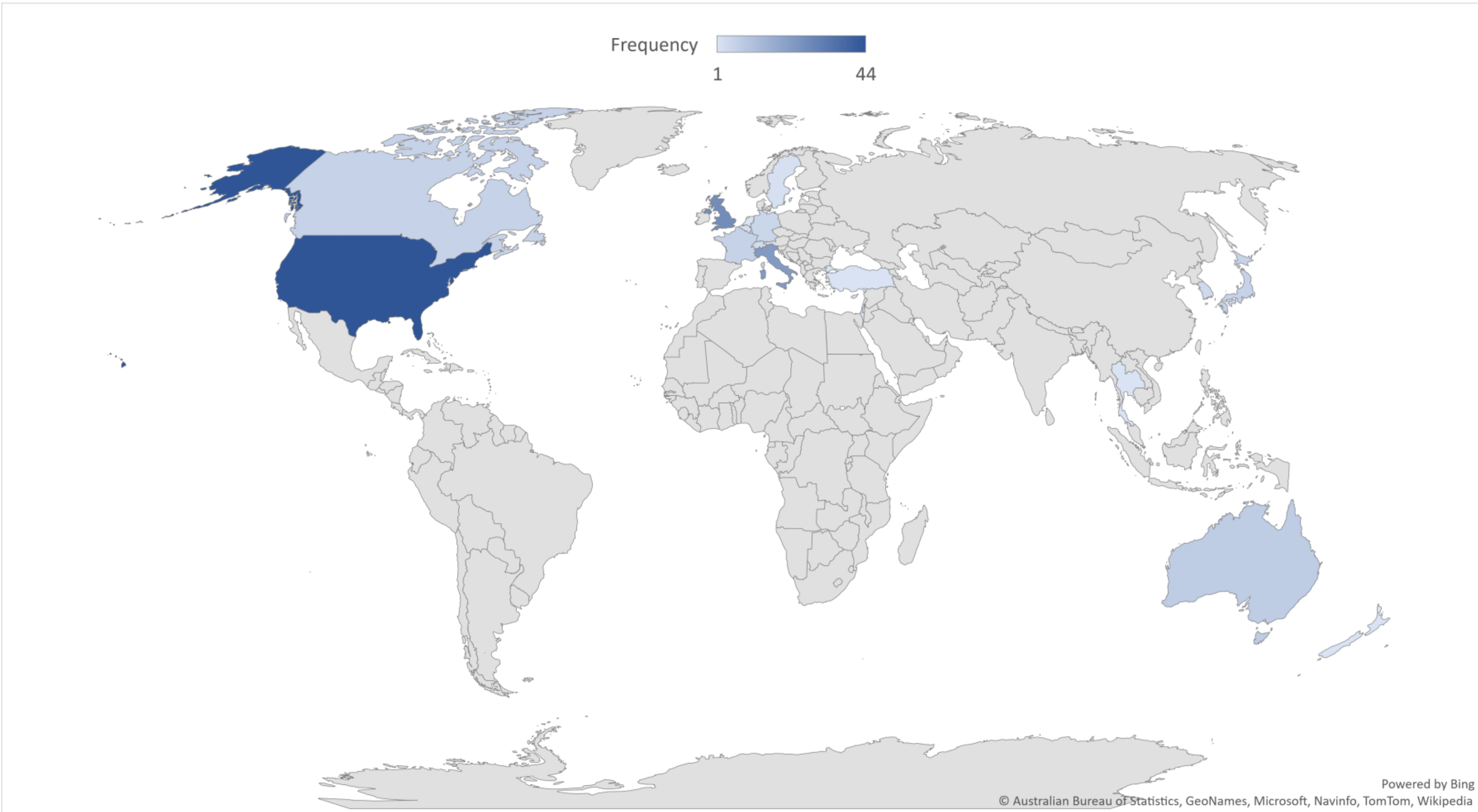


Figure 2.3 Geographical depiction of country of origin of included articles ($N = 110$).

A) B)

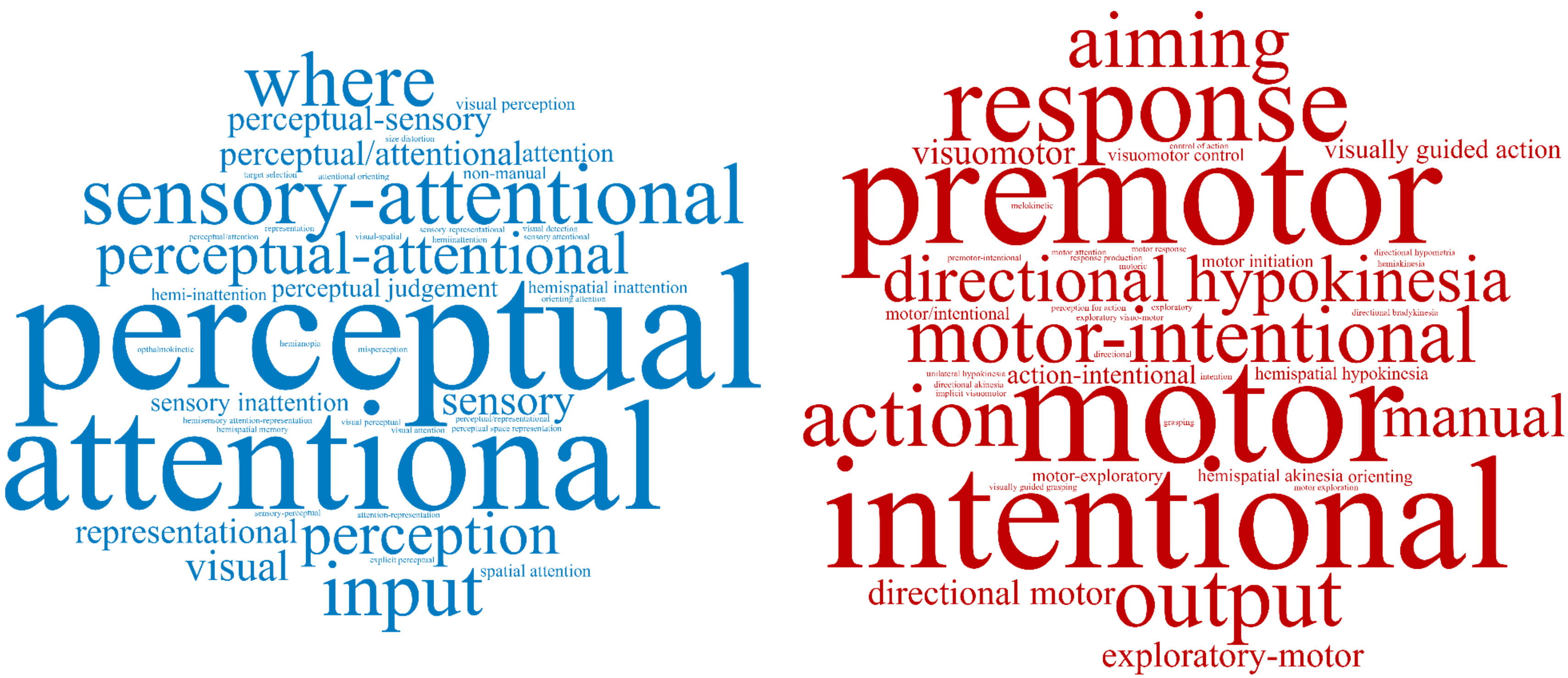


Figure 2.4 Word cloud of terminology used in included articles (*N*=110) for the Input neglect subtype (A) and the Output neglect subtype (B). Terms in larger font size were used in more articles. See Appendix C for frequency counts for all recorded terms.

We also conducted a more quantitative analysis of word associations in R studio (for source code and tutorial, see Henry, 2020). Figure 2.5 displays a word association map of subtyping terminology across all included articles. Each node in the map represents a term used by at least five included articles, with more common terms in darker font color. The lines between nodes represent Pearson's correlations between terms, which measure how frequently the two connected terms are used together (i.e., co-occur in the same article). Only correlations greater than $r = .2$ are displayed. This word map shows that certain words are consistently used together, such as "perception" and "action," or "input" and "output." By contrast, other words are paired differently across included articles. For example, the term "perceptual" could be paired with "motor", "premotor", or "response", depending on the article. Furthermore, the term "manual" was used in at least five articles but was not used consistently enough with other terms (i.e., $r < .2$) to be connected to any other terms on the map. Figure 2.6 shows the same analysis but split by subtyping task category (described in the next Results section), and depicts the different distributions of subtyping terminology use by methodological approach.

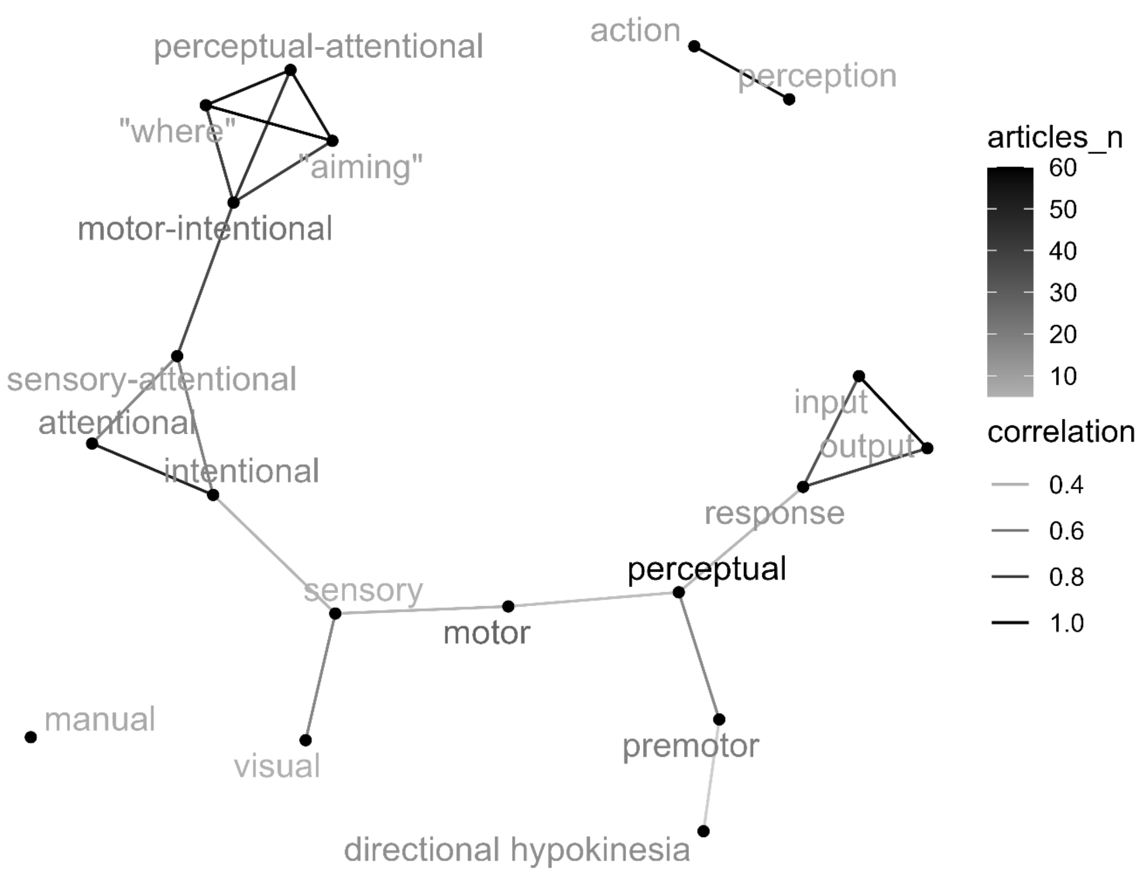


Figure 2.5 Word association map of Input-Output terminology across all included articles ($N = 110$). *Note*. Darker words indicate more articles using that term, and darker lines indicate stronger correlations between terms. To increase clarity, this map only includes terms that were used by at least five articles, and only depicts correlations between terms that are greater than $r = .2$.

2.3.3 Categorization of Subtyping Approaches (Research Question 2)

Subtyping tasks were organized into categories based on what stage of processing (i.e., input or output) was mainly manipulated to produce the subtype dissociation. To present the different subtyping approaches, we created tables summarizing the charted data for each subtyping task category, focusing on descriptions of what was manipulated and measured to dissociate the subtypes (Tables 2.1-2.5). We summarize the subtyping tasks within each category below. While terminology varied by subtyping approach, the terms Input and Output are generally used in the following sections to facilitate comparisons across tasks. We also note that 17 articles were counted under more than one category because they included more than one subtyping task (e.g., Harvey et al., 2002), or their subtyping task included more than one of the above manipulations (e.g., Hughes et al., 2008); see Appendix D for a complete list of these articles.

2.3.3.1 Manipulation of input: Congruence of input with output

There were 37 articles with subtyping tasks that manipulated the congruence of visual input with motor output (i.e., spatial opposition tasks; see Table 2.1). All tasks required participants to complete a conventional neglect measure (i.e., manual line bisection, cancellation, or drawing task) under congruent and incongruent visual feedback conditions. The assumption of these subtyping tasks was that Input-Output neglect subtypes could be dissociated by comparing a PwN's performance in the congruent condition when the Input and Output components are additive, to their performance in the incongruent condition when a left-right reversal of visual feedback places the Input and Output components in opposition. There appeared to be two general methods of creating the incongruent condition, each with a different prediction of Input and Output neglect symptom patterns. The first general method was a left-right reversal of the entire visual workspace, including the hand's position and surrounding visual stimuli (e.g., video monitor apparatus, epidiascope techniques, mirror reversal; see Figure 2.7 for a depiction of the mirror reversal technique from Tegnér & Levander, 1991). For this 'work-space left-right reversal' method, a person with Input neglect would show left-sided neglect in the congruent condition, but right-sided neglect in the incongruent condition as the left-sided stimuli are reflected into the right hemi-space. By contrast, a person with Output neglect would display left-sided neglect in both conditions due to a difficulty initiating leftward movements regardless of visual feedback (Schwartz et al., 1997; Tegnér & Levander, 1991). The second method of creating the incongruent condition was left-right reversing visual feedback of hand movement in relation to visual stimuli without reversing the visual stimuli as well (e.g., cursor inversion software, pulley device, Overhead Task, moveable aperture). With this 'hand movement left-right reversal' method, a person with Input neglect would show left-sided neglect in both the congruent and incongruent conditions due to difficulty interacting with the left hemi-space (i.e., moving the pulley pointer or cursor into the left hemi-space, or moving the aperture to make the stimuli in the left hemi-space visible), regardless of whether they are physically moving the apparatus to the left or to the right. By contrast, a person with Output neglect would show left-sided neglect in the congruent condition and right-sided neglect in the incongruent condition because they would have difficulty interacting with whichever hemi-space required a leftward movement[5] (i.e., the left hemi-space in the congruent condition, and the right hemi-space in the incongruent condition). Thus, while both methods involved comparing the person's performance across congruent and incongruent conditions, the expected patterns for Input and Output neglect with the 'hand movement left-right reversal' method necessarily differed from the expected pattens with the 'work-space left-right reversal' method.

[5]The expected performance patterns for Output neglect with this 'hand movement left-right reversal' method resemble the conceptualization of Output neglect in the subtyping category of tasks that manipulated direction of manual output (i.e., difficulty initiating contralesional movements; see Section 2.3.3.5).

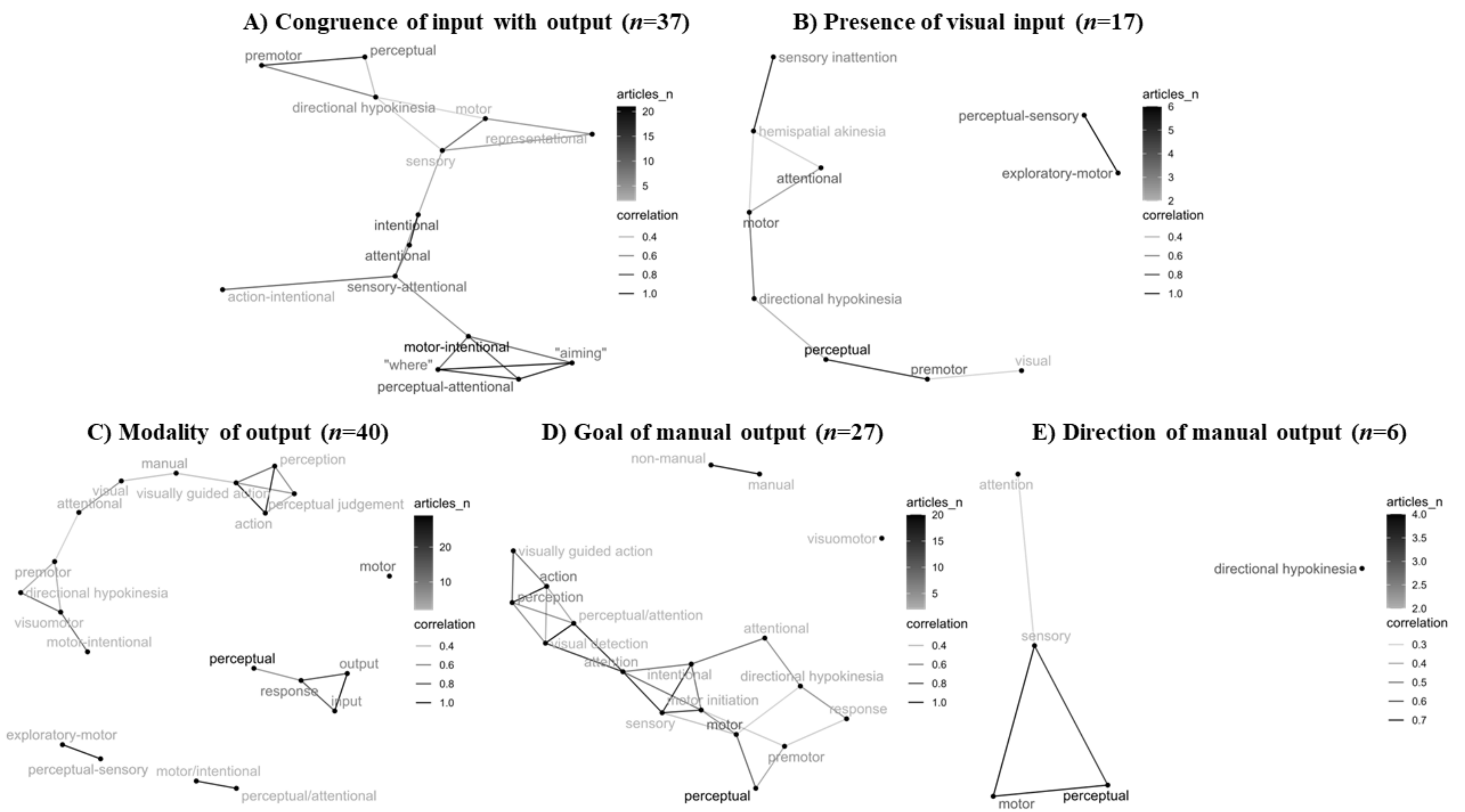


Figure 2.6 Word association map of Input-Output terminology by subtyping approach. *Note*. The *n*s refer to the number of articles describing a subtyping task from that given category (see also Figure 2.9). Darker words indicate more articles using that term, and darker lines indicate stronger correlations between terms. To increase clarity, these maps only include terms that were used by at least two articles, and only depict correlations between terms that are greater than $r = .2$.

Table 2.1 Manipulation of input: Congruence of input with output.

Task[a]	What is manipulated?	What is the outcome measure?[b]
Video monitoring apparatus[1-15]	congruent vs. incongruent (left-right reversed) visual feedback of hand position and task work-space on video monitor	Paper line bisection; line cancellation
Cursor inversion software during bisection[16-24] / cancellation task[25]	congruent vs. incongruent (left-right reversed) visual feedback of mouse cursor/laser position on computer monitor	Computerized line bisection; computerized line cancellation
Mirror reversal task[26-28]	congruent vs. incongruent (left-right reversed) visual feedback of hand position and task work-space through wedge mirror	Paper line cancellation
Epidiascope/overhead technique[29-31]	normal vs. left-right mirror-reversed viewing of hand position via epidiascope or overhead projector	Paper line/figure cancellation; paper line bisection; size/symmetry of daisy drawing
Pulley device[29,32-35]	congruent vs. incongruent pointer movement via pulley device	Paper line bisection
Moveable aperture technique[36-37]	direct search (move aperture over stationary stimuli) vs. indirect search (move stimulus sheet under stationary aperture)	Paper line cancellation

[a]*Note.* [1]Adair et al. (1998); [2]Adair et al. (2003); [3]Barrett & Burkholder (2006); [4]Barrett et al. (1999); [5]Barrett et al. (2001); [6]Barrett et al. (2002); [7]Braun and Kirk (1999); [8]Coslett et al. (1990); [9]Ghacibeh et al. (2007); [10]Khurshid et al. (2009); [11]Kim et al. (1999); [12]Kodsi and Heilman (2002); [13]Na et al. (1998); [14]Schwartz et al. (1997); [15]Schwartz et al. (1999); [16]Chen et al. (2009); [17]Chen et al. (2011); [18]Fortis, Goedert, et al. (2011); [19]Fortis, Chen, et al. (2011); [20]Garza et al. (2008); [21]Goedert et al. (2012); [22]Goedert et al. (2014); [23]Halligan and Marshall (1989); [24]Sacchetti et al. (2015); [25]Bier et al. (2007); [26]Bisiach et al. (1995); [27]Làdavas et al. (1993); [28] Tegner & Levander (1991); [29]Harvey et al. (2002); [30]Nico (1996); [31]Rode et al. (2006); [32]Bisiach et al. (1990); [33]Chapin et al. (2022); [34]de Los Angeles Hoffmann et al. (2011); [35]MacLeod and Turnbull (1999); [36]Gold et al. (1994); [37]Mijović (1991).

[b]*Note*. Performance on line bisection is typically measured by absolute or percent deviation from the line's central bisection point, whereas performance on line cancellation is typically measured by number of marks and omissions in each hemispace (with the exception of Schwartz et al., 199), who also measured performance based on the order of searched quadrants).

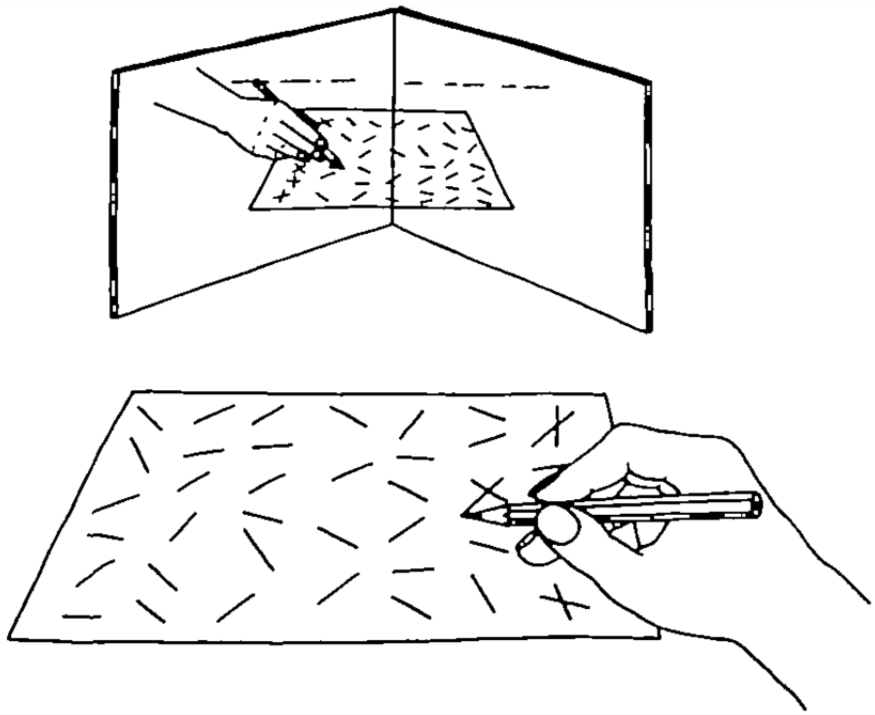


Figure 2.7 The mirror reversal task. Note. Figure reproduced from Tegnér, R., & Levander, M. (1991). Through a looking glass. A new technique to demonstrate directional hypokinesia in unilateral neglect. *Brain, 114*(4), 1943–1951, by permission of Oxford University Press (see Appendix H).

2.3.3.2 Manipulation of input: Presence of visual input

There were 17 articles with subtyping tasks that manipulated the presence of visual input (Table 2.2). The two general methods of manipulating visual input were visual occlusion versus visual guidance (n = 8), and presence versus absence of visual cues (n = 9). With respect to visual occlusion methods, five articles described a manual exploration task during which participants searched for targets (e.g., marbles) while blindfolded (Daffner et al., 1990; Liu et al., 1992; Maeshima et al., 1996, 1997; Pierce et al., 2022). Performance on this blindfolded manual exploration task was compared to a "visual-counting" condition wherein participants verbally counted the number of targets by vision alone (Maeshima, Nakai, et al., 1997), presence of visual extinction behaviour (Daffner et al., 1990; Liu et al., 1992; Maeshima et al., 1996), or performance on conventional line bisection and cancellation tasks (Pierce et al., 2022). In terms of other visual occlusion studies, Jackson et al. (2000) described a reaching task that manipulated whether information about the target's location was acquired visually (i.e., participant reached for targets with the right hand under visual guidance) or proprioceptively (i.e., left hand was passively moved to the target's location under visual occlusion of 1) left hand and target, or 2) entire work-space), and differences in reaching trajectories were measured using an optoelectronic recording device. In addition, Hughes et al. (2008) measured error in rod bisection under either binocular, monocular (eye patch), or occluded (eyes-closed) viewing conditions (rod bisection tasks are described in greater detail in the "Goal of manual output" section below). Finally, one article described a stand-alone procedure whereby participants were asked to point to their subjective straight-ahead with their eyes closed (Heilman et al., 1983); this study did not compare directly to an eye-open condition but was included for its historical significance. Overall, the assumption of these visual occlusion methods was that neglect symptoms occurring in the absence of any visual input cannot be due to visual-perceptual factors and thus are more likely due to exploratory-motor factors, and/or distortion of space representation.

For the tasks manipulating presence and absence of visual cues ($n = 9$), the most common approach was a cued line bisection or Landmark task: a letter or number was placed at the left or right end (or middle) of the line, and the participant was asked to read the letter or number out loud before responding (e.g., Heilman & Valenstein, 1979; Olk & Harvey, 2002; Reuter-Lorenz & Posner, 1990). In addition to these letter/number cues, Samuelsson (1990) included visual and verbal cues provided by the experimenter (i.e., the experimenter pointed to, or verbally instructed the participant to start at, the left or right end of the line). Finally, Sato et al. (2000) described a task wherein PwN either traced or erased a line leftward on a whiteboard. A person with Output neglect would have difficulty moving leftward in both conditions, whereas a person with Input neglect would have more difficulty moving leftward when tracing than when erasing because the presence of the line to the right of their hand would cue their attention rightward as they completed the task. Overall, these approaches distinguished Input from Output by using visual cueing to direct attention to different spatial locations and measuring changes in performance on manual line bisection and cancellation tasks. In the context of left-sided neglect, if a PwN's bisection performance improves (i.e., moves leftward) with left-sided cueing, it was assumed that their rightward bisection error was due at least in part to attentional Input factors.

Table 2.2 Manipulation of input: Presence of visual input.

Task[a]	What is manipulated?	What is the outcome measure?
Exploratory-motor and perceptual-sensory tasks[1-3]	blindfolded manual exploration or cancellation vs. visual extinction	time to locate left-sided targets or side of cancellation omissions vs. evidence of visual extinction
Exploratory-motor and visual counting tests[4]	manually moving marbles while blindfolded vs. verbally counting marbles by vision alone	number of marbles moved/counted in each hemispace
Manual spatial exploration and pencil-and-paper tasks[5]	(Eyes-closed) manual exploration of touch screen vs. (eyes open) line bisection and cancellation tasks	Centre of cancellation (CoC) across manual exploration and cancellation tasks
Reaching task[6]	visual vs. proprioceptive (i.e., left hand passively placed at target position) information of target location	Reaching trajectories
Hemispatial pointing task[7]	Blindfolding during straight-ahead pointing	Error in subjective straight-ahead pointing
rod-bisection task under different viewing conditions[8]	rod-bisection under binocular vs. monocular vs. occluded viewing	Rod bisection error
Line tracing and line erasing task[9]	tracing vs. erasing a line leftward on a whiteboard	accuracy and velocity of leftward movement between conditions
Cued line bisection and Landmark tasks[10-15]	Presence of letter/number cue at left or right end (or middle) of line	Line bisection error or %/number left/right responses on Landmark by cue condition
Cued video monitoring apparatus[16]	attentional cue (i.e., read letter at end of line) vs. intentional cue (i.e., touch end of line) before bisecting	direction of line bisection bias in direct and indirect conditions
Cued mirror reversal task[17]	Cueing (i.e., cued to start cancellation from hemispace neglected on previous attempt)	side of marks on line cancellation

[a]*Note.* [1]Daffner et al. (1990); [2]Liu et al. (1992); [3]Maeshima et al. (1996); [4]Maeshima et al. (1997); [5]Pierce et al. (2022); [6](Jackson et al., 2000); [7]Heilman et al. (1983); [8]Hughes et al. (2008); [9]Sato et al. (2000); [10]Harvey et al. (1995); [11]Heilman & Valenstein (1979); [12]Milner et al. (1992); [13]Olk & Harvey (2002); [14]Reuter-Lorenz & Posner (1990); [15]Samuelsson (1990); [16]Schwartz et al. (1999); [17]Bisiach et al. (1995).

2.3.3.3 Manipulation of output: Modality of output

There were 40 articles with tasks manipulating the modality of output (Table 2.3). The most common method (n = 22) of manipulating output modality was to compare performance on a manual line bisection task to a 'perceptual' version of line bisection that involved verbally reporting a visuo-spatial judgement about a pre-transected horizontal line (Landmark task; Milner et al., 1992, 1993). The specific verbal response requirements varied by study, including: stating which line segment (left/right, red/black) was longer or shorter (e.g., Bisiach, Ricci, Lualdi, et al., 1998; Herlihey et al., 2012); stating whether the transection point was to the left or right of the line's centre (e.g., Colent et al., 2000; Gammeri et al., 2020); stating yes or no whether the line was centrally bisected (e.g., Gutierrez-Herrera et al., 2020); or reading the Japanese character that was positioned at the perceived line bisection point (Chiba et al., 2005). A few tasks had participants verbally report line judgements about the experimenter's pointer location: Reuter-Lorenz and Posner (1990), Samuelsson (1990), Marshall and Halligan (1996), and Hughes et al. (2004) asked participants to verbally indicate when the experimenter's moving pointer was at the line's midpoint, while Ishiai et al. (1998) asked participants to verbally indicate whether the experimenter's pencil was to the left or right of the participant's ocular fixation at their subjective midpoint on the line. Finally, one study asked participants to write down the direction (left/right) in which the transection point deviated from the line's midpoint (Rueckert et al., 2002); although writing is a motor response, the nature of the output is verbal rather than reach-based and was still considered a verbal judgement and thus a difference in response modality relative to manual line bisection.

The assumption behind comparing the Landmark task (described above) to the line bisection task was as follows. On the line bisection task, PwN tend to transect lines to the right of centre, but this could be due to perceptual and/or response factors. The (verbal) Landmark task removes the manual (Output) component of line bisection, so biases on this task are considered to be due to only perceptual/attentional (Input) factors. Specifically, a person with Input neglect would be expected to underestimate the length of the left line segment, and thus would verbally indicate that the left line segment appears shorter even if the presented line is centrally bisected.

Table 2.3 Manipulation of output: Modality of output.

Task(s)[a]	What is manipulated?	What is the outcome measure?
Manual line bisection and verbal judgement of pretransected lines (verbal landmark)[1-22]	Manually bisecting line vs. verbally indicating perceptual judgement (e.g., left/right; yes/no; stop moving the pointer; see text)	Manual line bisection error (% or mm deviation) vs. quantification of perceptual judgment (e.g., % correct; PSE[b]; see text)
LANDMARK-V and/or LANDMARK-M[23-32]	pointing to longer vs. shorter segment, or verbally indicating colour of longer vs. shorter segment of a pre-transected line	% responses of shorter/longer. Perceptual bias: high value of (a+d)/2 (judge left side shorter and right side longer); response bias: high value of (b+d)/2 (select right segment regardless of bisection point)
exploratory-motor and perceptual-sensory/visual-counting tasks[33-36]	Cancellation or blindfolded manual exploration vs. visual extinction or visual-counting	Side of omissions or time to locate left-sided objects vs. evidence of visual extinction or side of counted objects
Manual and verbal cancellation tasks[37-38]	Manual vs. verbal identification of cancellation targets	Number of targets identified in each hemispace
Grasping and perceptual discrimination tasks[39]	Grasping an irregular object vs. verbally indicating whether pairs of irregular objects were same or different	distance between grasp points and centre of shape vs. errors on discrimination task
Exploratory visuo-motor and perceptual "components"[40]	Cancellation tasks vs. line bisection and text reading	line bisection error and side of reading omissions vs. side of omissions on cancellation tasks

[a]*Note*. [1]Avraham et al. (2019); [2]Binder et al. (1992); [3]Chiba et al. (2005); [4]Colent et al. (2000); [5]Dellatolas et al. (1996); [6]Gammeri et al. (2020); [7]Gutierrez-Herrera et al. (2020); [8]Herlihey et al. (2012); [9]Hughes et al. (2004); [10]Ishiai et al. (1998); [11]Loetscher et al. (2012); [12]Macdonald-Nethercott et al. (2000); [13]Marshall & Halligan (1995); [14]Marshall and Halligan (1996); [15]Michel & Cruz (2015); [16]Milner et al. (1992); [17]Pitzalis et al. (2001); [18]Reuter-Lorenz & Posner (1990); [19]; [20]Samuelsson (1990); [21]Striemer & Danckert (2010); [22]Striemer et al. (2016); [23]Bisiach et al. (1998); [24]Bisiach, Ricci, and Mòdona (1998); [25]Bisiach et al. (1999); [26]Brighina et al. (2002); [27]Capitani et al. (2000); [28]Gammeri et al. (2023); [29]Ricci et al. (2012); [30]Vossel et al. (2010); [31]Toraldo et al. (2002); [32]Toraldo et al. (2014); [33]Daffner et al. (1990); [34]Liu et al. (1992); [35]Maeshima et al. (1996); [36]Maeshima et al. (1997); [37]Bottini et al. (1992); [38]Geminiani et al. (1998); [39]Marotta et al. (2003); [40]Vaessen et al. (2016).
[b]*Note*. PSE = point of subjective equality.

Bisiach et al. (1998) revised Milner et al.'s (1992, 1993) Landmark task into two versions: a verbal Landmark (LANDMARK-V) that involved verbally indicating the colour (red/black) of the longer or shorter line segment; and a manual Landmark (LANDMARK-M) that involved pointing to the longer or shorter segment. For both versions, they reasoned that PwN with mainly a "perceptual bias" would tend to select the left line segment as shorter and the right line segment as longer (even if this was not the case), due to underestimating the length of the left segment, as in Milner et al. (1992, 1993). By contrast, they reasoned that PwN with mainly "response bias" would tend to select the right line segment regardless of where the transection was located, due to a difficulty making responses toward leftward stimuli. Perceptual and response biases were quantified using formulas reflecting this logic (see Bisiach et al., 1998 for more details).

Toraldo et al. (2002) proposed a different way of scoring the LANDMARK-V and LANDMARK-M that aimed to overcome two main limitations of Bisiach et al.'s (1998) method: namely, the loss of information from averaging responses across different transection locations, and the potential for diagnostic errors due to the interdependent nature of the perceptual and responses bias quantification methods. Toraldo et al. (2002) suggested that input-related neglect (*IRN*) could be measured as the point of subjective equality (*PSE*), which is calculated by plotting the probability of perceiving the right segment as shorter over transection position, fitting a sigmoid function, and determining the transection point at the 50% probability mark. This point, the *PSE*, is interpreted as the transection point at which the line segments are perceived as equal length, with perceptual neglect defined as a pathological shift in this *PSE* to the left or right of centre. Toraldo et al. (2002) also proposed that output-related neglect (*ORN*) could be measured as the mean probability (*M*) that the PwN makes a response to one side of the line regardless of the perceptual properties of the line segments (i.e., a response that contradicts their *PSE*; see Figure 1 in Toraldo et al., 2002 for more details).

Aside from the line bisection and Landmark tasks, other methods of manipulating output modality included: cancellation tasks whereby participants either manually crossed out targets or verbally reported them (Bottini et al., 1992; Geminiani et al., 1998); a task that involved grasping an irregularly shaped object or verbally indicating whether pairs of irregular objects were the same or different (Marotta et al., 2003); or comparing manual cancellation to text reading (and line bisection, Vaessen et al., 2016; see "Goal of manual output" section for more details).

2.3.3.4 Manipulation of output: Goal of manual output

Twenty-seven articles had tasks manipulating the goal of manual output (Table 2.4). The most common method (n = 11) was to compare performance on a manual line bisection task to a *manual* version of the Landmark task described above; that is, participants were asked to perform a visuo-spatial judgement by manually indicating the left or right segment of a pre-transected horizontal line. The type of motor response required by the manual Landmark task was either pointing to the left or right line segment (e.g., Harvey et al., 1995; Milner et al., 1993) or pressing a button to indicate the left/right segment or a correct/incorrect transection (e.g., Dupierrix et al., 2008; Learmonth et al., 2015). A person with mainly Input neglect would show a rightward bias on the manual line bisection task, but a leftward bias on the manual Landmark task due to underestimation of the extent of the left line segment. A person with mainly Output neglect, by contrast, would have a rightward bias on both the line bisection and Landmark tasks due to a difficulty making movements toward the left line segment in the contralesional hemi-space (Harvey et al., 1995, 2002).

Another type of task that manipulated the goal of manual output was what we termed "detection versus reaching" tasks (n = 7; e.g., Bartolomeo et al., 1998; Hamilton et al., 2008). These tasks compared the reaction times for detecting lateralized targets to the reaction times for reaching for targets (either reaching to peripheral targets from a central starting position or reaching to central targets from a lateralized starting position). For these tasks, the *detection* task was thought to measure biases at the Input stage because there was no reach required, whereas the *reaching* task was thought to measure biases at the output stage.

Table 2.4 Manipulation of output: Goal of manual output.

Task(s)[a]	What is manipulated?	What is the outcome measure?
Manual line bisection and manual (pointing) judgement of pretransected lines (manual landmark)[1-11]	Manually bisecting line vs. manually indicating perceptual judgement (e.g., pointing to the left or right line segment, pressing a button; see text)	Manual line bisection error (% or mm deviation) vs. quantification of perceptual judgment (e.g., % correct; PSE[b]; see text)
Detection vs. reaching tasks[12-18]	Centrally responding to peripheral targets vs. laterally reaching to central or peripheral targets	RT/accuracy by target side/reach direction
Line bisection and cancellation tasks[19-20]	bisecting line vs. exploratory cancellation of lateralized targets	line bisection error vs. side of omissions on cancellation tasks
Rod bisection tasks[21-22]	Pointing vs. grasping to bisect a rod	Rod bisection error
Bisection task with cylinders[23-24]	pointing to bisect distance between cylinders vs. reaching as quickly as possible between cylinders in the "target zone"	Bisection error for each task instruction
Size estimation and grasping tasks[25]	indicate size of cylinder with hand vs. reach and grasp cylinder	distance (measured by Optotrak) between finger and thumb during size estimation and grasping movement
Visual and motor attention tasks[26]	index finger button press to cued peripheral targets vs. index/middle finger choice button press to cued central targets	RT/accuracy by target/response side
Stop light paradigm[27]	to respond (go-trial) or inhibit response (stop-trial); target eccentricity; inter-stimulus interval	Probability of inhibiting response, *P(i)*

[a]*Note*. [1]Çiçek et al. (2009); [2]Dupierrix et al. (2008); [3]Harvey & Olk (2004); [4]Harvey (1994); [5]Harvey & Milner (1995); [6]Harvey et al. (1995); [7]Harvey et al. (2002); [8]Learmonth et al. (2015); [9]Milner et al. (1993); [10]Varnava et al. (2013); [11]Weiss et al. (2003); [12]Bartolomeo et al. (1998); [13]Buxbaum et al. (2004); [14]Farne et al. (2004); [15]Hamilton et al. (2008); [16]Mattingley et al. (1998); [17]Rengachary et al. (2011); [18]Shimodozono et al. (2006); [19]Binder et al. (1992); [20]Vaessen et al. (2016); [21]Hughes et al. (2004); [22]Hughes et al. (2008); [23]McIntosh et al. (2004); [24]Milner & McIntosh (2004); [25]Pritchard et al. (1997); [26]Rounis et al. (2007); [27]Cavina-Pratesi et al. (2001).
[b]*Note*. PSE = point of subjective equality.

Other subtyping approaches in the “goal of manual output” category involved comparing: manual line bisection and cancellation tasks (Binder et al., 1992; Vaessen et al., 2016); bisections of a rod via pointing versus grasping (Hughes et al., 2004, 2008); bisections of the distance between two cylinders via pointing versus speeded reaching (McIntosh et al., 2004; Milner & McIntosh, 2004); and indicating the size of a cylinder using the index finger and thumb versus reaching to grasp the cylinder (Pritchard et al., 1997). One rTMS study described a “visual attention” task that involved detection via single button press of (cued) peripheral targets, and a “motor attention” task that required the participant to choose between pressing their index or middle finger in response to (cued) central targets, and thus was considered to have more motor involvement (Rounis et al., 2007). Finally, one study examined perceptual and premotor contributions to lateralized stimulus detection by measuring the probability of successfully inhibiting their response on stop-trials intermingled with go-trials at different stimulus eccentricities (Cavina-Pratesi et al., 2001).

2.3.3.5 Manipulation of output: Direction of manual output

Six articles described tasks that distinguished Input and Output neglect components by manipulating the movement direction of manual output (Table 2.5). Mattingley et al. (1994) described a visually cued sequential movement task that manipulated the reaching direction (i.e., ipsilesional or contralesional horizontal movements) while holding the visual cues constant, and then compared the difference in reach initiation time between reaching directions. This task set the context for the most prevalent task (n = 4) in this subtyping category, which was a reaching task that involved reaching for targets located in the left and right hemi-space (Husain et al., 2000; Mattingley et al., 1998; Rengachary et al., 2011; Sapir et al., 2007). The primary manipulation was the direction from which the individuals reached for the targets (i.e., leftward or rightward), which was achieved using three possible starting positions for their reach: to the left of both targets, in between both targets, or to the right of both targets. The primary outcome measure was reach initiation time toward the contralesional target. This subtyping approach aimed to separate Input and Output components by systematically examining the effect of reaching direction (Output) on reach initiation time, while holding the stimulus location (Input) constant. In terms of assumptions, if a person had mainly Input neglect, then they would be slower to reach for the contralesional target, but this effect would not be expected to differ by reaching direction because the visual target location has not changed. However, if a person had mainly Output neglect, then they should have a faster reach initiation time when reaching rightward to the contralesional target from the left-most starting position than when reaching leftward to this same target from the central starting position.

One other task was included in this category. Geminiani et al. (2002) described a line extension task that manipulated the direction (i.e., left or right) in which the PwN extended a horizontal line by drawing a half-line segment. In terms of assumptions, Input neglect on this task was described as an overextension to the left compared with the right, due to underestimating the length of their left line segment. By contrast, Output neglect was described as an under-extension to the left compared with the right, due to difficulty moving toward the left hemispace.

Table 2.5 Manipulation of output: Direction of manual output.

Task(s)[a]	**What is manipulated?**	**What is the outcome measure?**
Reaching task[1-4]	reach direction (ipsilesional vs. contralesional direction) toward peripheral targets	difference in reach initiation time (*iRT*) between reach directions toward the contralesional target
Visually cued sequential movement task[5]	reach direction (ipsilesional vs. contralesional direction) toward a series of cued targets	difference in reach initiation time (*iRT*) between reach directions
Line extension task[6]	direction of line extension (ipsilesional vs. contralesional direction)	Length of line extension

[a]*Note*. [1]Husain et al. (2000); [2]Mattingley et al. (1998); [3]Rengachary et al. (2011); [4]Sapir et al. (2007); [5]Mattingley et al. (1994); [6]Geminiani et al. (2002).

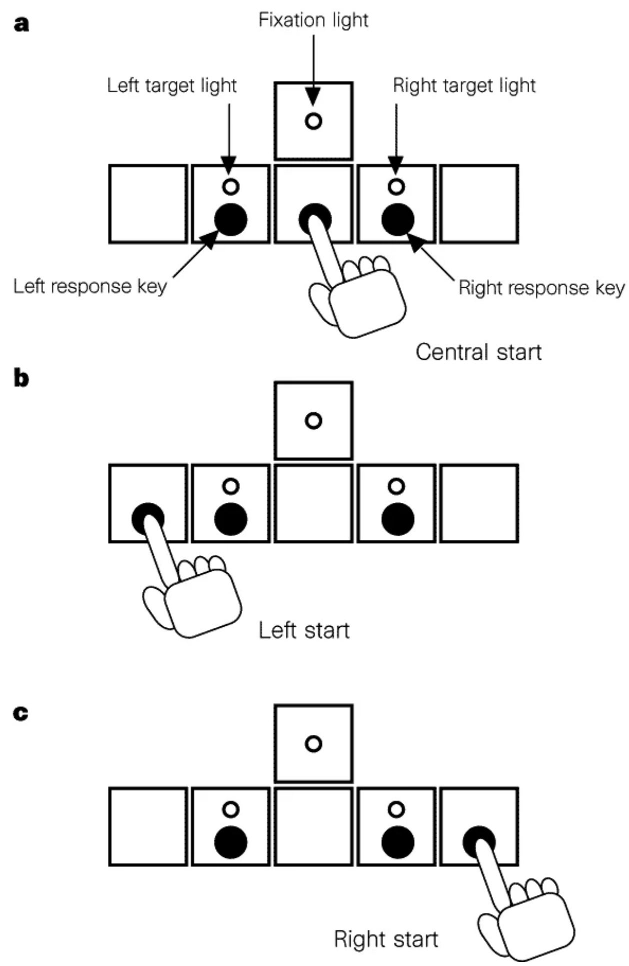


Figure 2.8 Reaching task manipulating direction of manual output. *Note.* Figure reproduced from Mattingley, J. B., Husain, M., Rorden, C., Kennard, C., & Driver, J. (1998). Motor role of human inferior parietal lobe revealed in unilateral neglect patients. *Nature, 392*(6672), 179–182. https://doi.org/10.1038/32413, with permission from Springer Nature (see Appendix I).

2.3.4 Prominent Neural Theories (Research Question 3)

Included articles were reviewed to identify neural theories that were referenced to explain the neural substrates of Input and Output neglect. Given that this review focused on the distinction between Input and Output neglect, we did not report on theories that only described neural substrates of either Input or Output neglect. The most broadly cited theories across included articles were Mesulam's (1981, 1990) cortical network theory (*n* articles = 35), Goodale and Milner's (1992) two-stream theory of visual processing (*n* articles = 15), and Corbetta and Shulman's (2002) theory of fronto-parietal attention networks (*n* articles = 10). We briefly review these three theories below and their connection to the Input-Output neglect subtyping dimension.

Mesulam (1981) proposed that the control of directed attention is governed by four anatomical components: a posterior parietal component that forms an internal sensory representation of the external world; a frontal component that coordinates the motor programs for exploratory movements; a limbic component in the cingulate gyrus that provides a spatial map of motivational valence; and a reticular component that coordinates basic arousal and vigilance. Mesulam (1981) argued that damage to certain components of this network would give rise to different presentations of neglect. Many authors of included articles referenced the first two anatomical components of Mesulam's (1981) theory to make the claim that posterior parietal lesions are more likely to produce Input neglect, whereas frontal lesions are more likely to produce Output neglect (Binder et al., 1992; Bisiach et al., 1990; Goedert et al., 2014). In further discussing the link between frontal lesions and Output neglect, Sacchetti et al. (2015) noted that the frontal lobes control motor exploration and preparation in three-dimensional space (Passingham 1995; as cited in Sacchetti et al., 2015). They also stated that "frontal systems may inhibit subcortical or parietal regions stimulating approach behaviors, and thus frontal cortical damage may cause a pathologic release of asymmetric approach motor behaviors" (p. 8, Denny-Brown & Chambers, 1958; Drago et al., 2006; as cited in Sacchetti et al., 2015). Numerous authors (e.g., Gold et al., 1994; Halligan & Marshall, 1989) acknowledged that evidence for Mesulam's (1981) proposal is mixed, likely because frontal, subcortical, and parietal brain areas form a distributed network (Mesulam, 1990), such that damage to any of these areas could result in Input and/or Output neglect.

Goodale and Milner's (1992) two-stream theory of visual processing described: 1) a ventral visual stream extending from occipital to lateral temporal areas that processes visual information for perception; and 2) a dorsal visual stream extending from occipital to dorsal parietal areas that processes visual information for the control of action. Striemer and Danckert (2010a) noted that neglect is often caused by lesions to the right inferior parietal lobule (IPL) or the temporoparietal junction (TPJ), which disrupts the neural pathways that connect the dorsal stream to the ventral stream. They claimed that this disrupted network may explain why certain task manipulations (e.g., line bisection and Landmark tasks) and interventions (e.g., prism adaptation) may differentially affect perception and action in PwN (for a review of this theory, see Striemer & Danckert, 2010b). Whereas Mesulam’s (1981) proposal was widely cited across subtyping approaches, Goodale and Milner’s (1992) two-stream theory was specifically cited in relation to tasks manipulating the extent of motor response involvement (i.e., modality and goal of motor output). This observation fits with the fact that Goodale and Milner’s (1992) two-stream theory describes how visual input is processed by different neural pathways for different behavioural purposes (discussed further in Milner & McIntosh, 2002).

Lastly, Corbetta and Shulman’s (2002, 2011) theory of fronto-parietal attention networks described a bilateral dorsal attention network (DAN) extending from the SPL/IPS to the FEF that governs voluntary orienting of attention toward visual targets, and a right-lateralized ventral attention network (VAN) extending from the TPJ to the VFC that governs more automatic orienting to salient or unexpected visual targets. Importantly, Corbetta and Shulman (2002, 2011) did not explicitly link the VAN and DAN to Input- and Output-related neglect processes; rather, they argued that neglect arises from a core egocentric deficit in spatial attention and salience, which can produce spatial biases in both stimulus processing and motor behaviour. However, McIntosh et al. (2004) drew a relevant parallel between Corbetta and Shulman’s (2002) theory and Goodale and Milner’s (1992) theory; that is, both theories describe a dorsal fronto-parietal network that exerts top-down control over a more ventral (e.g., inferior parietal, occipitotemporal) network. Thus, McIntosh et al. (2004) noted that while perceptual and visuomotor attentional processes would be tightly linked in healthy adults, neural damage could uncouple these processes. Specifically, damage to ventral areas may only affect perceptual attention, whereas damage to dorsal areas (e.g., SPL) would negatively impact both perceptual and visuomotor attention, given the dorsal network’s top-down control over both networks.

2.3.5 Neural Correlates of Subtypes (Research Question 3)

We created a table summarizing the neural correlates of Input and Output neglect subtypes, separated based on the subtyping approach manipulating either properties of the input (Table 2.6) or output (Table 2.7). Of the 110 total articles, 42 articles measured neural correlates of the identified subtypes. Most articles used CT and/or MRI as the type of imaging, except for the following articles that used SPECT imaging (Sato et al., 2000), DTI (Vaessen et al., 2016), and a virtual lesion (TMS) paradigm in healthy controls (Brighina et al., 2002; Ghacibeh et al., 2007; Ricci et al., 2012; Rounis et al., 2007). To create Tables 2.6 and 2.7, two reviewers independently checked off major neural areas correlated with each subtype within each article. We note that the major neural areas (e.g., frontal, parietal) in these tables were checked off based on the included article's authors' conclusions rather than our own assessment of the PwN's lesion sites in the studies, because this information was not available for all articles. Next, we created a semi-quantitative visual summary of neural correlates by subtyping approach (Table 2.8). This visual summary indicated an association between frontal-subcortical lesions and Output neglect symptoms and, to a lesser extent, posterior lesions with Input neglect symptoms.

2.3.6 Intervention Findings in Persons with Neglect (Post-Hoc Summary)

While the relationship between Input-Output neglect subtypes and intervention effects was not a formal question in this review, we summarize available findings here. Among the articles including PwN, 11 examined interventions for neglect, which included: prism adaptation (PA; *n* = 4); monocular patching (*n* = 3); PA and visual scanning training (VST; *n* = 1); cold caloric stimulation (*n* = 1); bromocriptine (*n* = 1); and apomorphine (*n* = 1). Here, we briefly summarize interventions that affected Input neglect symptoms, followed by interventions that affected Output neglect symptoms.

Table 2.6 Neural correlates of Input (blue I's) and Output (red O's) neglect on tasks manipulating input.

INPUT: Congruence of input with output											
Subtyping task(s)	**Article**	***N***	**Time since stroke**[a]	**Type of imaging**	**Neural correlates**[b]						
					Ant.	**F**	**SubC.**	**Post.**	**P**	**T**	**O**
Video monitoring apparatus	Barrett et al. (1999)	1	11 d (CT), 1 mo (MRI)	CT, MRI		O	O			O	
	Na et al. (1998)	10	7-270 d	CT (3), MRI (7)	O		O		I	I	
	Matthew et al. (2002)	1	15 mo	CT, MRI		O	O		O		
	Adair et al. (1998)	26	NR	CT, MRI		O	O	I			
	Adair et al. (2003)	16	< 30 d	NR	O			I			
	Ghacibeh et al. (2007)	10	NA (healthy controls)	virtual lesion (rTMS)		O			I		
	Khurshid et al. (2009)	1	1 yr	CT		O	O				
	Kim et al. (1999)	30	3 d-3 mo	CT, MRI		I O	I O				
Cursor inversion software	Halligan & Marshall (1989)	1	5 d	CT					I	I	
	Sachetti et al. (2015)	12	contra: *M* = 24 d (*SD* = 21); ipsi: 18 d (7)	CT, MRI		I	I				
Mirror reversal task	., 2014 & Levander (1991)	18	7-74 d	NR		O		I			
	Ladavas et al. (1993)	10	8-36 mo	CT, MRI		O			O I		
	Bisiach et al. (1995)	36	7 d-55 mo	NR	O		O	I			
Pulley device	Bisiach et al. (1990)	15	1-56 d	CT		O					
Moveable aperture	Gold et al. (1994)	1	2 d post-admission	CT					O	O	

INPUT: Presence of visual input											
Subtyping task(s)	**Article**	***N***	**Time since stroke[a]**	**Type of imaging**	**Neural correlates[b]**						
					Ant.	**F**	**SubC.**	**Post.**	**P**	**T**	**O**
Exploratory-motor and perceptual-sensory/ visual-counting tasks	Daffner et al. (1990)	1	NR	CT, MRI		O			I		
	Liu et al. (1992)	2	Upon hospital admission	CT, MRI		O	O		I		
	Maeshima et al. (1997)	30	4-32 wk	CT		O	O				I
Line tracing and line erasing task	Sato et al. (2000)	1	5 mo	MRI, SPECT					I		
Cued mirror reversal task	Bisiach et al. (1995)	36	7 d-55 mo	NR	O		O	I			

[a]*Note*: "Time since stroke" refers to the time since stroke that the imaging was done, if this was reported. If not, then this column reflects the time since stroke that the person's behaviour was studied. Kim et al. (1999) focused on ipsilesional neglect only, whereas the other papers focused on contralesional neglect.

[b]*Note*: Ant. = anterior; F = frontal; SubC. = subcortical; Post. = posterior; P = parietal; T = temporal; O = occipital. Decisions of neural correlates were based on authors' written descriptions of lesion-symptom correlates.

Table 2.7 Overview neural correlates of Input (blue I's) and Output (red O's) neglect on tasks manipulating output.

OUTPUT: Modality of output											
Subtyping task(s)	**Article**	***N***	**Time since stroke**	**Type of imaging**	**Neural correlates**						
					Ant.	**F**	**SubC.**	**Post.**	**P**	**T**	**O**
Manual line bisection and verbal landmark tasks	Chiba et al. (2005)	14	NR	CT, MRI	O		O	I			
	Gutierrez-Herrera et al. (2020)	19	13 chronic (>12 wk), 6 post-acute (>8 wk)	CT (10), MRI (9)		O	O			O	
LANDMARK-V and/or LANDMARK-M	Bisiach et al. (1998)	121	1-1507 d	CT		I	O				
	Brighina et al. (2002)	11	NA (healthy controls)	virtual lesion (rTMS)		I			I		
	Ricci et al. (2012)	3	NA (healthy controls)	virtual lesion (TMS)			O		I		
	Vossel et al. (2010)	68	*M* = 134 d (*SD* = 46)	CT, MRI		I	O		I		I
exploratory-motor and perceptual-sensory/visual-counting tasks	Daffner et al. (1990)	1	NR	CT, MRI		O			I		
	Liu et al. (1992)	2	9 mo, NR	CT, MRI		O	O		I		
	Maeshima et al. (1997)	30	4-32 wk	CT		O	O				I
Manual and verbal cancellation tasks	Bottini et al. (1992)	2	1 wk	CT		O	I O		I O	I	
Exploratory visuo-motor and perceptual "components"	Vaessen et al. (2016)	9	1-38 d	CT, MRI, DTI		O	I O		I	I	

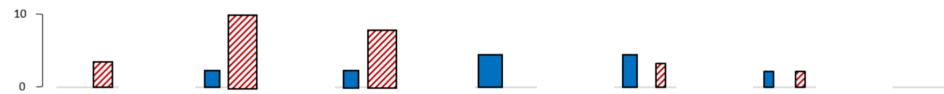
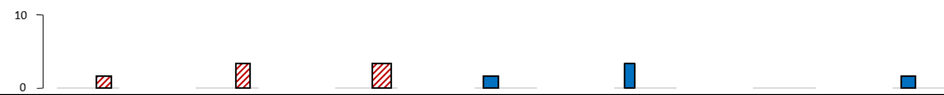
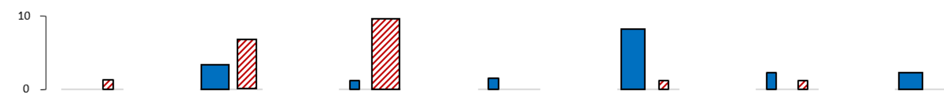
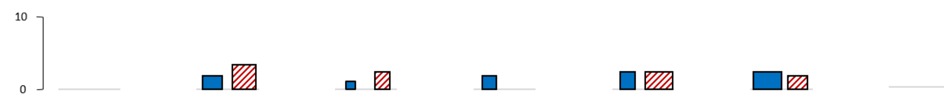
OUTPUT: Goal of manual output

Subtyping task(s)	Article	*N*	Time since stroke	Type of imaging	Neural correlates[b]						
					Ant.	F	SubC.	Post.	P	T	O
Detection vs. reaching tasks	Bartolomeo et al. (1998)	34	NR	NR					O		
	Rengachary et al. (2011)	61	T1: 8-29 d, T2: 29-45 wk	MRI		I			O	O	
	Buxbaum et al. (2004)	166	86 acute, 80 chronic (>3mo)	CT, MRI						I	
Line bisection and cancellation tasks	Binder et al. (1992)	34	~1 wk	CT		O	O	I			
	Vaessen et al. (2016)	9	1-38 d	CT, MRI, DTI		O	I O		I	I	
Bisection task with cylinders	McIntosh et al. (2004)	12	18-178 d	CT							
Visual and motor attention tasks	Rounis et al. (2007)	34	NA (healthy controls)	virtual lesion (rTMS)		O			I		

OUTPUT: Direction of manual output

Subtyping task(s)	Article	*N*	Time since stroke	Type of imaging	Neural correlates[b]						
					Ant.	F	SubC.	Post.	P	T	O
Reaching task	Husain et al. (2000)	6	6-77 d	CT, MRI		I			O		
	Sapir et al. (2007)	52	1-4 wk	CT, MRI			O				
	Rengachary et al. (2011)	61	T1: 8-29 d, T2: 29-45 wk	MRI		I			O	O	
Line extension task	Geminiani et al. (2002)	23	≥ 2 wk	CT		O	O				

Table 2.8 Overview visual summary of neural correlates of Input (solid blue) and Output (striped red) Neglect by subtyping approach.

Subtyping task category		**Visual summary of neural correlates***						
		Ant.	**F**	**SubC.**	**Post.**	**P**	**T**	**O**
Manipulation of input:	Congruence of input with output (*n* articles = 15)							
	Presence of visual input (*n* articles = 5)							
Manipulation of output:	Modality of output (*n* articles = 11)							
	Goal of manual output (*n* articles = 7)							
	Direction of manual output (*n* articles = 4)							

**Note.* For the summary bar graphs, the height of the bar represents the number of articles identifying that neural correlate (see y-axis for scale), and the width of the bar was linearly scaled to represent the combined sample size of the studies identifying that neural correlate (see the *N* column of Tables 2.6 and 2.7 for sample sizes by article).

When measured by spatial opposition tasks, Input neglect symptoms were reduced by cold caloric stimulation (Adair et al., 2003), and by monocular patching (Barrett & Burkholder, 2006; Khurshid et al., 2009), but Barrett et al. (2001) found a reduction in Input neglect with left eye patching and an increase in Input neglect with right eye patching. When measured by the Bisiach Landmark task, Input neglect symptoms were reduced more by PA than by VST (Gammeri et al., 2023). With respect to Output neglect symptoms, when measured by spatial opposition or Landmark-line bisection tasks, PA reduced Output neglect symptoms (Fortis, Chen, et al., 2011; Gutierrez-Herrera et al., 2020; C. L. Striemer & Danckert, 2010a), or presence of Output neglect symptoms predicted greater functional benefit from PA (Goedert et al., 2014). Bromocriptine administration worsened Output neglect symptoms when they were measured by a spatial opposition task (Barrett et al., 1999); by contrast, apomorphine administration improved Output neglect symptoms when they were measured by a task manipulating the modality of output (Geminiani et al., 1998). Finally, when measured by the Bisiach Landmark task, Output neglect symptoms were reduced more by VST than by PA (Gammeri et al., 2023).

In summary, a pattern emerges that monocular patching tends to affect Input neglect, whereas PA and dopaminergic agents tend to affect Output neglect. However, this pattern is only tentative given the small number of studies, contradictory findings (e.g., PA reducing Input neglect in Gammeri et al., 2023), and the general challenge of comparing across different samples and subtyping approaches.

2.3.7 Bias Induction Findings in Healthy Adults (Post-Hoc Summary)

As another post-hoc summary, we will briefly summarize findings from 11 articles that induced Input-Output biases in healthy adults using the following methods: prism adaptation (n = 7); monocular patching (n = 2); a lateralized pointing task (n = 1); and adaptation to lateralized temporally delayed visual feedback (n = 1). As above, we first summarize methods that induced Input biases, followed by methods that induced Output biases, and end with methods that induced both Input and Output biases, or neither bias.

When biases were measured by a spatial opposition task, monocular patching induced an Input bias ipsilateral to the side of the eye patch (Chen et al., 2009). When biases were measured by verbal Landmark and manual line bisection tasks, PA induced a stronger Input bias than Output bias (Colent et al., 2000). With respect to Output bias induction, adaptation to lateralized temporally delayed visual feedback induced an Output bias as measured by a blindfolded manual line bisection task, with no effect on Input biases measured by a verbal Landmark task (Avraham et al., 2019). Similarly, PA induced an Output bias as measured by a manual line bisection task, but a 30-degree prism shift was required (Gammeri et al., 2020). When biases were measured by a spatial opposition task, LPA produced a shift in Output biases (Fortis, Goedert, et al., 2011). Several studies found that PA induced both an Input and Output bias as measured by verbal Landmark and manual line bisection tasks, though effects did vary somewhat by prism shift (Herlihey et al., 2012; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Danckert, 2010a). Furthermore, a lateralized pointing task (no prisms) induced Input and Output biases on manual Landmark and line bisection tasks in the direction of the lateralized pointing (Dupierrix et al., 2008). Finally, when biases were measured using a spatial opposition task, monocular patching did not induce Input or Output biases in healthy adults (Barrett & Burkholder, 2006).

Overall, the majority of articles discussed here used PA to induce biases in healthy adults. In general, these studies have found that PA induces either Output biases in isolation, or both Input and Output biases. It is also worth noting that studies with healthy adults seem more likely to induce both Input and Output biases, whereas studies with PwN seem more likely to affect either Input or Output biases.

2.4 Discussion

The objective of this scoping review was to explore the Input-Output neglect subtyping dimension, which characterizes neglect symptoms as arising at different stages of information processing. Using a systematic search strategy, we identified 110 articles describing tasks that tapped into the Input-Output neglect subtyping dimension, and we created a summary of the terminology, measurement approaches, and neural theories and correlates of these neglect subtypes. Our review results highlight four important issues to consider in this area of neglect subtyping: 1) the clarity of the Input-Output neglect concept and its associated terminology; 2) the methodological issues associated with distinguishing Input and Output neglect; 3) the association between measured subtypes and neural regions identified by relevant neural theories; and 4) the application of subtyping measurement to the clinical assessment and treatment of spatial neglect. We discuss these four issues in turn, referencing specific examples identified through our review process, and for each issue we make conclusions and recommendations for future research.

2.4.1 The Concept of Input and Output Neglect Subtypes

Our scoping review demonstrates that the concept of Input and Output neglect is broad and encompasses many different cognitive operations and behaviours. This is evidenced by the wide range of terminology and measurement approaches that have been used to describe these subtypes (see Figures 2.4-2.6). Thus, our first review conclusion was that Input-Output subtyping terminology will necessarily vary by study purpose and conceptual model of the subtypes.

In line with this conclusion, we specifically chose to use the terms Input and Output neglect throughout this review: while these terms were not the most commonly used terms amongst the included articles, we selected them because they are informed by theories of human information processing that are grounded in computationalism (Cohen et al., 2014; Turing, 1950; Wickens et al., 2021), and they served our study's purpose of encompassing the wide range of terminology used across the literature. As depicted in the bottom half of Figure 2.9, Input processes serve to sense and/or perceive information, which may arise in the brain from either internal (e.g., mental imagery, proprioception) or external (i.e., through sense organs) sources; by contrast, Output processes serve to prepare, initiate, and/or execute motor responses. When applied to neglect, this model suggests that some PwN may have greater difficulty perceiving contralesional stimuli (Input neglect), whereas others may have greater difficulty planning, initiating, and/or executing movements in or toward contralesional space (Output neglect); a PwN may also display both forms of neglect to variable degrees.

While Figure 2.9 organizes these Input and Output processes along a single information processing pathway from sensation to motor execution, we are not claiming that neglect behaviour can be solely described by a reflex (stimulus-response) theory. This view is not only overly simplistic, but also contradicts subtyping tasks based on Goodale and Milner's (1992) theory of parallel processing of visual input for the purposes of either perception or action (this point was directly addressed in this included article: McIntosh et al., 2004; see also p. 158 of Milner & McIntosh, 2002). Thus, the bottom half of Figure 2.9 lacks arrows between the boxes and instead serves to cluster different forms of processing into two broad categories (Input and Output processing).

Another reason why we chose to use the terms Input and Output is that they can describe not only cognitive processes, but also the observable variables that were manipulated and measured to produce Input-Output neglect dissociations. For increased clarity, we use upper-case Input and Output to refer to cognitive processes (bottom half of Figure 2.9), and lower-case input and output to refer to these measured and manipulated variables (e.g., presence of visual input, goal of manual output; top half of Figure 2.9). Taken together, Figure 2.9 shows how the Input and Output processes affected in neglect have been operationalized using behavioural manipulations of input (i.e., stimulus) and output (i.e., response) properties of the subtyping task in question.

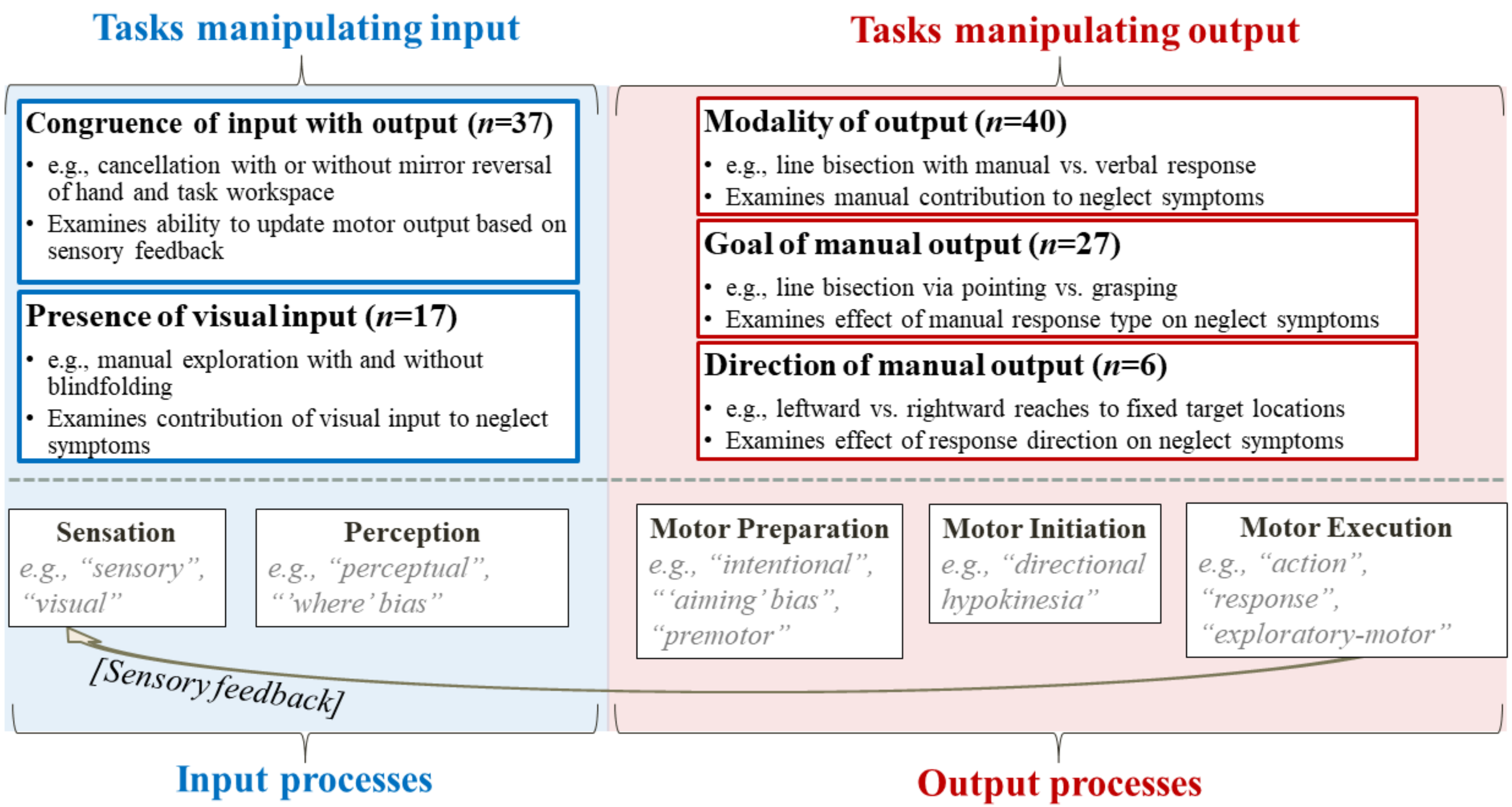


Figure 2.9 Organization of subtyping task categories in relation to Input-Output processes. *Note*. The *n*s refer to the number of articles describing a subtyping task from the given category; note that 17 articles were counted under more than one category because they included more than one subtyping task (e.g., Harvey et al., 2002), or their subtyping task included more than one of the above manipulations (e.g., Hughes et al., 2008); see Appendix D for a complete list of these articles. The grey quoted text in the lower boxes includes examples of common subtyping terminology that we believe would correspond to the processing stage labelled in that box.

While we have chosen an information processing model to describe the overall Input-Output subtyping dimension, the specific model and associated terminology will necessarily vary by study depending on its specific aims and the measures used to operationalize the subtypes. We are not suggesting that all articles in this area should use the terminology of “Input” and “Output”; we are merely suggesting that there should be a clear link between a given study’s conceptualization of the subtypes and the terms that are chosen to describe them. This link was evident in many included articles, such as using the terms “perception” and “action” in reference to Goodale and Milner’s (1992) two-stream theory of visual processing (e.g., Hughes et al., 2004, 2008; McIntosh et al., 2004; Milner & McIntosh, 2004), or using the term “hemispatial hypokinesia” as a behavioural prediction of the attention-arousal hypothesis (Heilman & Valenstein, 1979; Heilman & Watson, 1977). Other terms, however, were less clear in their conceptual basis. For instance, our word clouds (Figure 2.4) show that some articles used the term “sensory” to describe Input neglect, which in other contexts could refer to primary sensory impairments that are not classically considered symptoms of the neglect syndrome (Heilman, 1979). Another example is the use of the term “motor” to describe Output neglect, which could be easily confused with motor neglect (i.e., underuse of the contralesional limb not attributable to sensorimotor impairments). Furthermore, our word maps (Figure 2.5-2.6) illustrate that the same Input term (e.g., “perceptual”) may be paired with different Output terms (e.g., “motor”, “premotor”, “response”) in different articles, and it is unclear to what extent the meaning of this “perceptual” term would correspond across these articles. Some included articles noted that the subtyping terms they were using lacked specificity (Binder et al., 1992; Bisiach et al., 1990). Overall, these observations are suggestive of variable specificity of subtyping terminology across the literature, which further highlights the importance of drawing clear links between the subtyping terminology of choice and study’s purpose and conceptual models of neglect subtypes. With our Input-Output neglect concept as a backdrop, the next section discusses methodological issues associated with the measurement of Input and Output neglect subtypes.

2.4.2 Methodological Considerations of the Subtyping Approach

We categorized subtyping tasks based on what was specifically manipulated to produce the Input-Output neglect dissociation. As shown in Figure 2.9, we described tasks as manipulating characteristics of the task's input (i.e., congruence of visual input with motor output, presence of visual input) or output (i.e., the modality, type, or direction of output) properties. In reviewing these subtyping approaches, we came across numerous methodological issues that may complicate the interpretation of performance on these tasks. These issues could be grouped into two broad categories: 1) task-related confounds, including differences in task difficulty, bias quantification methods, or measurement error between conditions; and 2) the contribution of different body systems and environmental factors (e.g., sensory input modalities, motor output effectors, reference frames, and spatial sectors) to task performance. Thus, our second conclusion was that valid interpretation of Input-Output subtyping tasks requires consideration of all these potential methodological issues. The rest of this discussion section provides some illustrative examples of these methodological issues compiled by our review.

With respect to task-related confounds, one key assumption underlying all subtyping tasks is that if two task conditions are being used to dissociate Input and Output processing, the only difference between those two conditions should be the variable that is directly related to the desired Input-Output dissociation. Conditions should be otherwise matched as much as possible on other unrelated variables, otherwise these variables could confound the interpretation of task performance. For instance, spatial opposition tasks were criticized by some authors (e.g., Adair et al., 1998; Husain et al., 2000) for not matching task difficulty across the congruent and incongruent conditions. Specifically, PwN may perform poorly in the incongruent condition due to deficits in inhibitory control or other aspects of executive functions that are common sequelae of stroke (Chung et al., 2013; Foster et al., 1994; Skidmore et al., 2023). Thus, Output neglect identified by spatial opposition tasks could be due to other cognitive confounds rather than reflecting a specific behavioral manifestation of neglect. While spatial opposition tasks may be the most obvious example of task difficulty confounds, other subtyping approaches could also have this issue, such as the comparison of blindfolded to visual manual exploration. Three other potential design confounds are differences in response demands, bias quantification methods, and measurement error. All three of these confounds are illustrated by the subtyping approach of comparing performance on a manual line bisection task to the verbal Landmark task (Marshall & Halligan, 1995; Milner et al., 1992), as these two tasks do not just differ in modality of output (i.e., manual vs. verbal). The line bisection task is a free response task that is administered with relatively few (typically ~10) trials that are averaged to calculate bisection error. By contrast, the Landmark task requires a forced-choice response administered over more (typically ~50-100) trials, and bisection error may be quantified through various formulae (e.g., Bisiach et al., 1998; Milner et al., 1992; Toraldo et al., 2002). These differences in response demands and bias quantification methods can complicate comparisons between line bisection and Landmark task performance by affecting the relative sensitivity and measurement error of the two tasks, as has been reported in the prism adaptation literature (Colent et al., 2000; McIntosh et al., 2019). Overall, these examples demonstrate how design confounds can complicate the interpretation of performance patterns on subtyping tasks.

We now expand upon our second category of methodological issues: the potential contribution of different body systems and environmental factors to task performance. Importantly, we limited our review to tasks that focused on the visual modality and upper-limb movements in peri-personal space (i.e., within reaching distance). This was done partially for feasibility reasons given the large number of included articles, and partially to limit our inter-task comparisons to the same sensory system, effector, and spatial sector. However, tasks that are centered on the visual modality do not preclude involvement of other sensory-representational systems in task performance. For instance, as noted by several authors of articles using blindfolding methods (e.g., Heilman et al., 1983; Maeshima, Nakai, et al., 1997), blindfolding may remove visual input, but it does not prevent involvement of mental imagery in performance, which can also be impacted in neglect (Bisiach & Luzzatti, 1978, as cited in Heilman et al., 1983; for a review of representational neglect, see Salvato et al., 2014). In addition, blindfolding does not remove somatosensory input (e.g., touch, proprioception) from the upper limb completing the exploration task; while PwN often use their ipsilesional (less affected) upper limb to complete these tasks, ipsilesional somatosensory and motor deficits could still affect their blindfolded exploratory behaviour (Son et al., 2013). Furthermore, neglect symptoms may occur in auditory or tactile modalities (Gainotti, 2010), which do not rely on vision, and may influence a PwN's performance in blindfolded conditions as well. Similar issues arise when attempting to isolate effectors: tasks that are centered on upper-limb movements do not necessarily preclude involvement of other effectors in task performance. Movements of the eyes, arms, head, trunk, and whole body (e.g., ambulation) are associated with reference frames that shape our visuo-manual exploration of the environment (Jeannerod & Biguer, 1987; Niemeier & Karnath, 2003). For instance, PwN often show ipsilesional biases in eye movements (Fruhmann-Berger & Karnath, 2005), which could impact performance on any task aiming to measure Input neglect that does not restrict eye movements, including any conventional pencil-and-paper test of neglect (e.g., Wilson et al., 1987), and the vast majority of tasks included in this review (one exception was a lateralized reaching task during which PwN were trained to maintain central fixation, Husain et al., 2000; Mattingley et al., 1998). Finally, with respect to spatial sectors, it is well-known that neglect symptoms can vary across personal, peri-personal (near, within reaching distance), and extra-personal (far, beyond reaching distance) space (Beschin & Robertson, 1997; Vuilleumier et al., 1998; Whitehouse et al., 2019). While most tasks we reviewed took place in peri-personal space, one exception was Nico's (1996) epidiascope spatial opposition task, whereby stimuli in the congruent condition were on a piece of paper in the peripersonal (near) space, whereas stimuli in the incongruent condition were projected onto a screen in the extrapersonal (far) space. Another exception was Gammeri et al.'s (2020) virtual reality (VR) line bisection that involved bisecting a line beyond reaching distance using a beam of light projecting from a hand-held controller. Symptoms of Input and Output neglect may differ by spatial sector (Vuilleumier et al., 1998).

In summary, we assert that any attempt to distinguish Input and Output neglect should consider possible confounds between conditions being used to produce said distinction. Furthermore, while the subtyping tasks included in this review generally focused on visual input and manual output in peri-personal space, the known contributions of different sensory input modalities, motor output effectors, reference frames, and spatial sectors to neglect behaviour highlight the challenge of isolating subtyping task performance to one Input-Output processing system (e.g., visuo-manual) when multiple systems can be impacted in neglect. In addition, these systems may be differentially engaged by different subtyping tasks, with some tasks manipulating multiple stages of information processing (for examples of such tasks from this review, see Appendix D). While directly examining all these factors in a single study may not be feasible, these methodological issues should still be considered when designing Input-Output subtyping tasks and interpreting their findings.

2.4.3 Neural Theories and Correlates of Subtypes

Our third objective was to summarize the neural correlates and prominent neural theories of Input and Output neglect. Most Input-Output neural correlates came from discrete lesion data rather than the network-based measures that are becoming increasingly popular in neglect research (Brodtmann & Loetscher, 2022). This discrepancy is likely because the publication dates of included articles peaked in the late 1990s (see Figure 2.2), and more advanced imaging techniques were not as widely accessible then as they are now. Thus, our third conclusion is that any future research on the neural substrates of Input and Output neglect would need to update their neural theories and correlates to better reflect the current network views of neglect that have been advanced by contemporary neuroimaging techniques (e.g., see Lunven et al., 2019; Vaessen et al., 2016). The results of our review do prompt the question: why have studies of Input-Output neglect been declining in recent years (see Figure 2.2)? One potential reason could be difficulty connecting Input-Output concepts to neural networks. It was acknowledged decades ago that "an anatomical dichotomy (i.e., anterior/posterior) [is likely as oversimplified] as a functional dichotomy (i.e., perceptual/premotor)" (p. 363, Adair et al., 1998). A strict separation of Input- and Output-related processing may not be compatible with the complex and interdependent nature of neural networks. However, the interactions *between* Input- and Output-related processing could perhaps be more readily modelled by network-based measures, as has been done in the study of perception-action cycles (Rossetti et al., 2017). We will leave this point as an avenue for future work.

Given the large number of articles that referenced Mesulam's (1981, 1990) cortical network theory to associate posterior brain regions with Input neglect, and anterior regions with Output neglect (Binder et al., 1992; Bisiach et al., 1990; Goedert et al., 2014), we will now use our review results to evaluate this brain-behaviour relationship. As shown in Tables 2.6-2.8, our review of the neural correlates of Input and Output subtypes provided some support for this claim. In particular, the spatial opposition tasks showed a strong link between frontal-subcortical-anterior lesions and Output neglect. The spatial opposition tasks were the subtyping category with the most data on neural correlates (*n* = 15 articles), which may have biased the field toward the anterior lesion-Output neglect link, given the relationship between frontal systems dysfunction and difficulty with spatially incompatible movements (discussed in Adair et al., 1998 and Husain et al., 2000). Table 2.8 also demonstrates that across all subtyping approaches, evidence for the anterior-Output neglect link was generally stronger than evidence for the posterior-Input neglect link. This difference could be due to the range of sensori-motor functions that have been ascribed to the parietal lobe (Huang & Sereno, 2018). For instance, Mattingley et al. (1998), who found a correlation between parietal lesions and directional hypokinesia (an Output neglect symptom), described the inferior parietal lobule as a "sensorimotor interface" (p. 182) that is important for both perceptual and motor processing. Furthermore, Mesulam (1981) discussed human and monkey studies that have identified neurons in the posterior parietal cortex that fire not only when coding sensory location, but also when planning reaches to specific locations in space (e.g., Lynch, 1980; Robinson et al., 1978). Based on these descriptions, it is likely that the parietal cortex plays a role in the manifestation of both Input and Output neglect symptoms. Finally, we note that Mesulam (1981)'s cortical network theory of directed attention also described a limbic component that provides a motivational valence map and a reticular component that coordinates basic arousal and vigilance. These motivational and arousal components of Mesulam's (1981) theory were seldomly mentioned amongst the included articles, and they provide two more factors to consider when characterising Input and Output neglect.

In sum, while our review provides some support for the posterior-Input, anterior-Output distinction suggested by Mesulam's (1981, 1990) theory, future neuroimaging research on Input and Output neglect should seek to update the neural theories and correlates of this subtyping dimension in concert with advancements of network-based models of neglect and associated neuroimaging techniques.

2.4.4 Considerations for Clinical Assessment and Treatment

So far, we have discussed the terminology, measurement approaches, and neural theories/correlates of the Input-Output neglect concept mainly from a theoretical standpoint. How can this subtyping approach be applied to the clinical assessment and treatment of spatial neglect? A primary goal of subtyping the neglect syndrome has been to help us understand differences in neglect treatment response to guide rehabilitation (Barrett et al., 2012; Brodtmann & Loetscher, 2022). One takeaway message from summarizing the intervention effects by Input-Output neglect subtype (see Section 2.3.6), was that these effects may vary considerably by study sample, subtyping approach, and intervention method. Thus, our fourth and final conclusion is that clarifying the relationship between neglect subtypes and treatment response requires a joint understanding of: 1) the neurocognitive operations being captured by the Input-Output neglect subtyping task under study; 2) the therapeutic mechanisms of the intervention under study; and 3) their interface. One approach to investigating this interface has been to test whether neglect interventions can induce Input-Output biases in healthy controls (see Section 2.3.7), as this would suggest that the intervention could normalize these same biases in PwN. However, we noted that these healthy control studies were more likely to report changes in both Input and Output biases than studies of PwN. This difference could be because Input and Output processing are more highly integrated in the non-lesioned brain, whereas lesions may disconnect these networks in PwN after stroke (Bartolomeo et al., 2007; Striemer & Danckert, 2010a). While this difference could limit the generalizability of healthy adult studies to PwN, studies in healthy adults are still instrumental in advancing basic science and providing normative benchmarks for the interpretation of data from PwN.

We will end this section by noting some further considerations for the clinical application of neglect subtyping. While we have already noted that the Input-Output dichotomy is likely oversimplifying a highly interactive neural network, one advantage of dichotomous subtype assessment is that it allows for PwN to be categorized into discrete groups. Given that clinical decisions are also often dichotomous as well (e.g., should X patient receive treatment A or treatment B?), developing assessment methods that can reliably and parsimoniously identify treatment responders and non-responders could optimize these types of rehabilitative decisions (Bernhardt et al., 2017; Scheffels et al., 2022). Another point to consider in clinical application is the balance between internal and external validity. Our discussion thus far of isolating Input and Output processing prioritizes internal validity as we are interested in distinguishing different cognitive processes. However, since rehabilitative settings focus more on real-world functional outcomes, external (specifically, ecological) validity becomes a higher priority (for a review of ecological assessment of neglect, see Azouvi, 2017). One example of a more ecologically valid measure of Input-Output neglect comes from Goedert et al. (2012), who developed a method of fractionating Input and Output neglect symptoms using a standardized administration of the Catherine Bergego Scale (CBS; not included in this review as it did not focus on reaching movements in peri-personal space). Given that we did not assess study quality or compare psychometrics, our scoping review cannot be used to determine which Input-Output subtyping task is the 'best' to use in clinical practice (Tricco et al., 2018). Nevertheless, some feasibility considerations when implementing a subtyping task in clinical settings would include the task's administration time, cost and portability of equipment, and the level of assessor training required to administer the task.

2.4.5 Limitations

The present review has several limitations. First, the included articles and their associated Input-Output terminology could be biased by the search terms we used in our database searches. While search terms were determined through an iterative process based on preliminary searches, it is possible that some relevant articles were missed if their Input-Output terminology was not captured by our final search string (provided in Appendix A). As noted earlier, another limitation is that we only considered studies that focused on visual input and manual output in peri-personal space. It is unclear to what extent our discussion of terminology, methodological issues, neural theories and correlates, and clinical considerations would represent neglect research focused on other modalities, effectors, or spatial sectors. One additional limitation specific to our neural correlate findings (Tables 2.6-2.8) is that we did not extract neuroimaging data, as this information was not available for all included articles; rather, we based our tabular results on the authors' written descriptions of their findings. This indirect method restricted our ability to quantitatively summarize neuroimaging data and compare these data across articles. Finally, given that this was a scoping review and not a meta-analysis, we did not assess study quality or risk-of-bias. Thus, we could not make claims about the quality of data across included articles, and instead we focused on qualitative descriptions. Similarly, this review was more focused on the methodology of subtyping tasks (i.e., methods) than the subtype patterns found using each method (i.e., results). A subsequent review of bias patterns and study findings in this literature would yield further insights into the Input-Output neglect subtyping dimension.

2.4.6 Conclusions and Significance

Spatial neglect is a complex and debilitating neurocognitive disorder with a range of clinical presentations that have been organized into various subtypes (Buxbaum et al., 2004; Williams et al., 2021). This scoping review provides an integrative summary of the terminology, measurement approaches, and neural correlates of what we are terming the Input and Output neglect subtypes, which characterize neglect symptoms across different stages of information processing. We used a systematic search strategy (https://osf.io/bvtxf/) and included a total of 110 articles. Our review of the diverse Input-Output neglect literature resulted in four main conclusions: 1) subtyping terms will necessarily vary by study purpose and conceptual model; 2) methodological issues, such as potential confounds and other neglect subtyping dimensions, must be considered when designing and interpreting Input-Output tasks; 3) neural theories and correlates of Input-Output neglect require updating to reflect advances in neural models of neglect and neuroimaging techniques; and 4) there is potential value in directly connecting neurocognitive mechanisms underlying subtyping task performance to those underlying treatment effects.

Overall, our review has implications for theorists, neuroscientists, and clinicians working with spatial neglect. First, the four conclusions described above apply not only to the study of Input-Output neglect, but could also inform the study of any neglect subtyping dimension. With respect to implications for clinical practice, while recommending specific subtyping tools for clinical practice is beyond the scope of our review, our work does provide clinicians with a summary of the range of Input-Output subtyping tools that have been used in the literature. Researchers can use this summary to design studies comparing the psychometric properties of different subtyping approaches in both PwN and healthy control populations.

2.5 Deviations from Protocol

The original protocol (https://osf.io/bvtxf/) used the terms "perceptual" and "premotor" in the title and throughout the proposal, instead of "input" and "output" as done here. This change was made after summarizing the subtyping terminology for our first objective. As noted in our Discussion, the terms "Input" and "output" were more general terms than "perceptual" or "premotor" and thus could better encompass the range of subtyping terminology observed. We also made a few iterative changes to our inclusion/exclusion criteria at the full-text review stage to further limit our scope, given the large number of included articles. Specifically, we decided to only include tasks that focused on ipsilesional upper-limb movements as the output effector. This criterion necessarily excluded studies focusing on oculomotor movements or ambulation, as well as studies of motor neglect, which is commonly described as underuse of the *contralesional* limb in comparison with ipsilesional limb use (Saevarsson, 2013). Finally, we added the "Summary of Intervention Findings in PwN" and "Summary of Bias Induction Findings in Healthy Adults" results sections post-hoc, as this was an area of interest for the writers and relevant for clinical implications of the present review.

CHAPTER 3 DOES PRISM ADAPTATION INDUCE A PREMOTOR BIAS ON THE SPEEDED REACH TASK?

The contents of this chapter closely resemble an article published in Neuropsychological Rehabilitation (Aziz, J. R., & Eskes, G. A. (2023). Investigating premotor reaching biases after prism adaptation. *Neuropsychological Rehabilitation*, 1–25. Advance online publication. https://doi.org/10.1080/09602011.2023.2247153). My contributions to this project include: conceptualization, experimental program development, project management, data collection and analysis, interpretation, and write-up. Given that the present chapter does not exactly replicate the published article, this chapter would not be suitable for citation in lieu of the published article.

3.1 INTRODUCTION

Stroke is a leading cause of disability worldwide (Feigin et al., 2021). Many persons experience post-stroke deficits in cognitive function, limiting their independence and quality of life (Rost et al., 2022). One such deficit is spatial neglect, defined as a failure to report, respond, and/or orient to meaningful or novel stimuli on the side of space or body contralateral to the lesioned hemisphere (Heilman, 1979). Because of brain hemispheric differences in stimuli processing and the control of attention, neglect is more common and severe following right hemisphere stroke and therefore manifests itself mainly as problems with left-sided space (Corbetta & Shulman, 2011; Lunven & Bartolomeo, 2017). Persons with neglect (PwN) tend to show reduced engagement in rehabilitation and greater chronic disability (Katz, Hartman-Maeir, et al., 1999; Viken et al., 2012). Despite these impacts, there is currently no 'gold-standard' treatment for neglect (Teasell et al., 2020). One treatment under investigation is prism adaptation (PA), a visuomotor learning task whereby individuals repeatedly reach for visual targets while adapting to a lateral displacement in their visual field (Rossetti et al., 1998; Striemer & Danckert, 2010b). The leftward aftereffects that follow exposure to right-shifting prisms can help some individuals with left-sided neglect orient attention and perform visuomotor tasks in the previously neglected left space (Farnè et al., 2002; Rossetti et al., 1998), and improve their performance on both conventional neglect measures and functional tasks (Chen et al., 2022; Striemer & Danckert, 2010b). Despite these benefits in some studies, other studies have reported non-significant or transient effects of PA (Li et al., 2021; ten Brink et al., 2017).

The therapeutic benefits of PA may vary due to heterogeneity in neglect symptom presentation (Barrett et al., 2012). One prominent neglect subtyping dimension describes symptoms of neglect as occurring at different stages of information processing: some individuals have greater difficulty detecting or attending to stimuli on the left (perceptual or Input neglect), while others have greater difficulty planning or executing movements toward stimuli on the left (premotor or Output neglect; see Chapter 2; and Harvey, 2004; Saevarsson et al., 2014). Some research suggests that PA primarily acts on premotor neglect symptoms (Fortis, Chen, et al., 2011; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a; but see Gammeri et al., 2023, for conflicting evidence). One approach to investigating the relationship between PA and premotor neglect has been to test whether PA can induce biases in healthy controls that resemble the premotor biases seen in PwN (Colent et al., 2000; Fortis, Goedert, et al., 2011; Michel, 2006; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Borza, 2017; Striemer & Danckert, 2010a). Such a finding would suggest that part of PA's mechanism involves modulating premotor processes that are impacted in neglect.

Within this line of inquiry, Striemer and Borza (2017) tested whether PA could induce directional hypokinesia, a symptom associated with premotor neglect whereby individuals are slower to initiate reaches toward the contralesional side of space (Heilman et al., 1985). In Striemer and Borza's (2017) study, healthy adult participants were asked to make speeded reaches to left- and right-sided targets before and after a single PA session. After PA, participants were faster to initiate reaches in the direction of the prism aftereffect; that is, they displayed faster reach initiation time (*iRT*) to the right target after left-shifting PA and, to a lesser extent, faster *iRT* to the left target after right-shifting PA. These asymmetric results were line with other research indicating larger effects of left-shifting PA in healthy controls, attributed to baseline asymmetries in spatial attention (Clarke et al., 2022; Michel, 2016). While Striemer and Borza's (2017) results may indicate that PA modulates premotor processes, the authors noted that their task was unable to determine whether changes in *iRT* were due to faster perceptual processing of the target, and/or faster selection and initiation of the motor plan.

The task used by Striemer and Borza (2017) resembles a speeded reach task (our term for the task) that has been used previously to identify premotor symptoms in PwN (Harvey, 2004; Husain et al., 2000; Rengachary et al., 2011; Sapir et al., 2007). This speeded reach task aimed to disentangle perceptual and premotor components by examining the effect of horizontal reaching direction on *iRT* while holding the left and right target locations constant. Specifically, PwN are typically slower to initiate reaches to the left target, but this slowing could be due to a perceptual deficit and/or a premotor deficit. To distinguish between these possibilities, the start key is moved to the left of both targets so that the individual must reach rightward to the left target. Individuals with a premotor deficit should show an improvement in performance in this position (i.e., faster to reach rightward to the left target than when they reached leftward from the central start position). By contrast, individuals with a perceptual deficit should be slower to reach for the left target overall, but would show negligible change in *iRT* performance when changing hand position because the visual information about the left target's location has not changed. While this speeded reach task is a potential tool for separating perceptual and premotor biases, to our knowledge it has not yet been used for this purpose in PA research.

We sought to replicate and extend Striemer and Borza's (2017) work by examining whether PA induces the reaching bias reported by Striemer and Borza (2017), as well as whether this reaching bias could be attributed to the premotor stage of processing. Healthy adult participants completed the speeded reach task before and after either left-shifting (*n*=15) or right-shifting (*n*=15) PA. As in Striemer and Borza (2017), we predicted that PA would speed *iRT* from the central start key when reaching in the direction of the prism aftereffect. However, we hypothesized that this effect would be primarily explained by a shift in premotor biases on the speeded reach task, whereas perceptual biases on the speeded reach task would not change significantly from pre- to post-PA (for calculation method of perceptual and premotor biases, see Figure 3.2). Finally, we predicted that the PA-induced premotor bias would be greater following LPA than RPA, consistent with Striemer and Borza (2017) and past research showing larger cognitive aftereffects from LPA in healthy adults (Clarke et al., 2022; Michel, 2016). Results from the present healthy control study can inform both mechanisms of PA and future research examining whether perceptual/premotor subtype patterns could predict responses to PA in PwN.

3.2 METHOD

3.2.1 Participants

Thirty adult participants were recruited from Dalhousie University and the surrounding community in Halifax, Canada. This sample size was calculated using 95% power, an alpha level of 0.05, and the large effect size ($\eta_p^2 = .31$) of the interaction between PA shift direction, target side, and time on *iRT* found by Striemer and Borza (2017). Inclusion criteria were self-reported normal or corrected-to-normal vision and hearing, and no self-reported physical problems that affected their ability to use a keyboard and point to targets on a computer screen (e.g., limb injury). Exclusion criteria were self-reported current diagnosis of neurological disorders (e.g., Parkinson's disease, dementia). All participants were right-handed by self-report, further confirmed by the Edinburgh Handedness Inventory – Short Form (EHI-SF; Veale, 2014)[6]. Table 3.1 displays laterality scores and other sample demographics, which did not differ between prism shift direction groups (*p*s ≥ .2). All participants reported and demonstrated proficiency in English. Participants were recruited via community advertisements, the undergraduate psychology participation pool, and word of mouth, and individuals self-selected to participate. Participants received either financial reimbursement (e.g., for parking, travel), or credit points toward an undergraduate Psychology/Neuroscience course if they were an eligible Dalhousie student. All study procedures were in accordance with the Nova Scotia Health and Dalhousie University Research Ethics Boards.

Table 3.1 Sample demographics of right-handers by prism shift direction group.

Variable	LPA Group	RPA Group	Overall
Sample size	15	15	30
Mean age in years (*SD*)	26.73 (10.00)	22.73 (4.45)	24.73 (7.86)
Mean education in years (*SD*)	14.73 (2.84)	14.87 (2.72)	14.80 (2.73)
Gender (women:men:non-binary)	11:2:2	10:5:0	21:7:2
Mean EHI-SF laterality quotient (*SD*)	85.83 (19.97)	81.67 (24.03)	83.75 (21.81)

Note. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation; EHI-SF = Edinburgh Handedness Inventory – Short Form (Veale, 2014).

[6]The EHI-SF is a four-item version of the original EHI and has very good internal consistency (α = .93) and a strong correlation with scores on the widely used original 10-item scale (r^2 = .94; Oldfield, 1971; Veale, 2014). Handedness laterality quotients were calculated according to Veale (2014), with a positive quotient indicating a right-hand preference.

3.2.2 Design

This study used a mixed randomized experimental design, as in Striemer and Borza (2017). Prism shift direction was treated as a between-subjects factor, and participants were randomly assigned to receive either left-shifting (LPA; n = 15) or right-shifting (RPA; n = 15) PA glasses. Within-subjects factors included target side (left, right) and hand start position (left, centre, right) on the speeded reach task, and time (pre-PA, post-PA). The primary outcome measure was reach initiation time (*iRT*; in milliseconds) on the speeded reach task. Other variables measured were error size (in pixels relative to the screen's centre, converted to visual degrees) and movement time (*MT*; in milliseconds).

3.2.3 Materials

3.2.3.1 PLATO visual occlusion spectacles

During the speeded reach task and measure of prism aftereffects, participants wore PLATO goggles (Translucent Technologies Inc., TO, Canada), which are fitted with liquid crystal lenses that can switch between clear and occluded states. These goggles were used to occlude the participant's view of their task workspace during their reaching movement, as in Striemer and Borza (2017). The purpose of this visual occlusion was to reduce de-adaptation during the speeded reach and proprioceptive straight-ahead (PSA) pointing tasks after prism exposure, as individuals tend to de-adapt from PA more rapidly when they have full vision of their reaching trajectory (Redding et al., 2005; Redding & Wallace, 1996).

3.2.3.2 Speeded reach task

The speeded reach task was developed and presented using Superlab Version 6.1.2 for Windows (Cedrus Corporation, 2021), and was based on the program used for the reaching task in Striemer and Borza (2017). See Figure 3.1 for a depiction of the experimental setup. Participants were seated in front of a horizontally oriented 24-inch Asus touch screen computer and placed their chin in a centrally positioned chin rest, which maintained a distance of ~47 cm between their eyes and the centre of the screen for the duration of the experiment. A small Styrofoam occlusion board was attached to the chin rest to block the participant's view of their hand's starting position. The start key was a custom-built single keyboard button attached to a serial-to-USB converter that was connected to both the PLATO goggles and stimulus computer and programmed using Arduino software (Arduino, 2021). The start key had three possible equally spaced positions along the edge of the stimulus screen closest to the participant that were varied at the block level: centre start (i.e., at the halfway point between the two horizontal target locations, in line with the chinrest), left start (i.e., to the left of both target locations), or right start (i.e., to the right of both target locations).

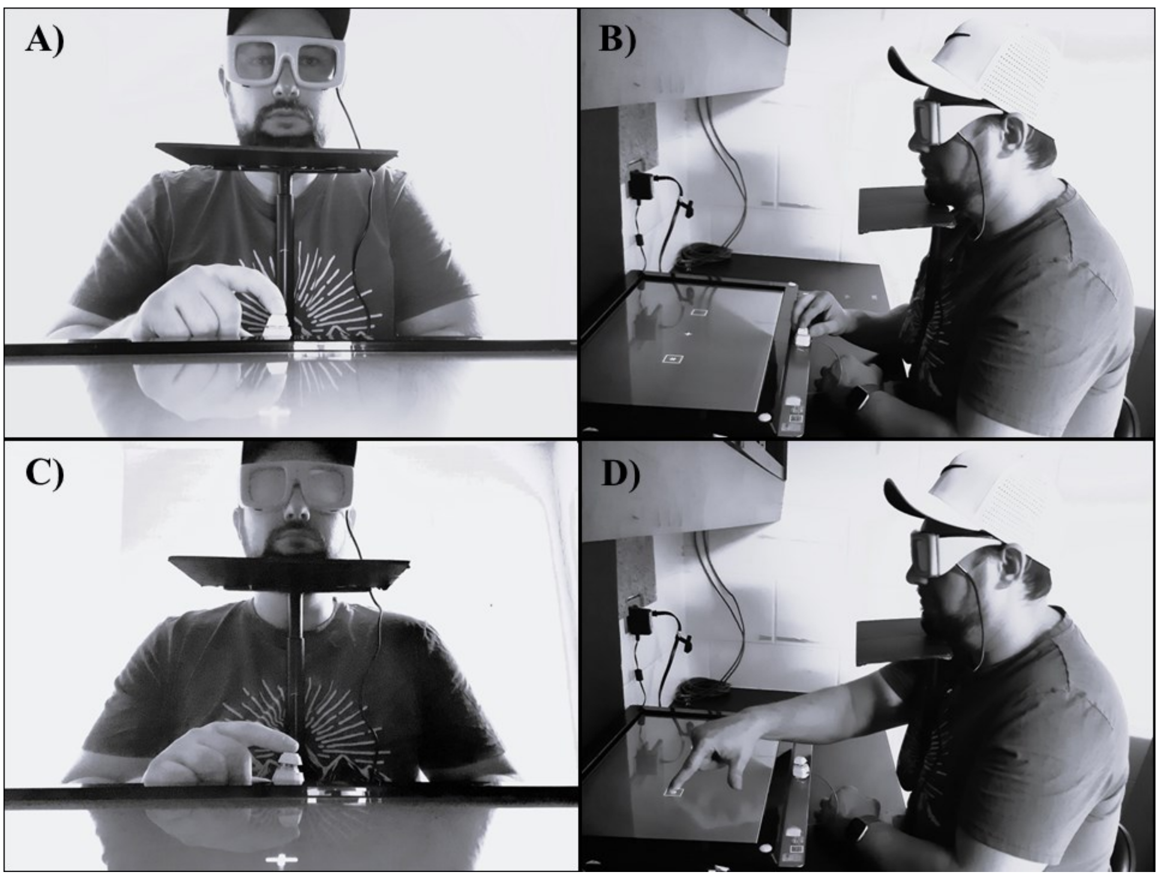


Figure 3.1 Experimental setup for the speeded reach task. To start the trial, the participant pressed down the start key to open their goggles (A) and reveal a visual target in one of the two boxes (B). After 150 ms, the goggles changed to their occluded state (C), and the participant reached under full visual occlusion to touch where the target was (D). The person depicted is a lab member who provided permission to use this photograph in the present thesis.

To initiate each trial, participants were asked to stare at a central fixation cross and press down the start key with their right index finger, which caused the PLATO goggles to open and reveal two empty boxes (2.5 cm x 2.5 cm) ~12 visual degrees to the left and right of central fixation. After a 1500-3000 ms delay, an asterisk-shaped target appeared in the centre of one of the two boxes for 150 ms, after which the goggles immediately (i.e., within 3-4 ms) changed to their occluded state. This short target presentation time was used to discourage eye movements from central fixation. Target onset was accompanied by an auditory cue. Participants were instructed to release the start key immediately after seeing the target and reach as quickly and accurately as they could to touch the target's location on the screen under full visual occlusion, while maintaining central fixation. There was a second auditory cue indicating their screen touch, and a 500 ms delay before they could again press the start key to re-open the goggles and initiate the next trial.

Participants completed six test blocks of the speeded reach task, with two blocks at each start position in a pseudorandomized order, such that the first three blocks and last three blocks had one block at each start position. Each block contained 20 reaching trials, with 10 left targets and 10 right targets (trial order randomized). Prior to completing the baseline (pre-PA) speeded reach task, participants completed 10 practice reaching trials (5 left target, 5 right target; randomized order) with no visual occlusion, and 20 practice reaching trials (10 left target, 10 right target; randomized order) with occluded reaching described above, but upon screen touch the goggles turned clear for 500 ms to provide visual feedback about their pointing accuracy. They also received binary (correct/incorrect) auditory feedback based on whether their endpoint was inside or outside the target's 2.5 cm x 2.5 cm box. These 30 practice trials were completed at each start position (block 1: centre start; block 2/3: left or right start, order counterbalanced across participants), amounting to 90 practice trials in total prior to starting the baseline speeded reach task. These practice trials were included for two main reasons: 1) to minimize reductions in *iRT* from pre- to post-PA due to practice alone, thus increasing our ability to detect our PA effects of interest; and 2) to allow participants to achieve near-zero error sizes on the baseline speeded reach task (Figure E1 in the Appendix E confirms that this was achieved), which ensured that pointing movements were of similar length and accuracy across participants.

3.2.3.3 Prism adaptation

Participants donned Fresnel prism glasses with a shift magnitude of ~17 visual degrees to the left or the right (30 diopters; Insight Optometry Group, Halifax, Canada). The targets were white lines 1.2 cm in width spanning the entire vertical distance of the screen, at four possible horizontal locations: ~6 or ~18 visual degrees to the left or right of centre. Unlike the speeded reach task, participants did not wear PLATO goggles and could see their reaching trajectory during PA (except for the hand's starting position, which was blocked by a small occlusion board). To initiate each trial, participants held down a spacebar, and after 400-600 ms, a target line appeared accompanied by an auditory cue. Participants were instructed to reach and touch the line as quickly and accurately as possible. The line disappeared 250 ms after screen touch, and participants could then return to the space bar to initiate the next trial. Every participant started with 40 practice reaching trials with clear glasses to measure baseline reaching. Then, the PA exposure took approximately 10-12 minutes and included 208 pointing trials, with an equal number of trials at each possible horizontal line location (trial order randomized).

3.2.3.4 Measure of prism aftereffects

Aftereffects were measured using a proprioceptive straight-ahead (PSA) pointing task, as done previously (Redding & Wallace, 1996; Striemer & Borza, 2017). Participants wore the PLATO goggles in their occluded state and were asked to hold down a space bar until they heard an auditory cue prompting them to release the space bar and touch where they considered to be the centre of the screen. The PSA task consisted of 10 reaching trials, all under full visual occlusion.

3.2.4 Procedure

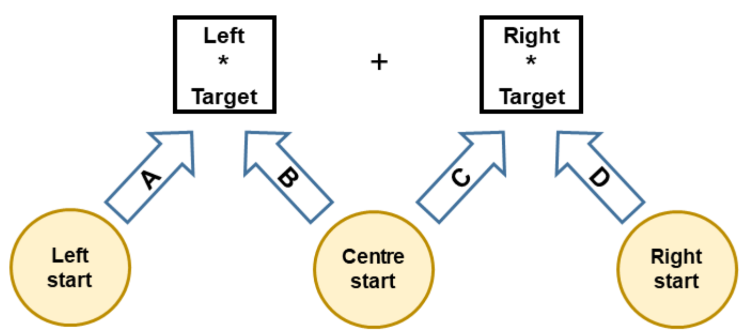
The single in-person study session took place on Dalhousie University campus in Halifax, Canada, from January to April, 2022. Prior to the in-person study session, participants were asked to sign the consent form and complete a health history form and EDI-SF on Research Electronic Data Capture (REDCap), a secure web-based software platform hosted at Nova Scotia Health (Harris et al., 2009, 2019). At the study session, a researcher reviewed informed consent with the participant to ensure that the participant understood the experiment requirements and had no questions. Following consent confirmation, participants donned the PLATO goggles and adjusted the chair and chin rest as needed. Next, participants completed the baseline speeded reach task. Participants then completed a baseline PSA task and baseline PA practice block, after which they donned their prism glasses and completed the PA exposure. Then, they donned the PLATO goggles again, and completed the post-PA PSA task and speeded reach task. One final PSA task was completed at the end of the experiment, to measure extent of de-adaptation. Once all study procedures were complete, participants received a debriefing form and compensation. The entire procedure took approximately 1-1.5 hours.

3.2.5 Statistical Analysis

Data were analyzed and visualized using R Studio Version 4.1.2. First, we tested for a replication of Striemer and Borza's (2017) effect of speeded *iRT* in the direction of the prism aftereffect, using the same statistical approach they had used. That is, we conducted a 2x2x2 mixed ANOVA of prism group (LPA, RPA), time (pre-PA, post-PA), and target side (left, right) predicting *iRT* on the speeded reach task for trials from the central start position only. Second, we examined the effect of PA on perceptual and premotor biases as measured by the speeded reach task. Figure 3.2 illustrates our calculation method for the perceptual and premotor Cohen's *d* effect sizes[7]. Specifically, we calculated a premotor bias for each participant and speeded reach task administration that represented the difference in *iRT* by reach direction, calculated separately for each of the left and right targets (thus holding the visual-perceptual input about target location constant). Having a *d* value near zero indicated that *iRT* did not vary by reach direction,

[7]Although Figure 3.2 displays perceptual and premotor biases separately, we do not intend this to suggest that these biases are mutually exclusive; rather, a PwN could display both biases to varying degrees.

suggesting a lack of premotor bias. By contrast, a larger *d* value indicated presence of a larger premotor bias, meaning that *iRT* depended on the direction that the participant was reaching in. A more positive premotor bias always indicated faster rightward reaches compared to leftward reaches, to a given target. We calculated perceptual biases with a similar method; that is, we calculated Cohen's *d* effect sizes for each participant and speeded reach task administration that represented the difference in *iRT* by target side, calculated separately for each of the leftward and rightward reach directions (thus holding the direction of the motor output constant). Note that only equidistant reaches were included in the calculations. After calculating these effect sizes for each participant for each speeded reach task administration, we conducted a 2x2x2 mixed ANOVA of prism group (LPA, RPA), time (pre-PA, post-PA), and target side (left, right) predicting the premotor bias effect size (*d*). The ANOVA predicting the perceptual bias effect size (*d*) was identical, except that reach direction (leftward, rightward) was included as a factor instead of target side (left, right). Significant effects ($p < .05$) were probed using pairwise *t*-test comparisons using a Bonferroni correction, as were differences in PSA error sizes between time points (baseline, post-PA, final). Data are visualized as means, with error bars representing standard error of the mean.



Perceptual neglect:

$$\frac{iRT_B - iRT_A}{SD_p} \cong 0; \frac{iRT_D - iRT_C}{SD_p} \cong 0$$

$$\frac{iRT_A - iRT_C}{SD_p} \neq 0; \frac{iRT_B - iRT_D}{SD_p} \neq 0$$

Premotor neglect:

$$\frac{iRT_B - iRT_A}{SD_p} \neq 0; \frac{iRT_D - iRT_C}{SD_p} \neq 0$$

$$\frac{iRT_A - iRT_C}{SD_p} \cong 0; \frac{iRT_B - iRT_D}{SD_p} \cong 0$$

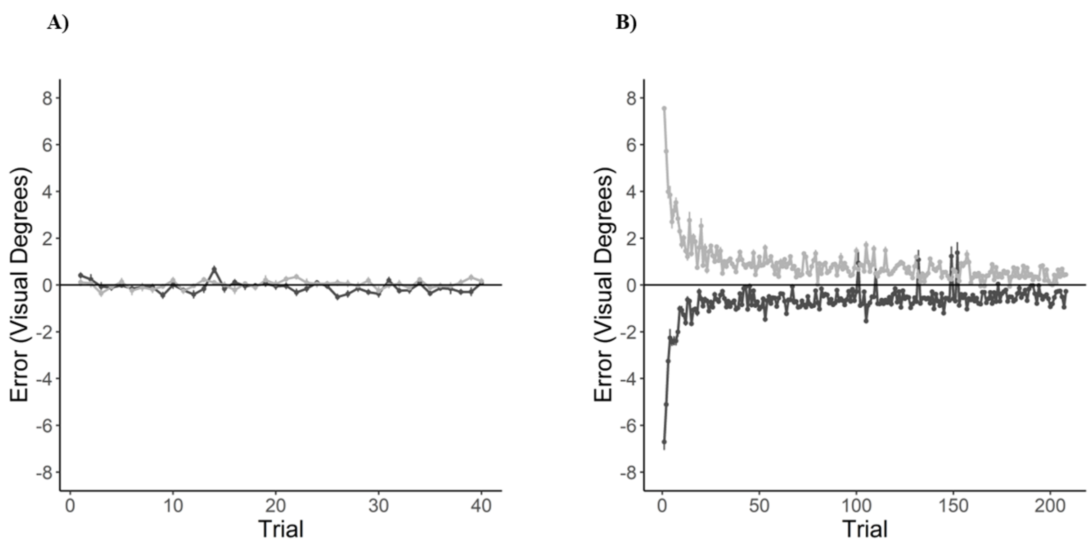
Figure 3.2 Calculation method for perceptual and premotor biases on speeded reach task. SD_p is the pooled standard deviation for the two variables in the numerator.

3.3 Results

3.3.1 Prism Adaptation Results

3.3.1.1 Direct effects during prism exposure

At baseline prior to prism exposure, pointing error size was close to zero for both the LPA group (mean = -0.10°, *SD* = 0.25°) and the RPA group (mean = 0.02°, *SD* = 0.25°; Figure 3.3a)[8]. During prism exposure, participants initially made reaching errors in the expected directions (i.e., leftward errors for LPA, rightward errors for RPA, Figure 3.3b). As expected, their error size decreased across the early stages of prism exposure, although the average absolute error size of the last 40 trials of prism exposure in both groups (LPA mean = -0.45°, *SD* = 0.53°; RPA mean = 0.41°, *SD* = 0.26°) remained significantly larger than the average error size of each group's 40 baseline trials (ps < .001).



[8] 1.1% of total baseline trials were removed due to behavioural artefacts.

Figure 3.3 Pointing error size in right-handers at baseline (A) and during prism exposure (B). LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

3.3.1.2 Aftereffects with goggle removal

Figure 3.4 displays error size (in visual degrees) on the PSA task by PA group and time point (baseline, post-PA, final)[9]. There was a main effect of PA group ($F_{1, 28}$ = 113.74, p < .001, η_p^2 =.68), qualified by a two-way interaction between PA group and time ($F_{2, 56}$ = 63.69, p < .001, η_p^2 =.52). Paired-samples *t*-tests with Bonferroni correction demonstrated that both the LPA and RPA group displayed aftereffects in the direction opposite to their prismatic shift that were significantly different from baseline both immediately after PA, and at the end of the study (*ps* ≤ .005). To determine whether the magnitude of aftereffects differed by PA group, we also examined the absolute value of baseline-corrected aftereffects by PA group and time point (post-PA, final). This analysis revealed a main effect of time ($F_{1, 28}$ = 29.19, p < .001, η_p^2 =.21), whereby aftereffects decreased in magnitude from post-PA to the end of the experiment. However, there was no main effect of PA group or interaction between PA group and time (*ps* ≥ .13).

[9]0.2% of total PSA data were removed due to behavioural artefacts.

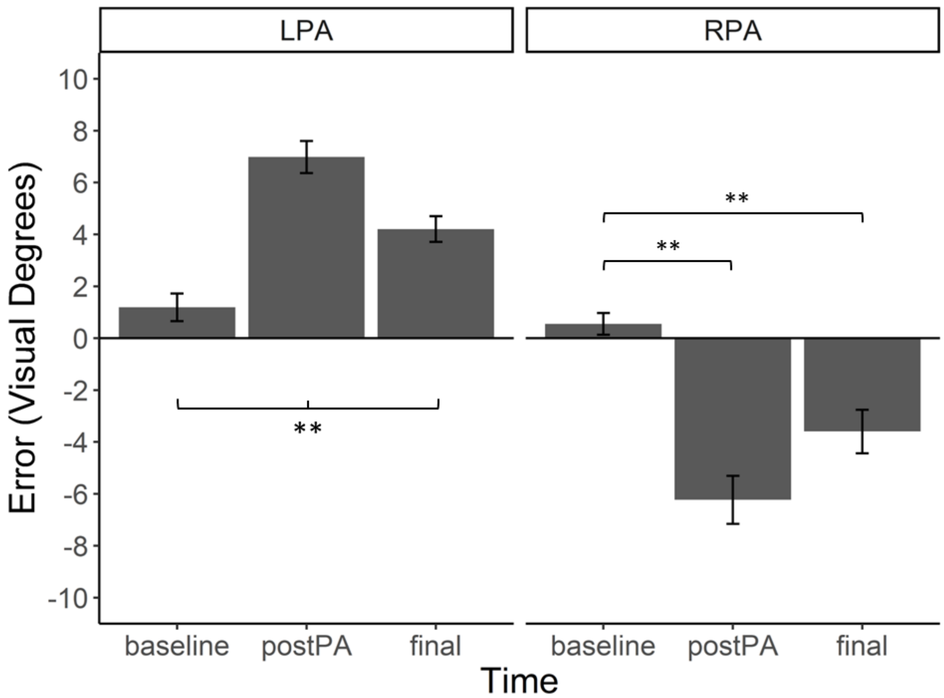


Figure 3.4 Proprioceptive straight-ahead (PSA) pointing error size in right-handers by PA group and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. ** $p < .01$ on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean.

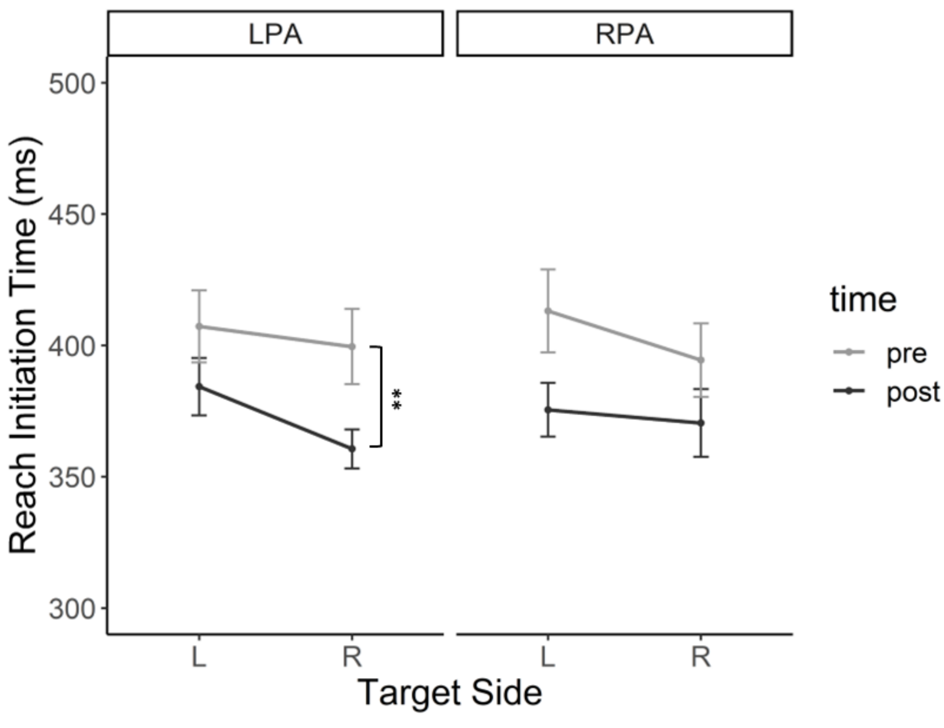
3.3.2 Speeded Reach Task Results

3.3.2.1 Data exclusions

Seventy individual trials were removed from the analysis due to a programming error (1.0 % of total speeded reach task data, missing completely at random, across 25 different participants). In terms of outliers, raw data were visually inspected for *iRT* and *MT*, and values greater than 5000 ms were manually removed ($n = 8$ trials). Then, outliers greater than 3 *SD* from a participant's mean *iRT* or *MT* were removed (180 trials, 2.5% of total speeded reach task data, across 29 different participants).

3.3.2.2 Replicating Striemer and Borza (2017)

Figure 3.5 displays *iRT* on the speeded reach task from the centre start position by PA group, target side, and time (for *iRT* means and *SD*'s for the left and right start positions, see Table E1 in Appendix E). There were main effects of time ($F_{1, 28} = 25.02$, $p < .001$, $\eta_p^2 = .47$), and target side ($F_{1, 28} = 16.69$, $p < .001$, $\eta_p^2 = .37$), which were both qualified by a three-way interaction between PA group, target side, and time ($F_{1, 28} = 6.97$, $p = .013$, $\eta_p^2 = .20$). We probed this three-way interaction by running a 2 (target side) x 2 (time) within-subjects ANOVA for each PA group separately. For the LPA group, there were main effects of time ($F_{1, 14} = 14.06$, $p = .002$, $\eta_p^2 = .50$) and target side ($F_{1, 14} = 13.86$, $p = .002$, $\eta_p^2 = .50$), qualified by an interaction between time and target side ($F_{1, 14} = 5.75$, $p = .031$, $\eta_p^2 = .29$), whereby *iRT* was faster after LPA for the right target ($p = .004$), but not significantly faster for the left target. For the RPA group, there were also main effects of time ($F_{1, 14} = 11.25$, $p = .005$, $\eta_p^2 = .45$) and target side ($F_{1, 14} = 5.08$, $p = .041$, $\eta_p^2 = .27$), but the two-way interaction was not statistically significant ($p = .15$).[10] No other effects were significant in the omnibus ANOVA (ps > .5).



[10]Given the RPA group's *iRT* pattern seen in Figure 3.5, we conducted exploratory pre-post pairwise comparisons for the RPA group, which showed that *iRT* was faster after RPA for the left target ($p = .002$), but not significantly faster for the right target. However, since the time-by-target side interaction for the RPA group was not statistically significant, we do not consider this pairwise comparison result to be a robust finding and thus it is not reflected in Figure 3.5.

Figure 3.5 Reach initiation time from centre start in right-handers by PA group, target side, and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. ** $p < .01$ on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean. Note that the time-by-target side interaction was not statistically significant for the RPA group.

3.3.2.3 Premotor biases pre-post PA

Figure 3.6 displays premotor biases (i.e., Cohen's *d* of effect of reach direction, calculated separately for each target) by PA group, target side, and time. There was a significant interaction between PA group and time ($F_{1,28} = 6.01$, $p = .02$, $\eta_p^2 = .18$). The LPA participants had a more positive premotor bias after PA compared to baseline (Cohen's *d* increase of 0.52 on average), indicating that they became faster to reach rightward than leftward, regardless of whether they were reaching to the left or right target ($p = .0075$). By contrast, the premotor bias of RPA participants did not differ from pre- to post-PA ($p > .5$). No other effects were significant in the omnibus ANOVA (ps $\geq .1$).

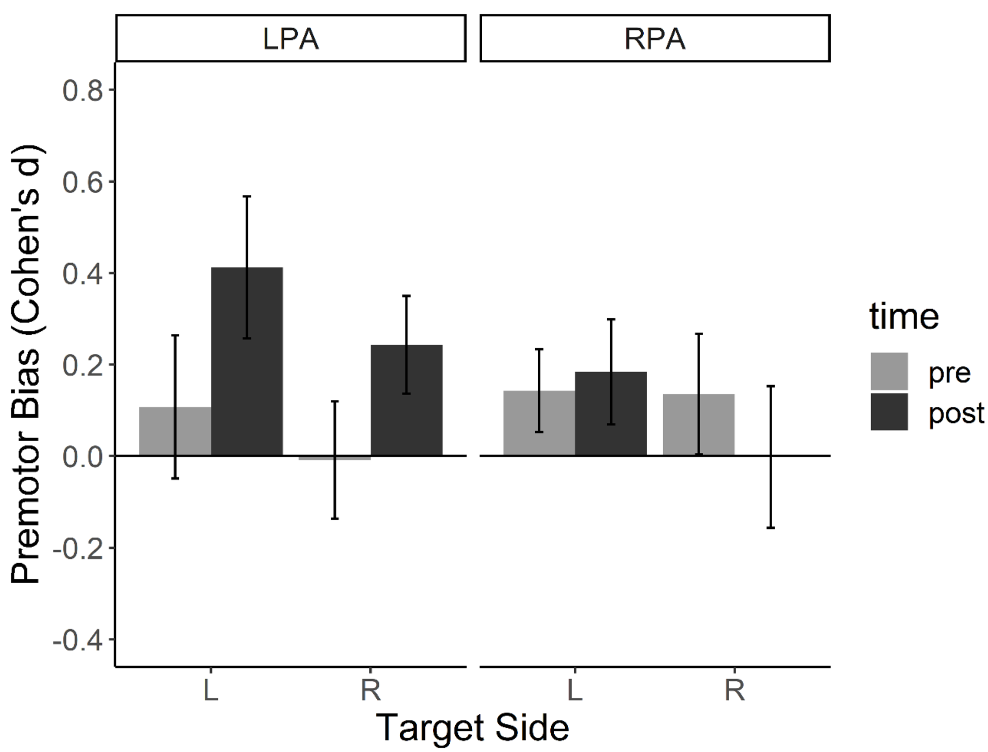


Figure 3.6 Premotor bias (Cohen's *d*) on speeded reach task in right-handers by PA group, target side, and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. A more positive premotor bias (Cohen's *d*) indicates being faster to initiate reaches in the rightward direction than the leftward direction to a given target. Error bars represent standard error of the mean.

3.3.2.4 Perceptual biases pre-post PA

When we analyzed perceptual biases (i.e., Cohen's *d* of effect of target side, for each reach direction) by PA group, reach direction, and time, there were no significant main effects or interactions (*p*s $\geq .2$; see Figure E2 in the Appendix E for a depiction of these data).

3.4 DISCUSSION

Prism adaptation is a potential treatment for spatial neglect, and its variable effectiveness in clinical trials has sparked interest in clarifying the mechanisms underlying its therapeutic effects. Past research has suggested that PA may have a greater impact on symptoms of premotor neglect than perceptual neglect (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020). In line with the large body of literature that has used PA to induce temporary spatial biases (Michel, 2016), the present study investigated whether PA could induce a premotor bias in healthy adults. Such a finding would suggest that PA modulates premotor processing, further substantiating the previously reported link between PA's therapeutic benefits and premotor neglect symptoms. We measured perceptual and premotor biases with a speeded reach task used previously to separate perceptual and premotor biases in PwN (Husain et al., 2000; Mattingley et al., 1998; Rengachary et al., 2011; Sapir et al., 2007). In a replication and extension of Striemer and Borza (2017), healthy adult participants completed the speeded reach task before and after either LPA ($n = 15$) or RPA ($n = 15$). Based on Striemer and Borza (2017), we hypothesized that PA would speed *iRT* when reaching in the direction of the prism aftereffect from the central start position. However, we predicted that this effect would be explained by a directional shift in the premotor bias measured by the speeded reach task, with no shift in the perceptual bias. Finally, we expected this premotor bias shift to be greater for the LPA group than the RPA group. Our results generally supported these hypotheses and are discussed below in relation to past research on PA mechanisms and perceptual/premotor processing.

3.4.1 Successful Replication of Striemer and Borza (2017)

As in Striemer and Borza (2017), our participants were faster to initiate reaches to the right target after LPA and, to a lesser extent, faster to initiate reaches to the left target after RPA (see Figure 3.5). Our effect size for this three-way interaction was somewhat smaller ($\eta_p^2 = .20$ versus $\eta_p^2 = .31$) than Striemer and Borza (2017), possibly because we had fewer reaching trials per target to accommodate our addition of two more hand start positions. Nevertheless, the stronger effect of LPA than RPA is consistent with Striemer and Borza (2017) and past research on spatial attention tasks in normative populations (Clarke et al., 2022; Michel, 2016). In addition, we replicated Striemer and Borza's (2017) main effects of time (faster *iRT* post-PA), and target side (faster *iRT* to the right target). The main effect of time was likely a practice effect, whereas the main effect of target side was likely a result of stimulus-response compatibility (i.e., Simon effect, Seibold et al., 2016), given that both studies had right-handed participants who used their right hand for the reaching task.

3.4.2 Inducing Premotor Bias on the Speeded Reach Task

Our next step was to extend Striemer and Borza's (2017) work by examining the effect of PA on perceptual and premotor biases as measured by the speeded reach task (see Figure 3.2 for calculation method). As expected, participants displayed a more positive premotor bias after LPA, meaning that they became faster to initiate reaches in the rightward direction, irrespective of the target location. This finding builds on past research suggesting a link between PA's effects and motor output processes in healthy adults (Bracco et al., 2018; Fortis, Goedert, et al., 2011; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Borza, 2017), and in persons with spatial neglect (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a).

Also as predicted, neither PA shift direction influenced perceptual biases on the speeded reach task, suggesting that our PA effect was stronger at the premotor stage of information processing. This finding seems inconsistent with other research showing that PA can modulate performance on tasks measuring perceptual and/or attentional processes, such as covert attention (Striemer et al., 2006), visual search (Saevarsson et al., 2009), local versus global processing biases (Bultitude et al., 2009; Bultitude & Woods, 2010), and perceptual judgments of pre-transected horizontal lines (i.e., Landmark task; Colent et al., 2000; Nijboer et al., 2010; Schintu et al., 2014). Furthermore, Gammeri et al. (2023) recently demonstrated that PA therapy in PwN was associated with reductions in perceptual biases on a landmark task, whereas visual scanning training was associated with reductions in response biases. Importantly, the speeded reach task differs from all these tasks in that it requires a speeded, lateralized reaching movement. This emphasis on reaching may make the speeded reach task less sensitive to shifts in perceptual biases following PA, and instead more suited to identifying premotor biases, as it has been used previously in PwN (Sapir et al., 2007). Indeed, it may not be feasible for any individual task to measure 'pure' perceptual and premotor biases because these cognitive processes are highly interdependent, particularly in healthy adults (discussed in McIntosh et al., 2004 and Striemer & Danckert 2010a), who were the focus of the present study. Furthermore, neurocognitive mechanisms of PA are known to differ between healthy adults and PwN (Boukrina & Chen, 2021), which could influence the relationship between PA effects and perceptual and premotor processing in these different populations. In summary, while our results provide evidence for a link between PA effects and premotor processing, more research is needed to determine how this link may vary by task and population.

The lack of observed shift in perceptual or premotor biases after RPA is consistent with previous findings of greater cognitive effects of LPA than RPA in healthy individuals (Clarke et al., 2022; Michel, 2016). Michel (2016) noted that PA is more likely to modulate performance on cognitive tasks in which individuals display a baseline spatial bias. For example, healthy adults show a slight but systematic leftward spatial bias on line bisection and landmark tasks (Jewell & McCourt, 2000), which may modulate LPA's ability to shift this bias rightward (Schintu et al., 2017). We considered whether baseline biases on the speeded reach task could explain PA's effects on the premotor bias observed here. There was a trend for a more positive premotor bias on the speeded reach task at baseline (see grey bars in Figure 3.6), although this bias was not significantly different from zero (one-sample *t*-test, $p = .2$). Premotor biases also did not significantly differ between PA groups at baseline (independent samples *t*-test, $p > .5$). These non-significant effects suggest that baseline differences were likely not a primary cause for the differing effects of LPA and RPA on premotor biases in our reaching task.

One important factor to consider when interpreting our results is our chosen PA method. To be consistent with Striemer and Borza (2017), we used concurrent exposure (i.e., view of reaching arm occluded for first ~1/3 of movement), and aftereffects were measured using a PSA pointing task. According to the directionality-of-guidance hypothesis, concurrent exposure is thought to promote proprioceptive aftereffects because the hand's felt position must adapt to the displaced visual gaze position; by contrast, terminal exposure (i.e., view of reaching arm occluded until last few cm of movement) is thought to promote visual aftereffects because the eye gaze position must adapt to the proprioceptively determined hand position (Redding et al., 1985; Redding & Wallace, 2001). It is possible that the proprioceptive shift facilitated by concurrent exposure contributed to the selective shift in premotor bias in our study (for a demonstration of such an effect using a different neglect subtyping approach, see Herlihey et al., 2012). It remains a question for future research as to whether we would still see a shift in premotor biases with terminal exposure, which would be more likely to promote visual aftereffects.

3.4.3 Potential Neural Mechanisms

We now shift our discussion to the putative underlying neural mechanisms for our behavioural results. One proposed explanation for PA's effect on premotor biases is that PA modulates activity in the dorsal visual stream, which gives rise to visuomotor behaviours (Clower et al., 1996; Milner & Goodale, 2006; Saj et al., 2013; Striemer & Danckert, 2010b; Tsujimoto et al., 2019). Other studies have identified the primary motor cortex (M1) as a key node in PA's mechanism (Bracco et al., 2018; Panico, Fleury, et al., 2020). For instance, Magnani et al. (2014) demonstrated that PA increases M1 excitability in the hemisphere contralateral to the side of the PA aftereffect. The hyperexcitable M1 may then create a local ‘field effect’ in that hemisphere and activate dorsal frontal-parietal areas that subserve planning of reaches toward the side of the aftereffect (discussed in Striemer & Borza, 2017). Alternatively, Clarke and Crottaz-Herbette (2016) proposed that PA may not directly modulate dorsal activity, but rather it modulates space representation in the ventral attention network (VAN), which could then have downstream effects on spatial attention and visuomotor behaviour subserved by the dorsal attention network (DAN; see Corbetta & Shulman, 2011 for a discussion of the VAN and DAN in relation to spatial neglect).

These proposed neural mechanisms of PA overlap with the potential neural correlates of speeded reach task performance. Initial research in PwN linked perceptual deficits on the speeded reach task to right inferior frontal gyrus (IFG) lesions ($n = 3$), and premotor deficits to right inferior parietal lobe (IPL) lesions ($n = 3$; Husain et al., 2000; Mattingley et al., 1998). Of note, the IPL is a key region in the VAN whose activity is modulated by PA (Clarke & Crottaz-Herbette, 2016; Crottaz-Herbette et al., 2017). A subsequent study with a larger sample of PwN ($n = 29$) linked premotor deficits on the speeded reach task to lesions in the right ventral lateral putamen, the claustrum, and precentral and inferior frontal white matter (Sapir et al., 2007). The authors noted that right basal ganglia lesions can cause right-lateralized hypoperfusion in nodes of the fronto-parietal attention network (e.g., IFG, IPL, superior temporal gyrus, STG), which overlaps with the DAN (Karnath et al., 2005; as cited in Sapir et al., 2007). Furthermore, Sapir et al.’s (2007) reported link between premotor deficits on the speeded reach task and subcortical lesions resembles the reported link between response biases on the Bisiach landmark task and basal ganglia lesions (Bisiach, Ricci, Lualdi, et al., 1998; Vossel et al., 2010). Exploring the neural correlates of perceptual and premotor biases across different subtyping tasks and populations is beyond the scope of this study, but could be investigated in future imaging research.

3.4.4 Limitations

One limitation of our study was that all participants were right-handed and used their right hand to complete the speeded reach task. This right hand use potentially explains why participants were faster overall to initiate reaches to the right target, due to stimulus-response compatibility (Seibold et al., 2016). It is unclear whether this pre-existing right-sided reaching bias had a differential influence on LPA and RPA's effects. Chapter 3A describes the same experiment conducted in a sample of left-handed participants to test whether our results differ by handedness/hand use. Next, we note some limitations in our study's clinical application. First, our use of visual occlusion during the speeded reach task differs from past studies where individuals had full view of their reaching arm during the task (Husain et al., 2000; Mattingley et al., 1998; Rengachary et al., 2011; Sapir et al., 2007). Persons with neglect tend to show greater deficits in memory-guided reaching tasks than visually guided reaching tasks (Ogourtsova et al., 2015). However, blindfolding PwN may also reduce spatial biases in posture and head position (Chen et al., 2021). The influence of our specific visual occlusion procedure on the performance of PwN remains unknown. Another clinically relevant limitation of the speeded reach task is the potential for the hand's position to influence performance by acting as an attentional cue. For example, a PwN may have a faster *iRT* from the leftmost start position not because they are better at reaching rightward, but instead because sensory input from the ipsilesional hand cues their attention to the contralesional space (Harvey, 2004). Husain et al. (2000) investigated this possibility by including a condition where PwN pressed a button to detect the targets instead of reaching, and they did not find an effect of hand position. However, as Harvey (2004) pointed out, this approach assumes that cueing for detection is the same process as cueing for action. Future research could use event-related potentials (ERPs) to examine how hand position affects the latency of different cognitive events leading up to reach initiation (Luck, 2014). Another future direction would be to correlate perceptual/premotor biases on the speeded reach task with those measured by the Landmark task, a neglect subtyping task that holds sensory input constant across response conditions (Bisiach, Ricci, Lualdi, et al., 1998; Bisiach et al., 1999; Harvey & Milner, 1995). Finally, since the speeded reach task involves reaching movements in peri-personal space during central fixation, it does not measure other motor-exploratory behaviours (e.g., eye movements, ambulation) that are also important to consider in neglect recovery and rehabilitation (e.g., Angeli et al., 2004; Goedert et al., 2012).

3.4.5 Conclusions and Significance

Our study investigated whether PA could induce a premotor reaching bias in healthy adults on a speeded reach task that has been used previously to separate perceptual and premotor neglect symptoms (Husain et al., 2000; Mattingley et al., 1998; Rengachary et al., 2011; Sapir et al., 2007). Here, we demonstrate that LPA induces a rightward premotor reaching bias in healthy adults that resembles the premotor biases seen in some persons with left-sided spatial neglect. Our results build upon those of Striemer and Borza (2017), as well as past evidence that one component of visuomotor learning during PA targets Output processing (Bracco et al., 2018; Panico et al., 2020; Striemer & Borza, 2017). With respect to clinical implications, the present study could be used as a normative benchmark for examining how PA impacts speeded reach task performance in a sample of PwN, where we would expect perceptual and/or premotor biases at baseline and larger shifts in premotor biases after RPA than LPA. More broadly, this line of research can inform future clinical studies seeking to improve PA procedures and selection of PwN for PA therapy.

CHAPTER 3A DOES PRISM ADAPTATION INDUCE A PREMOTOR BIAS IN LEFT-HANDERS?

This chapter consists of a manuscript in preparation. The authors of this work include Jasmine R. Aziz and Gail A. Eskes. My contributions to this project include: conceptualization, experimental program development, project management, data collection and analysis, interpretation, and write-up.

3A.1 INTRODUCTION

Prism adaptation (PA) is a potential treatment for spatial neglect, but therapeutic benefits vary across individuals, possibly due to differences in Input-Output neglect subtypes (Barrett et al., 2012). Specifically, some research has identified a link between PA effects and premotor (Output) neglect symptoms (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a), though this relationship is not always seen (e.g., Gammeri et al., 2023). One method of exploring the potential link between premotor neglect and PA effects is to test whether PA can induce 'neglect-like' premotor biases in healthy adults, as this finding would suggest that PA modulates the premotor stage of processing. Chapter 3 reported a study wherein healthy adults completed a speeded reach task measuring perceptual and premotor biases before and after either left-shifting or right-shifting PA. As hypothesized, LPA induced a premotor bias in the direction of the prism aftereffect, whereas neither prism shift direction impacted perceptual biases. One limitation in this study was that all participants were right-handed and used their right hand to complete the study tasks. Thus, directional effects of PA could not be distinguished from directional effects of left versus right hand use, such as differences in arm posture (i.e., crossed vs. uncrossed), or in the need for interhemispheric transfer of visual target information to the hemisphere controlling the motor effector (Anzola et al., 1977; Berlucchi et al., 1971; Brooks et al., 2005; Shore et al., 2002). These factors are especially relevant for the speeded reach task, which focuses on reaction time and varies the hand's starting position across egocentric space.

The present study repeated the experiment in Chapter 3 by investigating whether left-handed participants would show the same LPA-induced premotor bias as right-handed participants. We chose to recruit left-handed participants rather than ask right-handed participants to use their left hand because we wished to avoid confounds of directly comparing dominant and non-dominant hand performance. For instance, reaching behaviour with the dominant and non-dominant hand may differ in terms of stimulus-response compatibility effects (Rubichi & Nicoletti, 2006; Seibold et al., 2016), reach dynamics (Sainburg, 2002; Schabowsky et al., 2007), and spatial biases on open-loop pointing tasks (Daini et al., 2018). Studying the performance of left-handers allows us to examine the effect of hand use while minimizing these confounds. Furthermore, when using the dominant hand, direct effects and aftereffects of PA are comparable between right- and left-handers, suggesting similar adaptation processes in both groups (Redding & Wallace, 2011). Finally, recruiting left-handed participants allows us to determine whether our Chapter 3 findings generalize to this minority population, which has implications for the inclusion of left-handed individuals in studies of PA and spatial neglect.

3A.2 METHOD

The method for this study was the same as the method described for Chapter 3 (see Section 3.2), except that left-handed participants were recruited instead of right-handed participants, and participants used their left hand for all study tasks. Thus, we recruited 24 adult participants who were left-handed by self-report. Participants also completed the Edinburgh Handedness Inventory – Short Form (EHI-SF; Veale, 2014). One participant identified as ambidextrous and had a laterality quotient of zero; we ran the analyses below with this participant removed and got the same results, so we decided to keep this individual in the sample. All participants completed the speeded reach task before and after either left-shifting (LPA; $n = 12$) or right-shifting (RPA; $n = 12$) PA. Table 3A.1 displays the sample demographics, which did not differ between prism shift direction groups (ps $\geq .3$).

Table 3A.1 Sample demographics of left-handers by prism shift direction group.

Variable	LPA Group	RPA Group	Overall
Sample size	12	12	24
Mean age in years (*SD*)	37.42 (17.53)	30.67 (16.86)	34.04 (17.17)
Mean education in years (*SD*)	15.83 (2.29)	15.00 (2.98)	15.42 (2.64)
Gender (women:men:non-binary)	7:5:0	10:2:0	17:7:0
Mean EHI-SF laterality quotient (*SD*)	-59.38 (27.76)	-70.83 (32.13)	-65.10 (29.94)

Note. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation; EHI-SF = Edinburgh Handedness Inventory – Short Form (Veale, 2014).

3A.3 RESULTS

3A.3.1 Prism Adaptation Results

3A.3.1.1 Direct effects during prism exposure

At baseline prior to prism exposure, pointing error size was close to zero for both the LPA group (mean = -0.19°, *SD* = 0.26°) and the RPA group (mean = -0.19°, *SD* = 0.25°; Figure 3A.1a)[11]. During prism exposure, participants initially made reaching errors in the expected directions (i.e., leftward errors for LPA, rightward errors for RPA, Figure 3A.1b). As expected, their error size decreased across the early stages of prism exposure, although the average error size of the last 40 trials of prism exposure in both PA groups (LPA mean = -0.49°, *SD* = 0.21°; RPA mean = 0.60°, *SD* = 1.50°) remained significantly larger than the average error size of each group's 40 baseline trials (*p*s < .001).

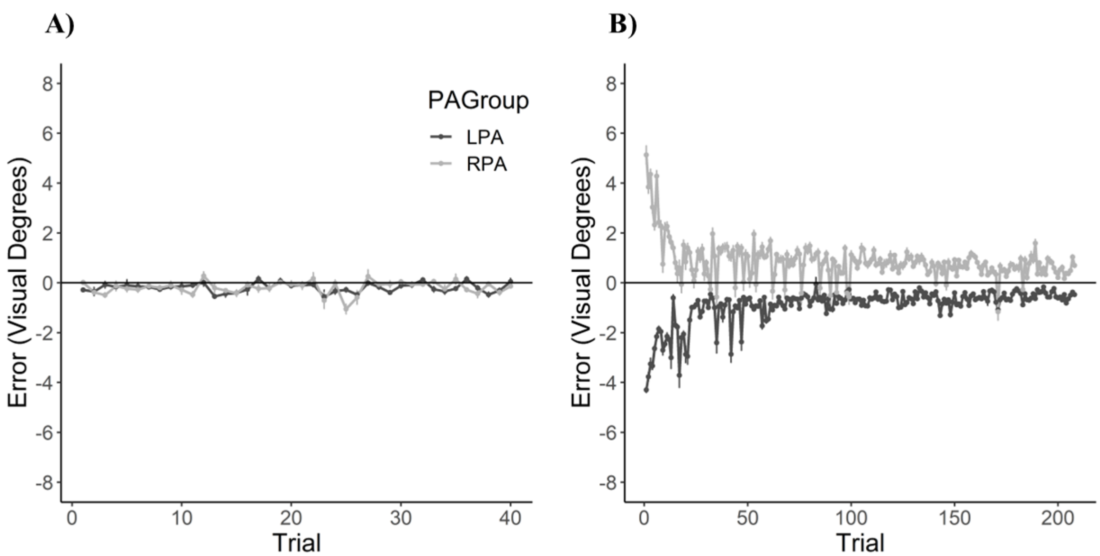


Figure 3A.1 Pointing error size in left-handers at baseline (A) and during prism exposure (B). LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

[11] 0.4% of total baseline trials were removed due to behavioural artefacts.

3A.3.1.2 Aftereffects with goggle removal

Figure 3A.2 displays error size (in visual degrees) on the PSA task by PA group and time point (baseline, post-PA, final). There was a main effect of PA group ($F_{1, 22}$ = 46.11, $p < .001$, η_p^2 =.54), qualified by a two-way interaction between PA group and time ($F_{2, 44}$ = 51.04, $p < .001$, η_p^2 =.50). Paired-samples *t*-tests with Bonferroni correction demonstrated that both the LPA and RPA groups displayed aftereffects in the direction opposite to their prismatic shift that were significantly different from baseline immediately after PA (*p*s ≤ .001). The LPA group's aftereffect was only marginally different from baseline at the end of the study (p = .060), whereas the RPA group's final aftereffect remained significantly different from baseline ($p < .001$, see Figure 3A.2). To determine whether the magnitude of aftereffects differed by PA group, we also examined the absolute value of baseline-corrected aftereffects by PA group and time point (post-PA, final). This analysis revealed a main effect of time ($F_{1, 22}$ = 15.72, $p < .001$, η_p^2 =.16), whereby aftereffects decreased in magnitude from post-PA to the end of the experiment. However, there was no main effect of PA group or interaction between PA group and time (*ps* ≥ .3). Appendix F contains a supplementary Figure F1 showing that pointing error size during the post-PA speeded reach task remained different from baseline, as in Chapter 3.

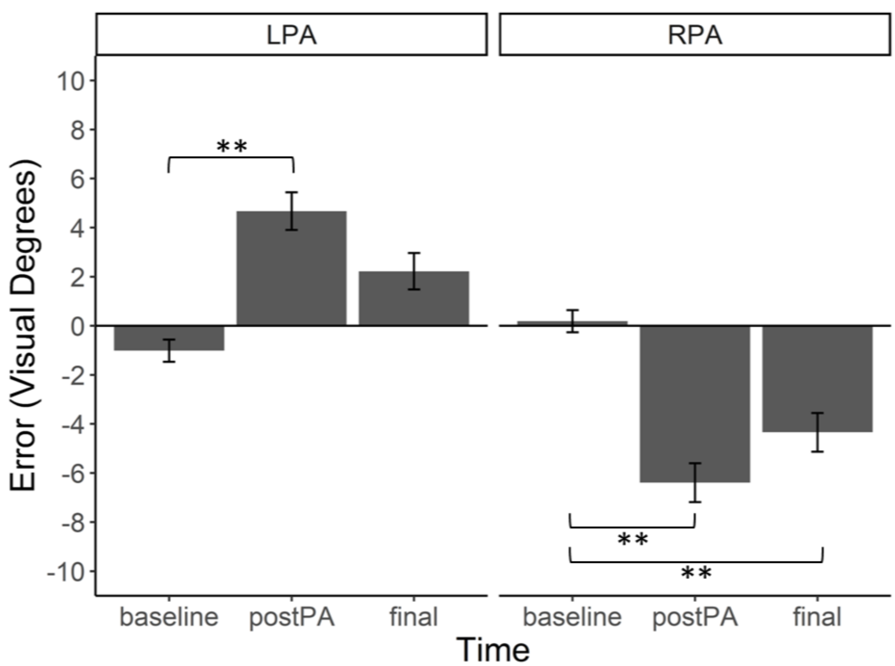


Figure 3A.2 Proprioceptive straight-ahead (PSA) pointing error size in left-handers by PA group and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. ** p < .01 on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean.

3A.3.2 Speeded Reach Task Results

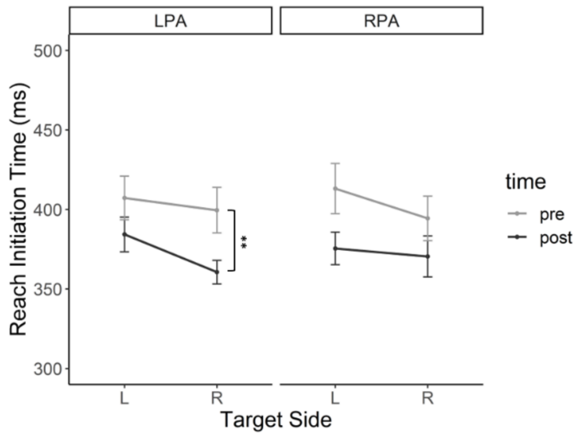
3A.3.2.1 Data exclusions

Forty-eight individual trials were removed from the analysis due to a programming error (0.8 % of total speeded reach task data, missing completely at random, across 19 different participants). In terms of outliers, raw data were visually inspected for *iRT* and *MT*, and values greater than 5000 ms were manually removed ($n = 4$ trials). Then, outliers greater than 3 *SD* from a participant's mean *iRT* or *MT* were removed (134 trials, 2.3% of total speeded reach task data, across 24 different participants). The percentage of outliers (2.3%) was comparable to the percentage of outliers in the right-handed sample (2.5%, reported in Section 3.3.2.1).

3A.3.2.2 Testing for Striemer and Borza (2017) replication

Figure 3A.3 displays *iRT* on the speeded reach task from the centre start position by PA group, target side, and time (for *iRT* means and *SD*'s for the left and right start positions, see Table F1 in Appendix F). There were main effects of time ($F_{1, 22} = 30.94$, $p < .001$, $\eta_p^2 = .58$), and target side ($F_{1, 22} = 41.20$, $p < .001$, $\eta_p^2 = .65$), whereby *iRT* was faster after PA than at baseline, and faster when reaching to the left target than the right target. No other main effects or interactions were significant (*p*s > .5).

Data from right-handed sample:
(Figure 3.5, Chapter 3)



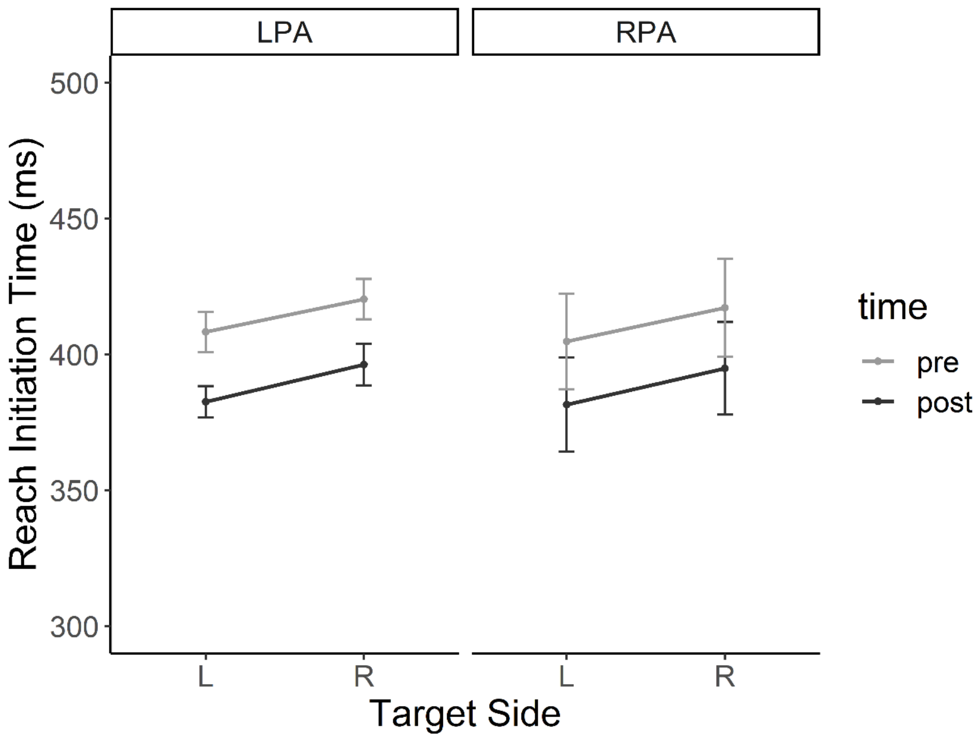
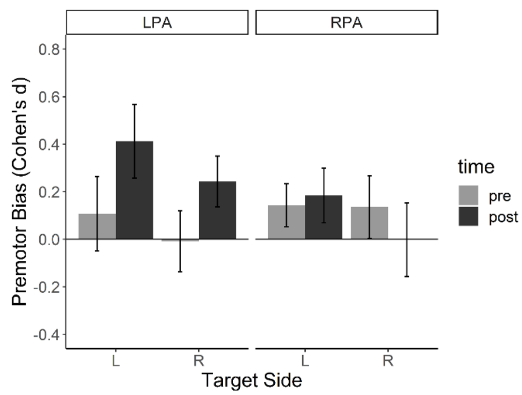


Figure 3A.3 Reach initiation time from centre start in left-handers by PA group, target side, and time (larger lower graph). For comparison purposes, data from the right-handed sample (Figure 3.5, Chapter 3) are shown in the smaller upper graph. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

3A.3.2.3 Premotor biases pre-post PA

Figure 3A.4 displays premotor biases (i.e., Cohen's *d* of effect of reach direction, calculated separately for each target) by PA group, target side, and time. There was a main effect of target side ($F_{1, 22} = 12.55$, $p = .002$, $\eta_p^2 = .36$), whereby participants in both PA groups had a more negative premotor bias for the right target than the left target; post-hoc one-sample *t*-tests confirmed that the mean premotor bias for the right target was significantly lower than zero (mean = -0.22, $SD = 0.27$, $p < .001$), whereas the mean premotor bias for the left target was not significantly different from zero (mean = 0.09, $SD = 0.39$, $p = .2$). No other main effects or interactions were significant (ps $\geq .2$).

Data from right-handed sample:
(Figure 3.6, Chapter 3)



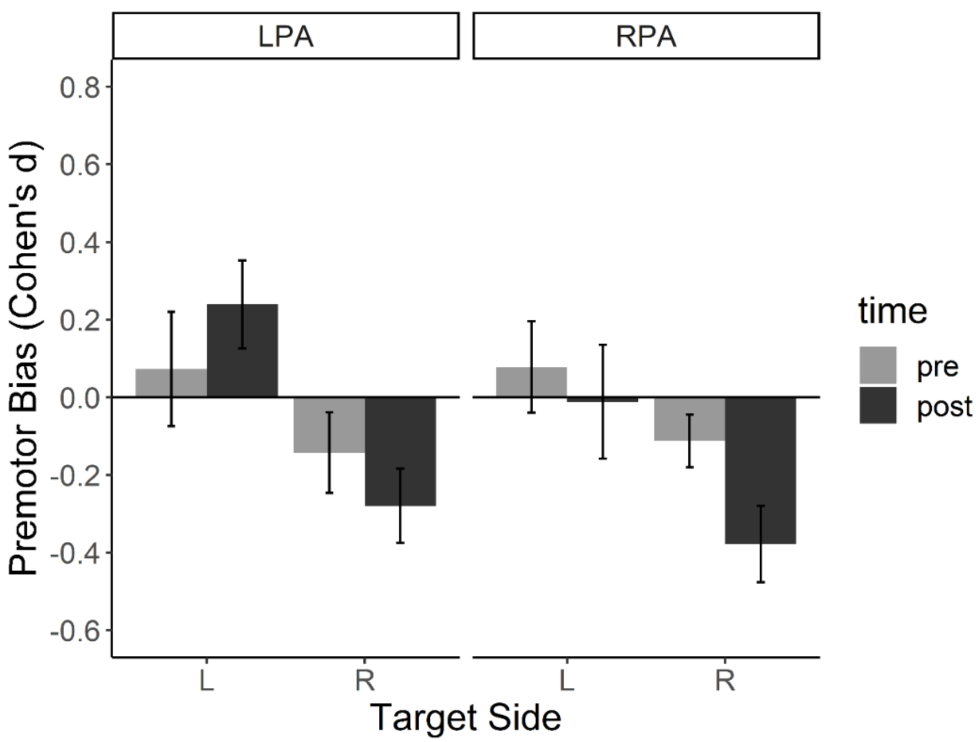
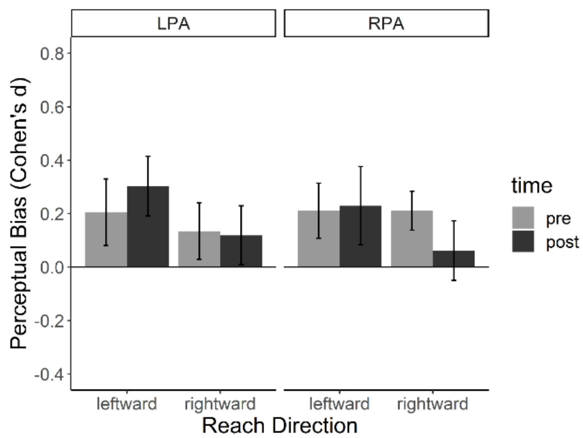


Figure 3A.4 Premotor bias on speeded reach task in left-handers by PA group, target side, and time (larger lower graph). For comparison purposes, data from the right-handed sample (Figure 3.6, Chapter 3) are shown in the smaller upper graph. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. A more negative premotor bias indicates being faster to initiate reaches in the leftward direction than the rightward direction to a given target. Error bars represent standard error of the mean.

3A.3.2.4 Perceptual biases pre-post PA

Data from right-handed sample:
(Figure E2, Appendix E)



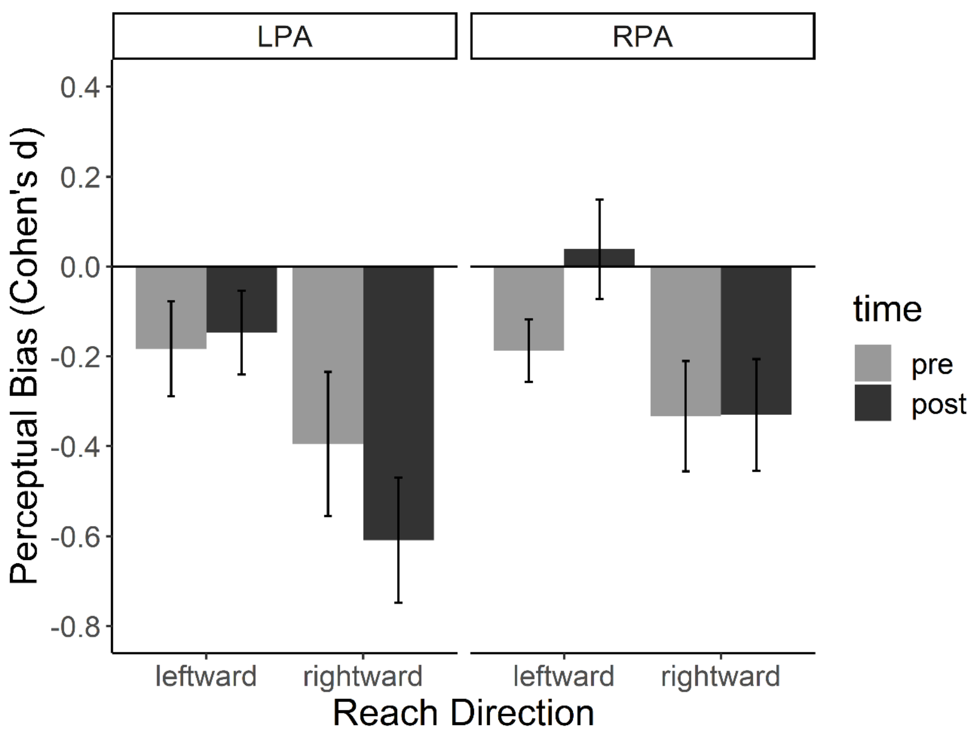


Figure 3A.5 Perceptual bias on speeded reach task in left-handers by PA group, target side, and time. For comparison purposes, data from the right-handed sample (Figure E2, Appendix E) are shown in the smaller upper graph. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. A more negative perceptual bias indicates being faster to initiate reaches to the left target than the right target for a given reach direction. Error bars represent standard error of the mean.

Figure 3A.5 displays perceptual biases (i.e., Cohen's *d* of effect of target side, for each reach direction) by PA group, reach direction, and time. There was a main effect of reach direction ($F_{1, 22} = 10.50$, $p = .004$, $\eta_p^2 = .32$), whereby participants had a more negative perceptual bias when reaching rightward than when reaching leftward; post-hoc one-sample *t*-tests confirmed that the mean perceptual bias for rightward reaches was significantly lower than zero (mean = -0.41, $SD = 0.42$, $p < .001$), whereas the mean perceptual bias for leftward reaches was only marginally lower than zero (mean = -0.11, $SD = 0.29$, $p = .054$). No other main effects or interactions were significant (*p*s ≥ .2).

3A.3.3 Exploratory Analyses Comparing Left- and Right-Handed Groups

The following exploratory analyses aimed to determine whether the left-handed sample (*N*=24) in the current chapter and the right-handed sample (*N*=30) from Chapter 3 showed similar prism direct effects, aftereffects, and effects of hand start position on the speeded reach task.

3A.3.3.1 Do left- and right-handed groups show similar direct effects?

To compare direct effects of PA across handedness groups, we conducted a between-subjects ANOVA of handedness group and PA group predicting average absolute error size across the first 10 trials of prism exposure. There were no significant main effects or interactions (ps ≥ .4), indicating similar direct effects across PA and handedness groups. To test whether these groups showed similar reductions in direct effects over the course of prism exposure, we also conducted a mixed ANOVA of handedness group, PA group, and time (i.e., average absolute error size across the 40 baseline reaching trials, versus average absolute error size during the last 40 trials of prism exposure). There was a main effect of time ($F_{1, 50}$ = 12.12, p = .001, η_p^2 =.20), whereby the average error size of the last 40 trials of prism exposure remained significantly different from baseline across all participant groups. No other main effects or interactions were significant (ps ≥ .3).

3A.3.3.2 Do left- and right-handed groups show similar aftereffects?

We also examined whether the magnitude of baseline-corrected prism aftereffects differed by handedness group. A mixed ANOVA of handedness group, PA group, and time resulted in a main effect of time ($F_{1, 50}$ = 42.99, p < .001, η_p^2 =.18), whereby aftereffects decreased in magnitude from post-PA to the end of the experiment. No other main effects or interactions were significant (*p*s ≥ .08), indicating similar aftereffect magnitudes across handedness groups.

3A.3.3.3 Do left- and right-handed groups show similar effects of hand start position on the speeded reach task?

While many statistical comparisons could be made between left- and right-handed groups, we were specifically interested in the effect of hand start position on *iRT*. There were two main reasons for this interest. First, start position effects have remained unexplored up to this point, since the Striemer and Borza (2017) replication analysis only includes the centre start position, and calculation of perceptual and premotor biases collapses across the different levels of start position. Second, the start position manipulation results in the greatest difference between handedness groups, as the hand's posture is mirrored; for example, for the left-handed group, the hand crosses the midline in the right start position, whereas for the right-handed group, the hand crosses the midline in the left start position. Thus, we conducted a mixed ANOVA of handedness group, target side, start position, PA group, and time predicting *iRT* on the speeded reach task. Although we will only report effects involving start position here, we included target side, PA group, and time in the analysis to statistically control for these other design factors, and to determine whether any of them interacted with start position effects (for a complete ANOVA table of this analysis, see Table F2 in Appendix F). In terms of start position effects, there was a main effect of start position ($F_{1, 100}$ = 12.97, p < .001, η_p^2 =.21), whereby participants were generally slower to initiate reaches from the centre start position than from left or right start position. However, this main effect was qualified by an interaction between start position and target side ($F_{2, 100} = 24.52$, $p < .001$, $\eta_p^2 = .33$), which was also qualified by a three-way interaction between start position, target side, and handedness group ($F_{2, 100} = 5.54$, $p = .005$, $\eta_p^2 = .10$). We probed this three-way interaction by running a 3 (start position) x 2 (target side) within-subjects ANOVA for each handedness group separately. For the left-handed group, there were main effects of start position ($F_{2, 46} = 11.06$, $p < .001$, $\eta_p^2 = .33$) and target side ($F_{1, 23} = 35.49$, $p < .001$, $\eta_p^2 = .61$), qualified by an interaction between start position and target side ($F_{2, 46} = 18.46$, $p < .001$, $\eta_p^2 = .45$), whereby *iRT* was faster to the left target than the right target at the centre and right start positions (*p*s < .001), but there was no difference in *iRT* by target side at the left start position ($p > .5$). For the right-handed group, there were also main effects of start position ($F_{2, 58} = 4.95$, $p = .01$, $\eta_p^2 = .15$) and target side ($F_{1, 29} = 18.64$, $p < .001$, $\eta_p^2 = .39$), qualified by an interaction between start position and target side ($F_{2, 58} = 16.02$, $p < .001$, $\eta_p^2 = .36$), whereby *iRT* was faster to the right target than the left target at the left and centre start positions (*p*s ≤ .002), but there was no difference in *iRT* by target side at the right start position ($p = .2$; see Figure 3A.6).

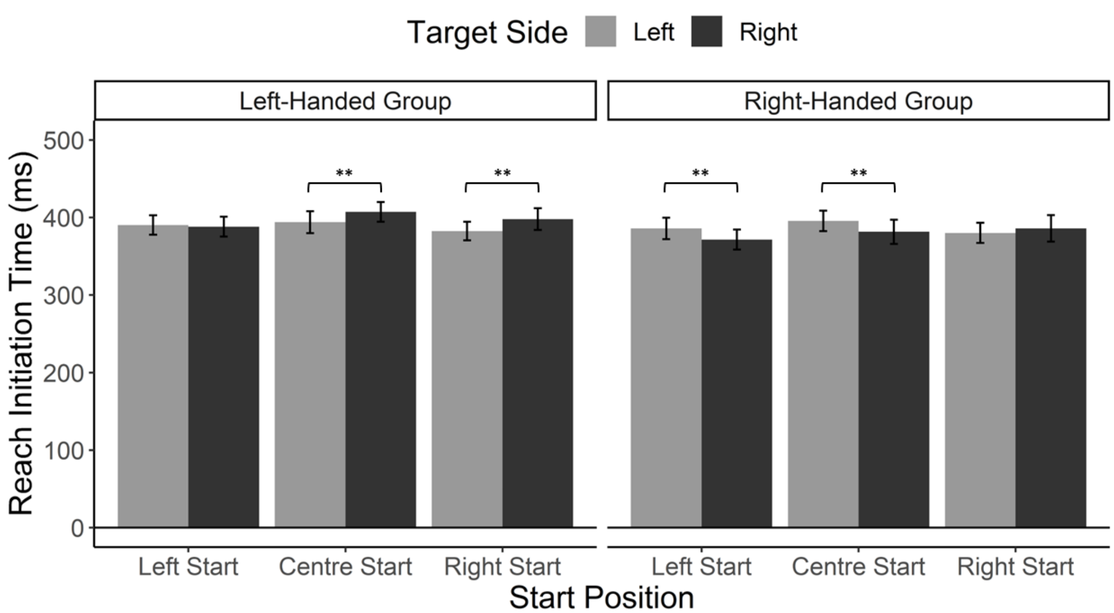


Figure 3A.6 Reach initiation time on the speeded reach task by handedness group, target side, and hand start position. ** $p < .01$ on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean.

3A.3.3.4 Do speeded reach task results correlate with age or EHI-SF laterality quotient in either handedness group?

Given the range of EHI-SF laterality quotients and ages of our left-handed sample, we explored whether these variables would predict the target side (premotor bias) and reach direction (perceptual bias) effects reported earlier in this chapter (see Sections 3A.3.2.3 and 3A.3.2.4). For each participant, we calculated difference scores for these two effects (i.e., $d_{\text{left target}} - d_{\text{right target}}$, $d_{\text{leftward reach}} - d_{\text{rightward reach}}$). A Pearson's correlation matrix of these two difference scores, laterality quotient, and age had no significant correlations ($ps \geq .2$).

A similar analysis was run in the right-handed sample, consisting of a correlation matrix of age, laterality quotient, and shift in premotor bias (d) from pre- to post-LPA (see Section 3.3.2.3). This matrix yielded no significant correlations ($ps \geq .3$).

3A.4 DISCUSSION

This study examined the effect of PA on perceptual and premotor biases in left-handed individuals. While LPA had induced a premotor bias in the direction of the prism aftereffect in right-handed participants (Chapter 3), the left-handed participants in the present study did not show any effect of PA on premotor biases. However, left-handed participants did show differences in premotor biases by target side and in perceptual biases by reach direction, neither of which were observed in right-handed participants. Here, we discuss potential reasons for differences between left- and right-handed participants, and end with limitations and implications for future work.

3A.4.1 No Prism Adaptation-Induced Premotor Bias in Left-Handers

Why did left-handed participants not show an LPA-induced positive shift in premotor bias? This null finding was not due to differences in PA behaviour, as the magnitude of prism direct effects and baseline-corrected aftereffects did not differ between left- and right-handed samples (see Sections 3A.3.3.1 and 3A.3.3.2), consistent with past research (Redding & Wallace, 2011). Rather, this null finding may have been related to the left-handed participants' significant differences in premotor biases by target side: Figure 3A.4 shows that their premotor biases were negative for the right target (i.e., faster to initiate leftward than rightward reaches). This pattern directly opposes expected reduction of rightward reach initiation time by LPA and thus may have diluted LPA's effects. The next question becomes: why did left-handed participants show an effect of target side on premotor biases? When considered alongside the observed effect of reach direction on perceptual biases (Figure 3A.5), these two effects suggest that left-handed participants were generally faster to initiate reaches when at the leftmost or rightmost hand start position, compared to when they were at the central start position. This pattern could be explained by Hick's law, which states that reaction time increases with the number of response alternatives (reviewed in Teichner & Krebs, 1974). On the speeded reach task, the central start position requires a decision between initiating a leftward or rightward reach, whereas the left and right start positions restrict this decision to a single reaching direction. Since premotor biases were calculated by comparing central start position to either the left or right start position, Hick's law would predict more a positive premotor bias for the left target and a more negative premotor bias for the right target (a similar logic would apply to perceptual biases for leftward and rightward reaches). This is the precise pattern observed in our left-handed sample.

This interpretation leads us to a third question: why did the left-handed participants show behavioural evidence of Hick's law, and not the right-handed participants? This difference is perplexing, since presumably the vast majority of work on Hick's law has been conducted in right-handed persons. One possibility is that left-handed participants were better able to optimize their response strategy because they have a more flexible problem-solving approach to reaching tasks. In support of this possibility, left-or mixed-handed persons tend to display better divergent thinking (in males) and cognitive flexibility than right-handed persons (Coren, 1995; Gunstad et al., 2007). The cognitive flexibility of left-handers may be further encouraged by their extensive experience navigating environments intended for right-handed people. However, this idea is conjectural and requires further investigation, possibly by asking left- and right-handed participants about their reaching strategies. Another possibility is that the stronger effects of PA in the right-handed group somehow diluted or masked their Hick's law pattern. In summary, left-handed participants may have not displayed an LPA-induced premotor bias because they displayed premotor biases that were not evident in the right-handed participants and that opposed the expected direction of LPA's effects.

Left- and right-handed persons may also show different PA effects due to differences in the lateralization of their spatial attention systems. Liu et al. (2009) found that the lateralization of brain areas corresponding to the ventral attention network (VAN) varied by handedness, with right-handers typically having a right-lateralized VAN and left-handers typically having either a bilateral or left-lateralized VAN. This reduced hemispheric lateralization in left-handers may make them less vulnerable to induction of spatial biases (Bareham et al., 2015). In the context of PA, Clarke et al. (2022) proposed that LPA has stronger cognitive effects in healthy adults than RPA because LPA exaggerates the right IPL's pre-existing topographic representation of the right visual field; this increased right lateralization of the VAN then produces functional imbalances in the dorsal attention network (DAN), biasing voluntary attention and visuomotor behaviours to the right (see also Clarke & Crottaz-Herbette, 2016, and Corbetta & Shulman, 2011). If left-handers have a less lateralized VAN than right-handers, then LPA may exert less influence on visuomotor behaviours subserved by the DAN, which in the case of our study may manifest as a lack of premotor bias induction in left-handers. Alternatively (or in addition), hand use may interact with the lateralized effects of PA on the attentional system. Farron et al. (2022) recently demonstrated that PA using the left hand resulted in less extensive topographic reorganization of the VAN than PA using the right hand. However, they were studying RPA in exclusively right-handed individuals, so it is unclear to what extent their findings apply to LPA in our left-handed sample.

This discussion subsection has highlighted that our observed differences in PA-induced premotor biases between left- and right-handed participants may arise from a combination of centralized (e.g., differences in cognitive flexibility or lateralization of the spatial attention system), peripheral (e.g., number of response alternatives across hand start positions), and/or socio-environmental (e.g., differences in experience within predominantly right-handed society) factors. Overall, the null effect of LPA on premotor biases in our left-handed sample casts some doubt upon the validity of LPA-induced premotor bias observed in right-handers. Specifically, it is unclear whether the LPA-induced premotor bias in right-handers reflects: a) an experimental artefact; or b) a true modulation of premotor processing that is just specific to right-handed persons. However, it *is* clear that performance on the speeded reach task differs by handedness and/or hand use, and these differences complicate the interpretation of PA's effects on this task.

3A.4.2 Mirrored Effects of Start Position and Target Side by Handedness Group

While PA's effects on premotor biases in right-handers were not observed in left-handers, effects of hand start position and target side on the speeded reach task were beautifully mirrored across handedness groups (see section 3A.3.3.3 and Figure 3A.6). In essence, this analysis revealed that both the left- and right-handed groups displayed a faster *iRT* to targets on the side of their dominant hand, but only when their dominant hand was at, or crossed over, their midline. This symmetrical finding supports a common criticism of the speeded reach task; that is, manipulating the hand's start position changes not just the reach direction, but also the hand's location relative to the body midline. This difference in hand location may act as an attentional cue, modulating response speed (discussed in Harvey, 2004). Our mirrored effects of start position and target side by handedness group provide useful normative information for the use of the speeded reach task to measure neglect behaviour. Specifically, our data suggest that healthy right-handed persons tend to display a 'mild left-sided neglect' at the left and centre start positions, while healthy left-handed persons display a 'mild right-sided neglect' at the centre and right start positions. These results highlight the importance of considering premorbid and current hand preference in PwN, particularly when using the speeded reach task to measure perceptual and premotor neglect.

3A.4.3 Limitations

One limitation of the present study is that handedness and hand use were confounded: right-handed participants used only their right hand, and left-handed participants used only their left hand. Disentangling handedness from hand use would require testing both left- and right-handed participants using their left or right hand to complete PA. Such a design would need to account for practice effects and potential inter-manual transfer of PA effects (Redding & Wallace, 2008). As discussed earlier, one limitation of the speeded reach task is the differences in response alternatives by start position. A future study could control for response alternatives by including two additional targets, one to the left of the left start position and one to the right of the right start position, so that participants must always make a choice about their reach direction. We did not use this design for feasibility reasons (e.g., limitations in stimulus computer width; disinclination to add conditions to an already modified and lengthened paradigm compared to Striemer & Borza, 2017). Another limitation was that our study lacked neural measures of cerebral lateralization; further neuroimaging research would be needed to evaluate our above speculations about the differential effects of LPA on VAN lateralization in left- and right-handed adults. Finally, we acknowledge that our sample sizes were unequal for our left-handed (*N*=24) and right-handed (*N*=30) groups, reducing the power of our analyses (Rusticus & Lovato, 2014). We are currently recruiting more left-handed participants to reach a final sample of 30 to match the right-handed group.

3A.4.4 Conclusions and Significance

In conclusion, left-handers did not show the LPA-induced premotor bias that was observed in right-handers. This finding suggests that LPA's effect on the premotor stage of processing, at least when measured by the speeded reach task, may be specific to right handedness and/or hand use. The reason for our null effects of PA on premotor biases in left-handers is unclear, but could be related to differences in reaching strategies or cerebral lateralization. Because only about 10% of the general population is left-handed (Papadatou-Pastou et al., 2020), and neuroscience studies routinely exclude left-handed individuals (Bailey et al., 2020; Willems et al., 2014), much remains unknown about the spatial behaviour and neural architecture of left-handers. The present study highlights the importance of considering handedness and hand use in future studies that use manual tasks to investigate PA's capacity to shift spatial biases in healthy adults.

This work also has implications for the assessment and treatment of post-stroke neglect. While neglect most commonly manifests on the left side of space after right-hemisphere stroke, right-sided neglect may also occur after left-hemisphere stroke (Hreha et al., 2017). Depending on their upper-limb sensorimotor impairments, persons with left-hemisphere stroke may need to use their left hand during neuropsychological assessments and treatments, regardless of their premorbid handedness. Thus, it is important to understand how handedness and hand use impact performance on different neglect measures, as well as on treatments involving upper-limb movements (e.g., PA). More broadly, because spatial neglect, PA, and handedness are all lateralized phenomena, studying them together may yield new insights. For instance, Bareham et al. (2015) drew a parallel between neglect and handedness by speculating that the increased prevalence of left-sided neglect after right-hemisphere stroke may be related to the fact that 90% of people are right-handed. One case study reported right-sided neglect in a left-hander after left frontal-subcortical stroke, with no symptoms of aphasia (Dronkers & Knight, 1988); it would be interesting to examine prevalence rates of left- and right-sided neglect in stroke survivors who are premorbidly left- or right-handed. If neglect prevalence rates differ by handedness, understanding why could teach us about causes of both neglect and handedness. Overall, while the data from the present study seem to raise more questions than they answer, they also highlight fruitful avenues for further study of lateralized behaviour in both experimental and clinical settings.

CHAPTER 4 PERCEPTUAL AND RESPONSE BIASES ON THE LANDMARK TASK BEFORE AND AFTER PRISM ADAPTATION

This chapter consists of a manuscript in preparation. The authors of this work include Jasmine R. Aziz and Gail A. Eskes. My contributions to this project include: conceptualization, experimental program development, project management, data collection and analysis, interpretation, and write-up.

4.1 Introduction

Prism adaptation (PA) is a visuomotor learning task wherein individuals reach for targets while wearing glasses fitted with prism lenses that displace their visual field horizontally (Prablanc et al., 2020; Redding et al., 2005). Initially, they make reaching errors in the direction of the visual shift (i.e., direct effects), but their accuracy improves with repeated pointing movements as their reaching plan and sensorimotor reference frames adjust to the visual perturbation (Redding & Wallace, 1996). When the prism glasses are removed, the individual now makes errors in the direction opposite the visual shift (i.e., aftereffects). These aftereffects are thought to reflect the strength of adaptation that has occurred (Redding & Wallace, 2006).

Prism adaptation was initially studied experimentally to understand the mechanisms of visuomotor learning (von Helmholtz, 1867, 1962). Decades later, Rossetti et al. (1998) demonstrated that the leftward aftereffects following right-shifting PA could reduce symptoms of spatial neglect, a common and disabling condition after (most often) right-hemisphere stroke whereby individuals have difficulty reporting, orienting, and/or responding to stimuli on the left side of space (Buxbaum et al., 2004). Rossetti et al.'s (1998) finding inspired considerable research into PA as a potential neglect therapy. While some studies have shown that PA can improve the performance of persons with neglect (PwN) on both standard neglect measures and functional tasks (Chen et al., 2022; Striemer & Danckert, 2010b), PA's therapeutic effects in other studies have been mixed and/or transient (Li et al., 2021; Longley et al., 2021; ten Brink et al., 2017). More research is needed to understand how PA impacts visuospatial attention, in both normative and clinical populations, to help understand why only certain PwN benefit from this treatment.

One proposed explanation for PA's variable effects is that they depend on the neglect presentation (Barrett et al., 2012; Goedert et al., 2014). Neglect is a highly heterogeneous disorder, and as a result many neglect subtypes have been proposed (for a review, see Williams et al., 2021). One neglect subtyping dimension that has been considered in PA research is Input (perceptual) versus Output (premotor) neglect (see Chapter 2, and Harvey, 2004; Saevarsson et al., 2014). In this taxonomy, neglect symptoms are described as occurring at different stages of information processing that underly responding to a stimulus. Persons with Input neglect may have greater difficulty detecting or attending to left-sided stimuli, whereas persons with Output neglect may have greater difficulty planning, initiating, and/or executing movements toward left-sided stimuli; a person could also show a combination of both deficits. There is some evidence that PA treatment response may differ between these subtypes, with Output neglect showing greater benefits (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a, but see Gammeri et al., 2023, for conflicting evidence). These Input-Output neglect subtypes have been measured in many ways, and no standard approach exists. However, in a narrative review of perceptual and premotor neglect subtyping approaches, Harvey (2004) identified the Landmark task as "the most appropriate, thoroughly researched tool" (p. 327). In keeping with this opinion, the systematic scoping review described in Chapter 2 of this thesis also identified the Landmark task as the most common Input-Output subtyping task across the literature, and the most used Input-Output subtyping task to investigate mechanisms of PA in healthy adults (see Chapter 2).

The Landmark task is a modified version of the line bisection task, a classic neglect measure that requires individuals to mark a horizontal line at its midpoint; persons with left-sided neglect tend to transect the line to the right of centre (Schenkenberg et al., 1980). In the Landmark task, the viewer is presented with horizontal lines that already have transection points (i.e., 'landmarks') at different locations along the line, and they are asked to judge the relative length of the two line segments created by the transection (Milner et al., 1992, 1993). While the response requirements vary by study, typically participants verbally indicate or point to which segment is longer or shorter (Bisiach et al., 1998; Capitani et al., 2000; Vossel et al., 2010). With respect to measuring Input and Output neglect, the Landmark task could be considered a 'perceptual' equivalent of the line bisection test as it does not require a manual transection movement. With this logic in mind, numerous studies have directly compared spatial biases on Landmark and line bisection tests to determine the contribution of manual responding to line bisection performance (e.g., Binder et al., 1992; Chiba et al., 2005; Loetscher et al., 2012; Macdonald-Nethercott et al., 2000; Marshall & Halligan, 1995; Milner et al., 1992; Pitzalis et al., 2001).

Specifically, a person with Input neglect may transect the horizontal line to the right of centre on the manual line bisection, but on the Landmark task, they would be expected to underestimate the length of the left line segment and thus select the left line segment as shorter even if the presented line is centrally bisected. By contrast, a person with Output neglect would transect the horizontal line to the right of centre on the manual line bisection, and they would select the right line segment on the Landmark task regardless of the transection point, as they would have difficulty making leftward responses.

To study PA's relative impact on Input and Output processing, numerous researchers have tested whether a single session of PA in healthy adults can induce temporary spatial biases on the verbal Landmark and manual line bisection tasks that might relate to PA's therapeutic effects in PwN (McIntosh et al., 2019; Michel et al., 2003). This methodological approach works to address the question of whether PA mainly impacts performance on tasks with a manual component (e.g., line bisection), or whether it can influence perceptual processes in absence of a manual component (e.g., verbal Landmark task). This is an important question because PA researchers often make a distinction between the 'lower-level' sensorimotor aftereffects of PA experienced by the adapted limb, and expansion of PA aftereffects to 'higher-level' functions like visuospatial perception or selection of a motor plan (Michel, 2016; Prablanc et al., 2020). Past research has shown that left-shifting PA (LPA) can shift spatial biases rightward on both the verbal Landmark task and manual line bisection task (Michel et al., 2003; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Danckert, 2010a). However, this pattern of findings has not been consistently demonstrated, with some potential explanations being variation in adaptation protocols (Gammeri et al., 2020; Herlihey et al., 2012), and individual differences in spatial biases at baseline (Schintu et al., 2017). Furthermore, and most pertinent to the present study, there are important limitations of directly comparing verbal Landmark task to the manual line bisection task. One issue is that these tasks differ not just in response modality (i.e., verbal versus manual), but also in their task demands (i.e., judgment of relative length of two lines via forced choice response, versus estimation of the midpoint of a line via free response). A related issue is that, when compared to the Landmark task, PA-induced shifts on the manual line bisection task have been criticized as having higher measurement error, and, moreover, their interpretation as a spatial cognition effect is conflated with the effector-specific sensorimotor aftereffects experienced by the adapted limb (Colent et al., 2000; McIntosh et al., 2019; Michel et al., 2003).

An alternative method for distinguishing Input and Output components of bisection performance that avoids the above confounds between the Landmark and line bisection tasks is to calculate Input and Output biases from only the Landmark task. Bisiach et al. (1998) reasoned that PwN with a left-sided *perceptual* deficit would tend to judge the left line segment as shorter and the right line segment as longer, even when the transection point is in the centre or to the right of centre. By contrast, PwN with a left-sided *response* deficit would tend to select the right line segment regardless of the transection point location. Based on this reasoning, Bisiach et al. (1998) developed formulae to measure these deficits: the perceptual bias (*PB*) was defined as the average percentage of 'left segment is shorter' and 'right segment is longer' responses, whereas the response bias (*RB*) was defined as the average percentage of 'right segment is shorter' and 'right segment is longer' responses. While the benefits of this method are that it quantifies both perceptual and response biases and their spatial direction using the same data set, there are two key drawbacks: 1) the formulae do not factor in different transection points, thus losing potentially useful information; and 2) because the formulae are not mathematically independent, extreme scores on one index restrict possible scores on the other index, thus reducing the ability to accurately evaluate an individual displaying both bias types (see Figure 3 in Bisiach et al., 1998). Toraldo et al. (2002) proposed two revised formulae that are mathematically independent and make use of all transection locations. Their index of input-related neglect (IRN) was a directional bias in the point of subjective equality (*PSE*), which is the transection point at which the left and right segments are perceived as equal length and is calculated by a cumulative distribution function of percentage of 'right shorter' responses plotted by transection point (note: this *PSE* method resembles what was used to analyze the original Landmark test of neglect by Milner et al., 1992). Their index of output-related neglect (ORN) was *M*, which is the mean probability of making a response to the left or right regardless of the stimulus properties and is essentially a linear transformation of *RB* that accounts for different transection locations in the calculation. While several studies have examined the effect of PA on the Landmark task (e.g., Colent et al., 2000; Gammeri et al., 2020; Herlihey et al., 2012; Michel & Cruz, 2015), they were using the Landmark task to measure perceptual biases only, rather than using it to distinguish perceptual and response biases. To our knowledge, the effect of PA on perceptual and response biases as measured by Bisiach et al.'s (1998) and Toraldo et al.'s (2002) formulae remains unexplored.

The present study investigated the Landmark task as a measure of Input (perceptual) and Output (response) biases, and whether PA could induce directional shifts in these biases, in a healthy adult sample. Participants completed two computerized Landmark tasks requiring a manual response (LM-M) or verbal response (LM-V)[12], before and after a single session of either left-shifting PA (LPA group; n = 15) or right-shifting PA (RPA group; n = 15). We included the LM-V to allow us to compare to past PA studies(e.g., Colent et al., 2000; Michel et al., 2003; Nijboer et al., 2010; Striemer et al., 2016). We included the LM-M because it has not (to our knowledge) been used in past PA studies with this type of design, but it has been used in research involving PwN (Bisiach, Ricci, Lualdi, et al., 1998; Vossel et al., 2010), and it allows us to explore whether PA effects differ by response modality on the Landmark task.

We had four hypotheses. First, we expected to observe a small left-sided perceptual bias on both Landmark tasks prior to PA. Termed 'pseudoneglect' (Bowers & Heilman, 1980; Jewell & McCourt, 2000), this small but reliable left-sided spatial bias has been repeatedly documented in healthy adult populations and is thought to arise from a complex interaction of neuropsychological (e.g., spatial attention asymmetries), biomechanical (e.g., hand usage), and sociocultural (e.g., language history) factors (Michel et al., 2003; Rinaldi et al., 2014, 2020). We did not have specific predictions regarding response biases at baseline, though they were not expected to deviate notably from centre. Second, we predicted that PA would induce both a perceptual bias (as measured by Bisiach et al.'s (1998) *PB* and Toraldo et al.'s (2004) *PSE*) and a response bias (as measured by Bisiach et al.'s (1998) *RB* and Toraldo et al.'s (2004) *M*) on both Landmark tasks. This prediction

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[12]While our Landmark tasks were based on Bisiach et al.'s (1998) LANDMARK-M and LANDMARK-V, we chose to use the acronyms LM-M and LM-V instead, in part for brevity and in part to make it clear when we are referring to Bisiach et al's (1998) original paper-based tasks versus our modified computerized tasks in the present study.

was based upon past studies that have shown PA-induced shifts in performance on verbal Landmark and manual line bisection tests (McIntosh et al., 2019; Michel et al., 2003; Michel & Cruz, 2015; Striemer et al., 2016; Striemer & Danckert, 2010a). Third, we expected these PA effects to be greater in the LPA group than the RPA group, in line with prior work and known normative asymmetries in spatial attention (Clarke et al., 2022; Michel, 2016). Fourth (and finally), we predicted that Toraldo et al.'s (2004) *PSE* and *M* indices would be more sensitive (i.e., show larger effect sizes) in measuring baseline pseudoneglect and post-PA bias shifts than Bisiach et al.'s (1998) *PB* and *RB* indices, because Toraldo's et al. (2004) method considers the data across different transection points rather than collapsing across them, and thus may offer greater precision of measurement. Overall, this line of research can provide further insight into a common measure of visuospatial attention and its potential to detect shifts in attention following PA, which can in turn inform future research on the cognitive effects of sensorimotor learning as well as PA's use as a treatment for spatial neglect after stroke.

4.2 METHOD

4.2.1 Participants

Thirty-one adult participants were recruited from Dalhousie University and the surrounding community in Halifax, Canada. Our sample size was calculated using 95% power, an alpha level of 0.05, and the expected medium to large sized effect of LPA on the *PSE* measured with the Landmark task. The anticipated effect size was based on a meta-analysis by McIntosh et al. (2019) that estimated an effect size of $d \approx 1.0$ when the prism strength is ~17 degrees and the prism exposure is 10+ minutes (see Figure 5 in McIntosh et al., 2019). This sample size was also the same as the prior experiment in this thesis (see Chapter 3), thus facilitating comparison of PA effects across the two experiments. Inclusion criteria included self-reported normal or corrected-to-normal vision and hearing, and no self-reported physical problems that affected their ability to use their right hand to point to targets on a computer screen (e.g., upper-limb injury). Exclusion criteria included self-reported current diagnosis of neurological disorders (e.g., epilepsy, multiple sclerosis, dementia, stroke). All participants were right-handed by self-report, further confirmed by the Edinburgh Handedness Inventory – Short Form (EHI-SF; Veale, 2014)[13]. Table 4.1 displays EHI-SF scores and other sample demographics, which did not differ between prism shift direction groups (*p*s ≥ .4). All participants reported and demonstrated proficiency in English. Participants were recruited via community advertisements, the undergraduate psychology participation pool, and word of mouth, and individuals self-selected to participate. Participants received either financial reimbursement (e.g., for parking, travel), or credit points toward an undergraduate Psychology/Neuroscience course if they were an eligible Dalhousie student. All study procedures were in accordance with the Nova Scotia Health and Dalhousie University Research Ethics Boards.

Table 4.1 Sample demographics by prism shift direction group after exclusions*.

Variable	LPA Group	RPA Group	Overall
Sample size	15	15	30
Mean age in years (*SD*)	25.93 (7.57)	28.80 (11.80)	27.37 (9.85)
Mean education in years (*SD*)	15.20 (2.34)	15.80 (1.93)	15.50 (2.13)
Gender (women:men:non-binary)	11:4:0	11:4:0	22:8:0
Mean EHI-SF laterality quotient (*SD*)	90.83 (20.85)	90.83 (17.97)	90.83 (19.12)

*Data from one participant were excluded from the analyses; see Data Exclusions section of the Results for more details.
Note. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation; EHI-SF = Edinburgh Handedness Inventory – Short Form (Veale, 2014).

4.2.2 Design

This study employed a mixed randomized experimental design. Participants were randomly assigned to receive either LPA or RPA, and thus PA group was treated as a between-subjects factor. Time (pre-PA, post-PA) was treated as a within-subjects factor.

[13]The EHI-SF is a four-item version of the original EHI, which measures handedness by asking how often the respondent uses their left or right hand for various manual activities (e.g., writing, throwing). The EHI-SF has very good internal consistency (α = .93) and a strong correlation with scores on the widely used original 10-item scale (r^2 = .94; Oldfield, 1971; Veale, 2014). Handedness laterality quotients were calculated according to Veale (2014), with a positive quotient indicating a right-hand preference.

All participants completed both the LM-V and the LM-M before and after PA. The order of the two Landmark task versions was counterbalanced across participants; that is, half the participants completed the LM-M followed by the LM-V at both time points, while the other half completed the LM-V followed by the LM-M. For each administration of the LM-V and LM-M, the following four primary outcome measures were calculated: *PB* and *RB* based on Bisiach et al.'s (1998) formulae; and the *PSE* and *M* based on Toraldo et al.'s (2002) formulae (see Statistical Analysis section for more details). Other variables measured were reaction time (*RT*; in milliseconds) and movement time (*MT*; in milliseconds). During PA and the measure of prism aftereffects, we also measured error size (in pixels relative to the screen's centre, converted to visual degrees).

4.2.3 Materials

4.2.3.1 PLATO visual occlusion spectacles

During the Landmark task described below, participants wore PLATO goggles (Translucent Technologies Inc., TO, Canada), which are fitted with liquid crystal lenses that can switch between clear and occluded states. The PLATO goggles interfaced with the experimental program using a serial-to-USB converter programmed using Arduino software (Arduino, 2021).

4.2.3.2 Landmark task

Our computerized Landmark task was created and run using Superlab Version 6.1.2 for Windows (Cedrus Corporation, 2021), and was based upon the LANDMARK-M and LANDMARK-V paper-based versions of the Landmark task developed by Bisiach et al. (1998). Participants were seated in front of an upright 24-inch Asus touch screen computer. They were asked to place their chin in a central chin rest, which maintained a ~47 cm viewing distance from the centre of the screen throughout the procedure. A small Styrofoam occlusion board was attached to the chin rest to block the participant's view of their hand's starting position. Participants viewed a series of 250x1 mm centrally positioned horizontal lines, which each consisted of a red line segment and a black line segment on a white background. The visual angle subtended by the line segment was ~32 degrees. There were nine different locations for the transection point (i.e., point relative to the line's centre at which the line switched from red to black): -12 mm, -6 mm, -3 mm, -1 mm, 0 mm, 1 mm, 3 mm, 6 mm, and 12 mm. These transection points were chosen because they are the same relative spacing as Bisiach et al. (1998) but five times closer to the midpoint for increased sensitivity in our non-clinical sample (A. Toraldo, personal communication, September 12, 2022). Each line had two versions: one version with the black segment on the left and red segment on the right, and one version with the converse. Each of these 18 lines were presented six times, except for the ± 12 mm lines, which were each presented three times. Thus, there was a total of 96 trials per Landmark task administration. These trials were organized into 12 blocks; for the first three and last three blocks, participants were asked to indicate the longer segment, whereas they were asked to indicate the shorter segment for the middle six blocks (Bisiach, Ricci, Lualdi, et al., 1998).

Participants completed two versions of this Landmark task that used the same set of lines but differed in their response requirements. In the Landmark-manual (LM-M), the participant initialized the trial by pressing down a space bar with their right index finger, which triggered their PLATO goggles to immediately (i.e., within 3-4 ms) switch from the occluded to clear state. They first saw a forward pattern mask for 500 ms, after which the stimulus line appeared. The participant was instructed to use their right hand to point to the end of the shorter or longer line segment, depending on the block. Upon releasing the space bar to start their pointing movement, the goggles returned to their occluded state. The goggles remained in their occluded state until the participant had touched the screen (triggering a beep sound), returned their index finger to the space bar, and pressed down to re-open the goggles and initiate the next trial. The purpose of this visual occlusion was to reduce de-adaptation during the LM-M administration that followed the PA task, as individuals tend to de-adapt from PA more rapidly when they have full visio(Redding et al., 2005; Redding & Wallace, 1996), 2005; Redding & Wallace, 1996). In the Landmark-verbal (LM-V), the participant first saw a forward pattern mask for 500 ms, after which the stimulus line appeared. The participant was instructed to verbally state the colour of the shorter or longer line segment, depending on the block. The experimenter recorded the participant's verbal response via keyboard press, which triggered the onset of the next trial.

During the LM-V, the PLATO goggles remained in their clear state throughout the task but were still worn to increase comparability to the LM-M performance (e.g., account for view of goggle frame in periphery). For both the LM-M and LM-V, if the participant did not respond within 5000 ms, an error beep was presented to encourage them to respond more quickly. Both the LM-M and LM-V were also preceded by five practice trials per response condition ("longer" or "shorter") to ensure they understood the response requirements.

4.2.3.3 Prism adaptation

Participants wore Fresnel prism glasses with a leftward or rightward shift magnitude of ~17 visual degrees (30 diopters; Insight Optometry Group, Halifax, Canada). The targets for the PA task were white lines 1.2 cm in width spanning the entire vertical distance of the screen, at four possible horizontal locations: ~6 or ~18 visual degrees to the left or right of centre. Unlike the Landmark task, participants did not wear PLATO goggles and could see their reaching trajectory during the PA task (except for the hand's starting position, which was blocked by a small occlusion board, as during the Landmark). To initiate each trial, participants held down a spacebar with their right index finger, and after 400-600 ms, a target line appeared accompanied by an auditory cue. Participants were instructed to reach and touch the line as quickly and accurately as possible. The line disappeared 250 ms after screen touch, and participants could then return to the space bar to initiate the next trial. Every participant started with 40 practice reaching trials with clear glasses to measure baseline reaching. Then, the PA exposure took approximately 10-12 minutes and included 208 pointing trials, with an equal number of trials at each possible horizontal line location (trial order randomized).

4.2.3.4 Measure of prism aftereffects

Aftereffects were measured using a proprioceptive straight-ahead (PSA) pointing task, as done previously (Redding & Wallace, 1996; Striemer & Borza, 2017), to confirm that participants successfully adapted to the visual displacement. Participants wore the PLATO goggles in their occluded state and were asked to hold down a space bar until they heard an auditory cue prompting them to release the space bar and reach straight ahead from the centre of their body to the centre of the screen under full visual occlusion. The PSA task consisted of 10 reaching trials.

4.2.4 Procedure

Data collection took place at the Dalplex on Dalhousie University campus in Halifax, Nova Scotia, Canada. Prior to the in-person study session, participants were asked to sign the consent form and complete a health history form and EDI-SF on Research Electronic Data Capture (REDCap), a secure web-based software platform hosted at Nova Scotia Health (Harris et al., 2009, 2019). At the study session, a researcher reviewed informed consent with the participant to ensure that the participant understood the experiment requirements and had no questions. Following consent confirmation, participants completed two tasks (i.e., a tablet-based reaching task and paper-based Landmark task) to collect normative data for future clinical studies. These tasks took approximately 15-20 minutes in total and were not analyzed in the present thesis. Next, participants donned the PLATO goggles and completed the baseline LM-M and LM-V (order counterbalanced across participants), followed by a baseline PSA pointing task. Participants then removed the PLATO goggles and completed the PA task, followed by another PSA pointing task (post-PA). Participants donned the PLATO goggles again and completed the post-PA LM-M and LM-V in the same order as their baseline administration. Once all tasks were complete, the researcher provided a debriefing form and an opportunity to ask questions about the study, and arranged their compensation. The entire study procedure, including both the online and in-person components, took approximately 1.5 hours.

4.2.5 Statistical Analysis

Data were analyzed and visualized using R Studio Version 4.1.2. Next, we analyzed the Landmark data in two ways. First, we calculated biases using the method in Bisiach et al. (1998). In brief, the perceptual bias (*PB*) was defined as (% left shorter responses + % right longer responses)/2, whereas the response bias (*RB*) was defined as (% right shorter responses + % right longer responses)/2. For both biases, a score of 50% would be indicative of no bias. Second, we calculated biases using the method in Toraldo et al. (2004). This method defines input-related neglect (IRN) as a shift in the point of subjective equality (*PSE*), which is the transection point at which the left and right line segment as equal in length, and is calculated by creating a cumulative distribution function of the percentage of right segment responses as a function of transection point, and determining the value of x when $y = 50$ %. By contrast, output-related neglect (ORN) is defined by *M*, which is the mean probability of making a 'default' response to the left or right, and is essentially calculated by determining the value of *RB* at each transection point and averaging them together. Before calculating *PSE*, we visually inspected the Landmark task data by plotting the percentage of right segment responses as a function of transection point, separately for each participant, Landmark version (LM-M, LM-V), and time point (pre-PA, post-PA). Binary response data from each participant and cell in the design were fitted with a sigmoid function (i.e., binary logistic regression), and we confirmed that each model was statistically significant (i.e., Wald's statistic $p < .05$). Then, both the *PSE* and *M* were calculated in the present study using Dr. Toraldo's open-source Excel workbook (downloadable here: http://psicologia.unipv.it/toraldo/toraldo.htm). Of note, since our transection points were five times closer to the line midpoint than those in Bisiach et al. (1998) and the Excel workbook, we took the *PSE* outputted by the workbook and divided it by five to obtain the appropriate value for our experiment (A. Toraldo, personal communication, September 12, 2022). We calculated *PB*, *RB*, *PSE*, and *M* separately for each participant, Landmark version (LM-M, LM-V), and time point (pre-PA, post-PA). We first conducted descriptive statistics and Pearson correlations for these bias measures at baseline. To test our first hypothesis, we conducted one-sample *t*-tests comparing each bias measure to the null hypothesis of no spatial bias, which was a value of 50 % for *PB* and *RB*, and a value of zero for *PSE* and *M*. To test our next three hypotheses, we ran a series of 2 (LPA, RPA) x 2 (pre-PA, post-PA) mixed ANOVAs predicting either *PB*, *RB*, *PSE*, or *M*, separately for the LM-M and LM-V data. Significant effects ($p < .05$) were probed using pairwise *t*-test comparisons using a Bonferroni correction, as were differences in PSA error sizes between time points (baseline, post-PA, final). Data were visualized as means, with error bars representing standard error of the mean. Effect sizes are represented by η_p^2 values for ANOVAs and Cohen's *d* values for *t*-tests.

4.3 RESULTS

4.3.1 Data Screening and Exclusions

After visually inspecting and fitting sigmoid functions to the Landmark data (as described in our Methods section), all models were statistically significant at ps ≤ .002, except for one participant whose models were significant at ps ≤ .017. This one participant was observed to be confused about response requirements during the study procedure. Furthermore, visual inspection revealed that their percentages of "right shorter" responses were below 50 % across all transection points for both the LM-V and LM-M, which was aberrant compared to the rest of the sample and also precluded the calculation of a valid *PSE*. For these reasons, data from this one participant were completely excluded from the analyses below. No further data were excluded from any other tasks.

4.3.2 Landmark Task Biases Prior to Prism Adaptation

Table 4.2 displays descriptive statistics for Landmark biases at baseline prior to PA, and results from one-sample t-tests comparing the observed data to the null hypothesis of no spatial bias. Using the Bisiach et al. (1998) quantification method, we found evidence for a significant perceptual bias (*PB*) on both LM-V and LM-M tasks, but no significant response bias (*RB*) on either Landmark task. Similarly, using the Toraldo et al. (2004) quantification method, we found evidence for a significant perceptual bias (*PSE*) on both LM-V and LM-M tasks, but no significant response bias (*M*) on either Landmark task.

Table 4.2 Descriptives for Landmark task biases at baseline prior to prism adaptation.

Measure	Mean bias	*SD*	Range	Bias *p* value	Bias Cohen's *d*
LM-V *PB*	43.61 %	12.65 %	25.00–71.30	.0098	-0.50
LM-M *PB*	39.07 %	15.23 %	12.96–75.93	.0005	-0.72
LM-V *RB*	48.89 %	4.23 %	40.74–56.48	.16	-0.27
LM-M *RB*	49.94 %	6.10 %	35.19–62.96	>.5	-0.01
LM-V *PSE*	-1.22 mm	2.02 mm	-5.50–3.00	.002	-0.61
LM-M *PSE*	-2.00 mm	3.02 mm	-9–5.17	.001	-0.66
LM-V *M*	-.02	.08	-.19 – .13	.15	-0.27
LM-M *M*	-.001	.12	-.30 – .26	>.5	-0.01

Note. Bias *p* values and effect sizes are for one-sample *t*-tests in comparison to 50 % for *PB* and *RB* values, and in comparison to zero for *PSE* and *M* values. *N* = 30. LM-V = Landmark task-verbal version; LM-M = Landmark task-manual version; *PB* = perceptual bias based on Bisiach et al. (1998); *RB* = response bias based on Bisiach et al. (1998); *PSE* = point of subjective equality, an input-related neglect (IRN) measure based on Toraldo et al. (2004); *M* = an output-related neglect (ORN) measure based on Toraldo et al. (2004).

Table 4.3 displays a correlation matrix of all eight bias measures that were reported in Table 4.2. When examining correlations of the same bias quantification across the LM-V and LM-M tasks, strong positive correlations were observed between *PB* values and between *PSE* values, but no significant correlations were observed between *RB* values or between *M* values. When examining correlations between perceptual biases and between response biases within each LM-V or LM-M task, *PB* and *PSE* values were almost perfectly positively correlated, and *RB* and *M* values were perfectly positively correlated. Lastly, within each LM-V or LM-M task, perceptual and response biases (i.e., *PB* and *RB*; *PSE* and *M*) were strongly negatively correlated, indicating that as *PB* or *PSE* values got smaller (i.e., more biased toward left side of space), *RB* and *M* values became more positive (i.e., more biased toward right side of space). We noted that this negative correlation between perceptual and response biases was only present between biases measured by the same Landmark task (i.e., within the LM-V or LM-M task); these correlations were not significant when the perceptual or response bias came from different Landmark tasks (e.g., the LM-V *PB* and the LM-M *RB*).

Table 4.3 Correlation matrix of Landmark task biases at baseline prior to prism adaptation.

Measure	2	3	4	5	6	7	8
1. LM-V *PB*	**.57****	**-.51****	-.21	**.95****	**.51****	**-.50****	-.21
2. LM-M *PB*	-	-.24	**-.47****	**.57****	**.96****	-.23	**-.47****
3. LM-V *RB*		-	.20	**-.45***	-.18	**1.00****	.20
4. LM-M *RB*			-	-.15	**-.45***	.19	**1.00****
5. LM-V *PSE*				-	**.54****	**-.45***	-.15
6. LM-M *PSE*					-	-.18	**-.45***
7. LM-V *M*						-	.19
8. LM-M *M*							-

Note. N = 30. LM-V = Landmark task-verbal version; LM-M = Landmark task-manual version; *PB* = perceptual bias based on Bisiach et al. (1998); *RB* = response bias based on Bisiach et al. (1998); *PSE* = point of subjective equality, an input-related neglect (IRN) measure based on Toraldo et al. (2004); *M* = an output-related neglect (ORN) measure based on Toraldo et al. (2004). $^{*}p < .05$, $^{**}p < .01$.

4.3.3 Prism Adaptation Results

4.3.3.1 Direct effects during prism exposure

At baseline prior to prism exposure, pointing error size was close to zero for both the LPA group (mean = 0.02°, *SD* = 0.08°) and RPA group (mean = 0.02°, *SD* = 0.16°; Figure 4.1a). During prism exposure, participants initially made reaching errors in the expected directions (i.e., leftward errors for LPA, rightward errors for RPA, Figure 4.1b). As expected, their error size decreased across the early stages of prism exposure, although the absolute average error size of the last 40 trials of prism exposure in both the LPA group (mean = 0.14°, *SD* = 0.10°) and the RPA group (mean = 0.22°, *SD* = 0.13°) remained significantly larger than the average error size of their respective baseline trials (p = .002).

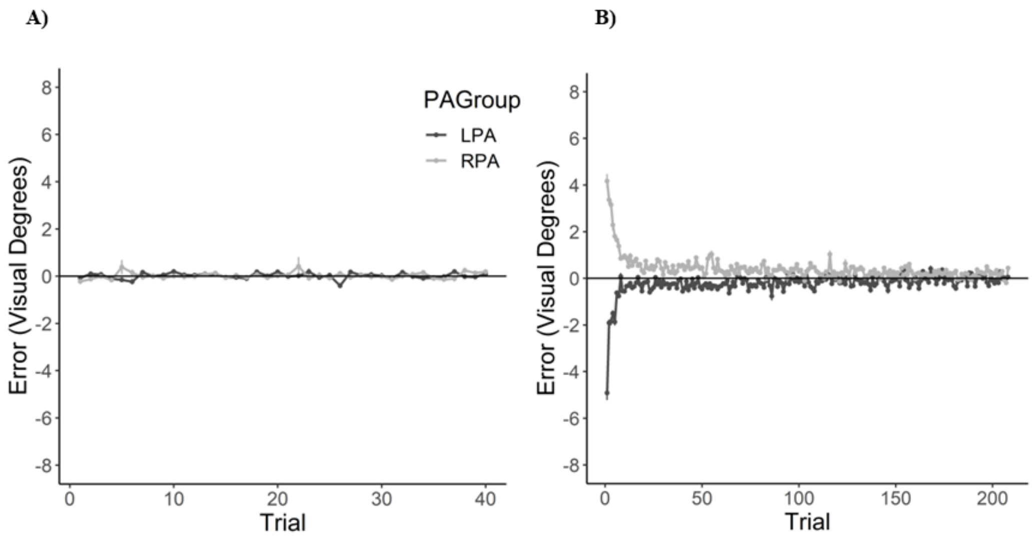

Figure 4.1 Pointing error size at baseline (A) and during prism exposure (B). LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

4.3.3.2 Aftereffects with goggle removal

Figure 4.2 displays error size (in visual degrees) on the PSA task by PA group and time (baseline, post-PA, final). There was a main effect of PA group ($F_{1, 28} = 40.06$, $p < .001$, $\eta_p^2 = .49$), qualified by a two-way interaction between PA group and time ($F_{2, 56} = 49.34$, $p < .001$, $\eta_p^2 = .37$). Paired-samples *t*-tests with Bonferroni correction demonstrated that both the LPA and RPA group displayed aftereffects in the direction opposite to their prismatic shift that were significantly different from baseline both immediately after PA, and at the end of the experiment (*ps* ≤ .002). To determine whether the magnitude of aftereffects differed by PA group, we also examined the absolute value of baseline-corrected aftereffects by PA group and time point (post-PA, final). This analysis revealed a main effect of time ($F_{1, 28} = 14.19$, $p < .001$, $\eta_p^2 = .18$), whereby aftereffects decreased in magnitude from post-PA to the end of the experiment. However, there was no main effect of PA group or interaction between PA group and time (*ps* ≥ .5).

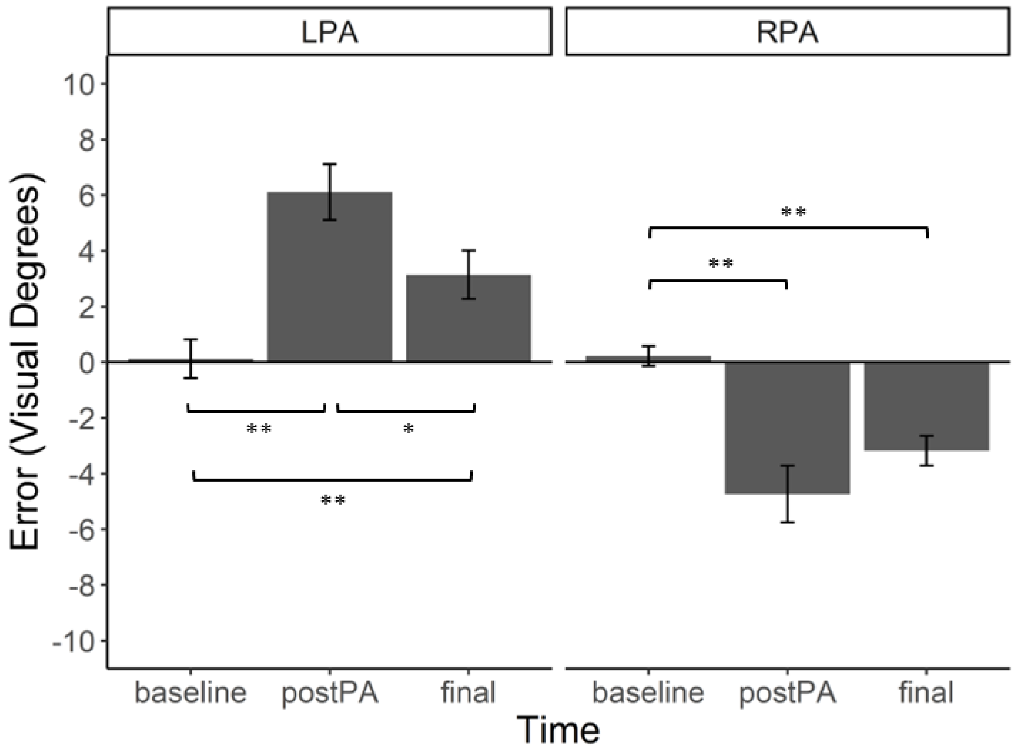

Figure 4.2 Proprioceptive straight-ahead (PSA) pointing error size by PA group and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. ** $p < .01$ on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean.

4.3.3.3 Effect of prism adaptation on Landmark biases

After conducting eight 2 (LPA, RPA) x 2 (pre-PA, post-PA) mixed ANOVAs predicting either *PB*, *RB*, *PSE*, or *M*, separately for the LM-M and LM-V data, there were no significant main effects or interactions (*p*s ≥ .14), suggesting that neither PA direction significantly impacted any of the biases measured by the Landmark tasks (Figures G1-G3 in the Appendix G for a depiction of these data).

Exploratory Analyses

4.3.4.1 Effect of Landmark task order

To test for Landmark task order effects, we conducted eight 2 (LPA, RPA) x 2 (pre-PA, post-PA) x 2 (LM-V first, LM-M first) mixed ANOVAs predicting either *PB*, *RB*, *PSE*, or *M*, separately for the LM-M and LM-V data. There were no significant main effects or interactions (*p*s ≥ .065), suggesting that the order of administration of Landmark task versions did not have a significant influence on bias measurement or PA effects.

4.3.4.2 Response time analysis

To determine whether response times on the LM-M task[14] differed by PA group, time, or side of response, we ran a 2 (LPA, RPA) x 2 (pre-PA, post-PA) x 2 (left-sided response, right-sided response) mixed ANOVA predicting response time. There was a significant main effect of time ($F_{1, 28} = 24.64$, $p < .001$, $\eta_p^2 = .47$), whereby response times were significantly faster after PA compared to baseline (mean $RT_{pre} = 1838$ ms, mean $RT_{post} = 1596$ ms, $p < .001$). There was also a main effect of side of response ($F_{1, 28} = 18.82$, $p < .001$, $\eta_p^2 = .40$), whereby response times were significantly faster for right-sided responses compared to left-sided responses (mean $RT_{left} = 1760$ ms, mean $RT_{right} = 1674$ ms, $p < .001$). No other main effects or interactions were significant (*p*s ≥ .12).

4.3.4.3 Comparing prism direct effects and aftereffects between Chapters 3 and 4

Given that Chapter 5 directly compares the results of Chapters 3 and 4, we wished to test whether prism direct effects and aftereffects were similar across these two samples of right-handers. To compare direct effects of PA, we conducted a between-subjects ANOVA of experiment and PA group predicting average absolute error size across the first

[14]We chose not to present results for response times on the LM-V because the (right-handed) experimenter inputted the participants' verbal responses by pressing the "r" key with the left index finger for "red" responses and the "b" key with the right index finger for "black" responses, and therefore any participant verbal response time effects would be confounded by the experimenter's bimanual response time effects.

10 trials of prism exposure. There was a main effect of experiment ($F_{1, 56} = 9.11$, $p = .004$, $\eta_p^2 = .14$), whereby average error across the first 10 prism exposure trials was higher in Chapter 3 (mean = 3.31°, *SD* = 2.45°) than in Chapter 4 (mean = 1.74°, *SD* = 1.42°). No other main effects or interactions were significant (ps ≥ .2). To test whether these groups showed similar reductions in direct effects over the course of prism exposure, we also conducted a mixed ANOVA of experiment, PA group, and time (i.e., average absolute error size across the 40 baseline reaching trials, versus average absolute error size during the last 40 trials of prism exposure). There were main effects of experiment ($F_{1, 56} = 31.80$, $p < .001$, $\eta_p^2 = .26$) and time ($F_{1, 56} = 43.11$, $p < .001$, $\eta_p^2 = .23$), qualified by an interaction between experiment and time ($F_{1, 56} = 12.69$, $p < .001$, $\eta_p^2 = .08$). Pairwise comparisons of experiment at each time point revealed that absolute error size was significantly larger in Chapter 3 than Chapter 4 at baseline ($p = .003$, $d = 0.86$) and in the last 40 trials of prism exposure ($p < .001$; $d = 1.36$), though as indicated by the effect sizes, the difference was larger for prism exposure (see Figure 4.3). No other main effects or interactions were significant (ps ≥ .2). Finally, we examined whether the magnitude of baseline-corrected prism aftereffects differed by experiment. A mixed ANOVA of experiment, PA group, and time resulted in a main effect of time ($F_{1, 56} = 39.67$, $p < .001$, $\eta_p^2 = .19$), whereby aftereffects decreased in magnitude from post-PA to the end of the experiment. No other main effects or interactions were significant (*p*s ≥ .2), indicating similar aftereffect magnitudes across right-handed samples. The differences in direct effects between Chapters 3 and 4 could be due to the fact that the stimulus computer was horizontally oriented in Chapter 3, but vertically oriented in Chapter 4. Despite these differences in direct effects, however, the aftereffect magnitudes were comparable across experiments.

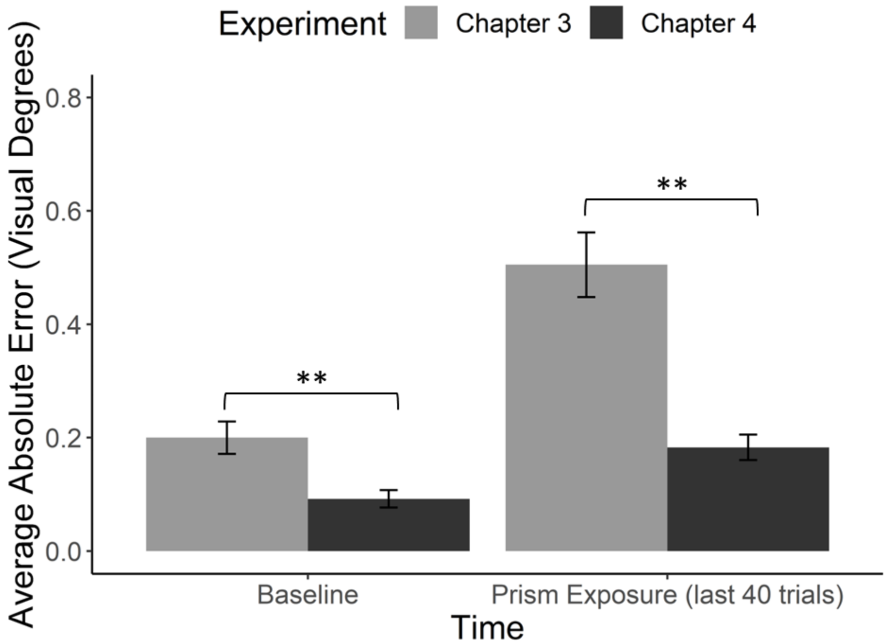

Figure 4.3 Average absolute error size during baseline and prism exposure (last 40 trials) in right-handed samples of Chapter 3 and 4. ** $p < .01$ on pairwise comparisons (Bonferroni correction). Error bars represent standard error of the mean.

4.4 DISCUSSION

While PA is a promising treatment for spatial neglect, therapeutic effects may vary by Input-Output neglect subtype (Barrett et al., 2012). One approach to studying how PA affects Input-Output processing is to test whether PA can induce temporary spatial biases in healthy adults (Colent et al., 2000; Michel, 2006, 2016). The present study explored Input (perceptual) and Output (response) biases as measured by the Landmark task, and whether PA could induce a temporary directional shift in these biases in a healthy adult sample. We found strong evidence for our first hypothesis, which predicted that participants would show a significant left-sided perceptual bias at baseline across two different bias calculation methods. However, we did not find support for our subsequent hypotheses regarding significant differences in measurement sensitivity between the Bisiach et al. (1998) and Toraldo et al. (2004) bias quantification methods, or any directional effects of PA on Landmark task biases. We discuss our interpretations of the pattern of Landmark biases at baseline, as well as possible reasons for the lack of observed directional shifts in these biases following PA.

4.4.1 Exploration of Landmark Biases at Baseline

As expected, our baseline (pre-PA) Landmark task data revealed a significant left-sided perceptual bias, resembling the well-documented 'pseudoneglect' phenomenon often observed in healthy controls (Bowers & Heilman, 1980; Jewell & McCourt, 2000). This 'pseudoneglect' was successfully detected using both bias quantification methods (*PB* and *PSE*) and across both Landmark tasks (LM-V and LM-M), suggesting that our Landmark task paradigm was sufficiently sensitive to detect normative biases in spatial attention. We note that our LM-V and LM-M Landmark tasks were based on Bisiach et al.'s (1998) verbal (LANDMARK-V) and manual (LANDMARK-M) Landmark tasks, with one key difference being that we chose to move our transection locations five times closer to the line centre, to ensure to the task was sufficiently challenging for our healthy adult sample, and to better resemble past PA-LM studies (e.g., Colent et al., 2000; McIntosh et al., 2019; Michel et al., 2003; Nijboer et al., 2010; Schintu et al., 2014). This increased difficulty likely explains why we found a significant left-sided perceptual bias, whereas past healthy normative studies of the LANDMARK-V and/or LANDMARK-M have not found significant directional biases using the *PB* or *PSE* quantification methods (Capitani et al., 2000; Toraldo et al., 2004).

Unexpectedly, we did not find any marked difference in sensitivity between Bisiach et al.'s (1998) and Toraldo et al.'s (2004) bias quantification methods to detect these baseline perceptual biases, evidenced by their broadly consistent medium-to-large effect sizes (range: d = -.50 to d = -.72; see Table 4.2, and Cohen, 1992). Furthermore, within each LM-V and LM-M task, *PB* and *PSE* values were nearly perfectly positively correlated (rs $\geq$ .95), and *RB* and *M* values were perfectly positively correlated (as expected, as *M* is a linear transformation of *RB*; see Toraldo et al., 2004). Just because these quantification methods were largely equivalent in our non-clinical sample does not mean that the methods would be similarly equivalent in a sample of individuals with post-stroke neglect, where more data variability and measurement error is expected. Indeed, one main advantage of Toraldo et al.'s (2004) quantification method is that it is more robust to data variability by considering data at all transection locations in the calculation. Furthermore, since they conceptualize the *PSE* and *M* values as point estimates of probability distributions, their method can quantify the uncertainty of these estimates using standard errors and confidence intervals. We did not examine these variables because our study was focused on using group-level analyses to test for overall biases in the sample and subsequent effects of PA shift direction (a between-subjects factor) on these biases. That said, Toraldo et al. (2004) discuss how standard errors can characterize the reliability of bias measurements in PwN, and confidence intervals can determine whether a particular bias is present in an individual case by checking whether the confidence interval includes zero. Future work using these bias measurements in individual PwN, particularly a small-*N* or single-case design, could benefit from considering these measures of spread in addition to the measures of central tendency.

In addition to comparing biases across different quantification methods, our design allowed us to compare biases across Landmark tasks with different response requirements. From a clinical perspective, having different response modality options may allow the task to be validly administered to a larger proportion of the stroke population. For instance, the verbal response version (LM-V) would be useful for individuals with severe motor impairments, whereas the manual response version (LM-M) would be useful for individuals with severe expressive language impairments (which are albeit less common in the typical left-sided neglect arising from right-hemisphere stroke). Verbal and manual versions have been developed for other neuropsychological tests, such as the trail-making test (Ricker & Axelrod, 1994) and the symbol-digit modalities test (Smith, 1982; Strober et al., 2020). To use different test versions to measure a similar cognitive construct, it is important to determine their relative psychometric properties, including reliability and validity. Bisiach et al. (1998) tested 121 PwN on modified verbal (LANDMARK-V) and manual (LANDMARK-M) versions of the Milner Landmark task (Milner et al., 1993). Bisiach et al. (1998) found that the LANDMARK-V identified more individuals as having perceptual neglect, whereas the LANDMARK-M identified more individuals as having response neglect. This pattern did not seem to be the case in our sample; if anything, the effect sizes of perceptual biases measured by the LM-M task were a bit larger than those measured by the LM-V task (see Table 4.2). We also found significant positive correlations between *PB* values and between *PSE* values measured across the LM-V and LM-M tasks, providing evidence of convergent validity between the two Landmark versions. The amount of variance explained in these correlations was approximately 30%, with other variance likely attributable to the differing task requirements and other unspecified measurement error. It is also interesting that there was only a weak, non-significant positive correlation between *RB* values and between *M* values measured across the LM-V and LM-M tasks, perhaps because these response bias measures had less variance (see Table 4.2). In line with Capitani et al.'s (2000) normative data (N = 240), we may have seen these weak positive correlations between *RB* values (and, by extension, between *M* values) reach statistical significance with a larger sample.

Our last point before shifting our discussion to the (lack of) PA effects is speculating on why our perceptual and response bias measures were negatively correlated. This result suggests that as a participant's Input (perceptual, *PB*, *PSE*) bias became more leftward, their Output (response, *RB*, *M*) bias became more rightward. For the Bisiach et al. (1998) quantification method, this association may exist because calculation methods of *PB* and *RB* are mathematically dependent. Specifically, when a participant's percentage of ‘left shorter’ responses decreases, this results in a lower *PB* value, but also implies a higher relative percentage of ‘right shorter’ responses, resulting in a higher *RB* value. This explanation would not necessarily hold for the *PSE* and *M* values, since these are considered mathematically independent (Toraldo et al., 2004), however given the strong *PSE/PB* and *M*/*RB* correlations, it is not surprising that *PSE* and *M* show a similar negative relationship. Furthermore, as the correlation between bias quantification methods may differ between neglect and control populations, so may the relationship between Input and Output processes. Given that neglect is considered a disconnection syndrome (Bartolomeo et al., 2007), these processes may be more dissociated in PwN (see Toraldo et al., 2014, for an example of a dissociation in the recovery pattern of *PSE* and *M* in a PwN).

4.4.2 No Effect of Prism Adaptation on Landmark Biases

Contrary to our hypothesis and past PA-LM studies (Berberovic & Mattingley, 2003; Michel et al., 2003; Michel & Cruz, 2015; T. Nijboer et al., 2010; Striemer et al., 2016; Striemer & Danckert, 2010a), we did not find any significant impact of PA on perceptual or response biases measured by our Landmark tasks. This null effect occurred within the context of strong sensorimotor aftereffects immediately post-PA that were smaller by the end of the experiment but remained significantly different from baseline. We considered whether this de-adaptation, combined with the counterbalancing of the LM-V and LM-M task order, may have diluted PA’s effects. However, these ‘diluting’ factors seemed negligible because our supplementary analysis did not show any significant difference in Landmark biases by Landmark task administration order post-PA. A more compelling explanation for our null findings comes from the work of McIntosh et al. (2023), which came to our attention after the present study was designed and launched. McIntosh et al. (2023) conducted a large-scale experiment examining the effect of either LPA (n = 102) or sham adaptation (n = 102) on the *PSE* measured by a computerized Landmark task in healthy adults. They found that, compared to sham adaptation, LPA induced a small rightward shift in the *PSE* that was not reliably different from zero. They noted that this finding differs from the results of their previous meta-analysis that “confirmed robust rightward shifts in visuospatial judgements following leftward prism adaptation" (p. 256, McIntosh et al., 2019), upon which our power analysis for the present study was based. McIntosh et al. (2023) discuss that the effect size of visuospatial aftereffects estimated by their prior meta-analysis was likely overestimated due to the small sample sizes in earlier included studies, amongst other extraneous factors such as the rightward shifts in perceptual biases attributed to decreased alertness over the course of an experiment (e.g., Manly et al., 2005) or regression to the mean (Campbell & Kenny, 1999, as cited in McIntosh et al., 2023). Overall, based on the data presented in McIntosh et al. (2023), the authors stated that detecting their revised estimate of the effect size for the rightward shift in *PSE* following LPA would require a sample of over 300 participants per group. Thus, our null findings are compatible with the work of McIntosh et al. (2023), as we were underpowered to detect such a small *PSE* shift. We note that we included additional Landmark task bias quantifications (i.e., *PB*, *RB*, and *M*) that were not explored by McIntosh et al. (2023), but given that their dataset is publicly archived, investigating these other calculation methods could be a direction for future research.

Another possible reason why PA did not impact Landmark task performance is because PA's effects in healthy adults do not extend to 'perceptual' judgements about line lengths. With reference to Goodale and Milner's (1992) two-stream theory of visual processing, Striemer and Danckert (2010b) proposed that PA mainly influences visuo-motor processing governed by the dorsal visual stream, with relatively minimal influence on visuo-perceptual processing governed by the ventral visual stream. In line with this proposal, some research suggests that PA primarily acts on premotor neglect symptoms in clinical studies[15] (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a), and primarily influences motor-intentional processes in healthy controls (Bracco et al., 2018; Fortis, Goedert, et al., 2011; Striemer & Borza, 2017). Although our LM-M task required a manual pointing response, the primary outcome was still a forced-choice perceptual judgement about the relative length of the two line segments, and thus may have been less sensitive to PA-induced shifts in Output biases. In

[15]However, it is worth noting that PA has reduced neglect symptoms on tasks that did not focus on manual responding, such as visual imagery (Rode et al., 2001), visual search (Saevarsson et al., 2009), and temporal order judgements (Berberovic et al., 2004). See Chapter 5 (General Discussion) for expansion on this point.

other words, perhaps we did not find any shift in response biases (*RB* or *M*) because these biases do not adequately capture the motor Output processes modulated by PA, at least in our sample of healthy adults.

It is possible that we would have found a significant effect of PA on manual line bisection task had we included it in our design. Our main rationale for using only the Landmark task in the present study was to avoid the drawbacks of directly comparing the Landmark task to the line bisection task, since the line bisection task has different response requirements, higher measurement error, and is more greatly influenced by basic sensorimotor aftereffects than the Landmark task (Colent et al., 2000; McIntosh et al., 2019; Michel et al., 2003). However, McIntosh et al. (2005) developed an alternative approach to line bisection that measures how varying the left and right endpoint locations of the horizontal line influences the location their transection mark relative to their body midline. The degree of asymmetry between the left and right endpoint 'weightings' (i.e., endpoint weightings bias, EWB) predicted the performance of PwN on conventional neglect measures with notable motor-exploratory demands, like cancellation and drawing tasks, and it was deemed more sensitive than the classic line bisection scoring method (McIntosh et al., 2005, 2017). It would be interesting to test whether PA could influence this EWB measure in PwN or healthy controls.

Yet another possibility is that PA modulated oculomotor activity during the Landmark task. While we restricted head movements by using a central chin rest, we did not restrict eye movements, nor did we measure them (for feasibility reasons given our PLATO goggle setup). Oculomotor activity is important to consider when discussing the line bisection task and its variants (e.g., the Landmark task) because visual scanning direction can influence perceptual judgements regarding horizontal lines (Chokron et al., 1998). Furthermore, PA can shift scanning behaviour in the direction of the prism aftereffect, though the impact of this shift in eye movements on perceptual judgements in PwN seems to be task-specific (Ferber et al., 2003; Sarri et al., 2006, 2011, as reviewed in Newport & Schenk, 2012). While we found no effect of PA on Landmark task performance in the present study, we cannot comment on whether PA influenced our participants' scanning behaviour.

Finally, it is possible that there was no effect of PA on the Landmark task in McIntosh et al. (2023) or the present study because we both used concurrent exposure in our PA paradigms. Concurrent exposure was used in the present study to match the PA method of Chapter 3, which was based on the use of concurrent exposure by Striemer and Borza (2017). There is some evidence that concurrent exposure during PA promotes proprioceptive aftereffects, whereas terminal exposure promotes visual aftereffects (Redding et al., 1985; Redding & Wallace, 2001). Indeed, in a healthy adult sample, Herlihey et al. (2012) found that LPA with concurrent exposure induced proprioceptive aftereffects accompanied a rightward shift in line bisection task performance, whereas LPA with terminal exposure induced visual aftereffects accompanied by a rightward shift in Landmark task performance. Thus, another future direction would be to examine the effect of different PA exposure paradigms on perceptual and response biases measured by the Landmark task. In such a design, it would be important to measure both proprioceptive aftereffects (i.e., PSA) and visual aftereffects (i.e., visual straight-ahead, VSA; Herlihey et al., 2012; Redding et al., 2005).

4.4.3 Limitations

One limitation of the present work concerns its generalizability to people with different linguistic backgrounds. Our participants were all proficient in English by self-report and recruited from a predominantly English-speaking community. While the English language is read by scanning left-to-right, other languages are read right-to-left, such as Arabic or Hebrew. The direction of pseudoneglect biases on line bisection-related tasks may vary systematically by reading habits (Chokron & Imbert, 1993; Muayqil et al., 2021), although this effect is not always seen and appears to differ by task requirements (Chokron et al., 1998; Chung et al., 2017). Furthermore, reading habits may predict egocentric biases on proprioceptive straight-ahead pointing (Kazandjian et al., 2009), which was our measure of PA's aftereffects. Another limit to our generalizability was our right-handed sample, since left-handed individuals may differ in their pseudoneglect patterns (Jewell & McCourt, 2000; Nelson et al., 2018; Sampaio & Chokron, 1992). Overall, normative biases in visuospatial attention likely arise from a complex combination of neurobiological (e.g., hemispheric differences), sociolinguistic (e.g., reading habits), and biomechanical (e.g., hand use) factors (Rinaldi et al., 2014, 2020). To further investigate the effect of PA on perceptual judgement tasks, more adequately powered studies with more diverse samples of the adult population would be needed. Finally, we acknowledge limitations in the clinical application of our work to individuals with post-stroke neglect: while perception and action are tightly bound in the healthy brain, the lesioned brain may be more likely to show a dissociation between perception and action, particularly if the area of damage occurs at a sensorimotor neural interface like the inferior parietal cortex or the temporoparietal junction, as is common in neglect (Lunven & Bartolomeo, 2017; Mattingley et al., 1998; Striemer & Danckert, 2010a, 2010b). Thus, the relationship between measures of Input (perceptual) and Output (response) biases in healthy adults may not necessarily translate to relationships between these processes in the manifestation of neglect after brain injury.

4.4.4 Conclusions and Significance

While PA is a promising therapy for spatial neglect, the mechanisms underlying its therapeutic effects remain unclear. Studies in healthy adults can enhance our knowledge of PA's effects on spatial cognition, which can inform models of PA's effects in spatial neglect (Clarke et al., 2022; Michel, 2006). This study investigated the Landmark task as a measure of Input (perceptual) and Output (response) biases in healthy adults, and whether PA could induce directional shifts in these biases. At baseline, participants showed a left-sided perceptual bias that was reliably measured across verbal (LM-V) and manual (LM-M) response versions of the Landmark task, and across two bias quantification methods (Bisiach, Ricci, Lualdi, et al., 1998; Toraldo et al., 2004). By contrast, we found no evidence of response bias at baseline using either Landmark version or quantification method. Furthermore, a single session of either leftward (n = 15) or rightward (n = 15) PA had no statistically significant effect on any of the Landmark task biases. In conclusion, our findings suggest that the Landmark task continues to be a robust method of quantifying normative biases in spatial attention (Bowers & Heilman, 1980; Jewell & McCourt, 2000;

McIntosh et al., 2023), but it does not appear to be as robust a measure of the cognitive aftereffects of PA in healthy adults.

CHAPTER 5 GENERAL DISCUSSION

The present thesis applied an Input-Output conceptualization of post-stroke spatial neglect to the study of PA's effects on normal spatial cognition. My first aim was to explore the Input-Output neglect subtyping dimension (Chapter 2), and my second aim was to test for differential effects of PA on Input and Output processing by investigating whether PA could induce spatial biases resembling Output neglect in healthy adults who have not had a stroke (Chapters 3, 3A, and 4). The present chapter links the results of these two thesis aims together. After summarizing the conclusions from my systematic scoping review on the Input-Output neglect concept, I use these findings to discuss my own experiments and position my work within the broader discourse of PA's mechanisms. I end with limitations, conclusions, and future directions of this body of research.

5.1 Exploring the Input-Output Neglect Subtyping Dimension (Thesis Aim 1)

The systematic scoping review described in Chapter 2 provides an integrative summary of the terminology, measurement approaches, prominent neural theories, and neural correlates that I have subsumed under the broad 'umbrella' concept of Input-Output neglect. Review results highlighted the wide range of terminology that has been used to describe these subtypes, and how the terms used tend to vary by study and measurement approach. Thus, our first conclusion when studying the Input-Output neglect concept was that subtyping terms will necessarily vary by study purpose and conceptual model. Through reviewing the many different subtyping approaches, we noted and compiled numerous methodological issues with Input-Output dissociation. We broadly organized these issues into contributions of task-related confounds (e.g., differences in task difficulty between conditions), and different body systems and environmental factors (e.g., sensory input modalities, motor output effectors, reference frames, and spatial sectors) to task performance. Thus, our second conclusion was that designing and interpreting data from Input-Output subtyping tasks requires careful consideration of all these potential factors. Moving to neural correlates and theories, our review results demonstrated that most research to date on neural substrates of Input-Output neglect is from discrete lesion data, possibly due to the publication date of included articles peaking in the late 1990's. Thus, our third conclusion was that the neural theories and correlates of Input-Output should be updated to reflect advancements of network-based models of neglect and associated neuroimaging techniques. Lastly, we briefly reviewed available findings of subtype-intervention interactions, and found variable effects by study sample, subtyping approach, and intervention method. Thus, our fourth and final conclusion was that clarifying the relationship between neglect subtypes and treatment response requires a joint understanding of: 1) the neurocognitive operations being captured by the Input-Output neglect subtyping task under study; 2) the therapeutic mechanisms of the intervention under study; and 3) their interface. We concluded the chapter by stating implications of the review for theorists, neuroscientists, and clinicians working with spatial neglect.

To address my second thesis aim, the next section serves to compare and contrast my two experiments (Chapters 3/3A and 4) through the lens of these scoping review conclusions. I then expand my discussion to the link between the Input-Output neglect concept and the mechanisms of PA.

5.2 Interpreting Experimental Findings Based on Scoping Review (Thesis Aim 2)

Before summarizing my experimental findings, I will briefly comment on how my scoping review conclusions informed my subtyping task selection for my experiments. Given that I was testing the proposal that PA acts on Output processing (see Sections 1.9 and 1.10), I selected two subtyping tasks that, according to my scoping review task categorizations, primarily manipulated properties of motor output. I selected the speeded reach task for its experimental control and for its focus on mental chronometry as the method of measuring information processing stages that was consistent with our conceptual model of Input-Output neglect. I then selected the Landmark task for my second task because it was identified by the scoping review as the most used subtyping task overall, as well as the most used subtyping task amongst the included articles that investigated PA.

To test for differential effects of PA on Input and Output processing, I conducted two experiments in healthy adults to test whether PA could induce Output biases as measured by the speeded reach task (task based on Husain et al., 2000; Mattingley et al., 1998; experimental design based on Striemer & Borza, 2017; Chapter 3/3A), and the Landmark task (Bisiach et al., 1998; Toraldo et al., 2004; Chapter 4). In my first experiment (speeded reach task), left-shifting PA (LPA) induced a rightward, 'neglect-like' premotor bias in the direction of the prism after-effect. However, this effect was specific to right-handed participants, and was not observed in a sample of left-handed participants who underwent the same procedure. Thus, the premotor bias induced by LPA in right-handed participants was interpreted as arising from an interaction between PA effects, hemispheric lateralization of spatial attention functions, and/or task-by-hand use interactions. In my second experiment, which recruited only right-handed participants, neither PA shift direction induced a perceptual or response bias on the Landmark tasks. I will now use my scoping review conclusions as a framework to discuss key similarities and differences between these two experiments and their associated PA findings.

5.2.1 Subtyping Terminology and Conceptual Models

My first conclusion was that subtyping terminology will necessarily vary by study purpose and conceptual model. As such, I will now comment on my rationale for choosing the terms "perceptual" and "premotor" for the speeded reach task (Chapter 3/3A) and the terms "perceptual" and "response" for the Landmark tasks (Chapter 4). I then use that context to help interpret differential effects of PA on these two tasks.

Starting with the speeded reach task, this task was developed by Mattingley et al. (1998) with reference to the phenomenon of directional hypokinesia, defined as slowed initiation of movements toward the contralesional side of space (Heilman et al., 1985). Original studies on this speeded reach task mainly used the terms "sensory" and "motor" to describe the Input and Output components being separated (Husain et al., 2000; Mattingley et al., 1998), whereas later studies mainly used the term "directional hypokinesia" and, importantly, did not use the speeded reach task to quantify both Input and Output components, but instead quantified the presence and magnitude of directional hypokinesia only (Rengachary et al., 2011; Sapir et al., 2007). I did not use the term "directional hypokinesia" in my study because it implies a clinical deficit, and my study was in healthy adults. My next logical option was to use the term “motor” or “directional motor”, as done in Husain et al. (2000) and Mattingley et al. (1998). However, seeing as my study used reach initiation time as the primary outcome and not also reach execution (i.e., movement or transport) time, “*pre*motor” seemed a more specific term for my purposes. I then selected the term “perceptual” to reflect the Input component of the speeded reach task because I found in my scoping review that “perceptual” was most often paired with “premotor.” However, it is worth noting that the original speeded reach task did not quantify perceptual biases, so the conceptual basis for the perceptual bias measured by the speeded reach task seems less developed than the premotor bias’ conceptual basis, which was observations of directional hypokinesia in PwN.

For the Landmark tasks, I used the terms “perceptual” and “response” as these were the terms used by the group who developed the version of Landmark task that I used (Bisiach, Ricci, Lualdi, et al., 1998). Toraldo et al. (2014) described a conceptual model of Bisiach’s et al. (1998) Landmark task that included three stages: a perceptual stage that involves forming an internal representation of the line based on visual input; a judgement stage that involves deciding which line segment is shorter or longer; and a response selection stage that involves deciding which binary response is needed (i.e., saying “red” or “black” in the verbal version, or pointing to the left or right line segment in the manual version). While the speeded reach task appeared to have a clearer conceptual basis for its premotor bias than its perceptual bias measure, the Landmark task seems to have the opposite issue: in their discussion, Bisiach et al. (1998) acknowledged that while their perceptual bias measure could be more readily linked to specific cognitive processes disrupted in neglect (i.e., anisometric representation of space), their response bias measure was more ambiguous. They reasoned that although a response bias could arise from a manual response bias (as the task intends to measure), a response bias could also arise from a spatial bias in oculomotor scanning, and/or a higher-level conceptual preference to select one side of space. Bisiach et al. (1998) acknowledged that their task does not provide precise information about such cognitive events leading up to the person’s binary response.

Taken together, this passage highlights that the speeded reach and Landmark tasks conceptualize Input-Output neglect rather differently. In particular, the speeded reach task appears to be better suited to measuring Output biases (e.g., directional hypokinesia), whereas the Landmark appears to be better suited to measuring Input biases (e.g., anisometric space representation). If PA does mainly act upon Output processes (Striemer & Danckert, 2010b), this task difference could explain why PA modulated the premotor bias on the speeded reach task but did not modulate the response bias on the Landmark. Another key difference between these two tasks is that the reach task conceptualizes the subtypes using a speeded measure, whereas the Landmark uses a measure of accuracy. There is some evidence in PwN that timed tasks are more sensitive to attentional biases than untimed tasks (Dukewich et al., 2012). Similarly, the reach task's speeded outcome measure may have been more capable of detecting PA's effects than the Landmark task.

5.2.2 Methodological Considerations

My second conclusion was the importance of considering methodological issues, such as potential confounds between task conditions and other neglect subtyping dimensions, when designing and interpreting Input-Output tasks. The main methodological consideration when interpreting the LPA-induced premotor bias in my first experiment was the differences in sensory input and response alternatives by hand start position on the speeded reach task. As discussed in Chapter 3, changing the hand start position on this task manipulates not just the reaching direction (i.e., the intended manipulation of Output), but also the hand's encoded position relative to the body midline and the targets. Crossing the hand across the body midline can cue attention to objects within reaching distance (Brooks et al., 2005; Shore et al., 2002), which could subsequently impact reach initiation times. Furthermore, the two start positions used to calculate premotor biases differ in the number of response alternatives (Hick's law; Teichner & Krebs, 1974), which on this task would inflate premotor biases measured for the left target, and deflate premotor biases measured for the right target. Since both these sensory and response alternative confounds would have been present in both the LPA and the RPA groups, these confounds cannot account for the result that only the LPA group showed a shift in the premotor bias (in right-handers). However, my result that left-handers showed no premotor bias, but did show the precise response pattern predicted by Hick's law, suggests that handedness and/or hand use may interact with PA's effects on the speeded reach task. This generalizability issue extends somewhat beyond the internal confounds of the speeded reach task, but nevertheless warrants further study.

Aside from low power (see McIntosh et al., 2023), there were two main methodological considerations when interpreting the null effects in my Landmark task experiment: mathematical confounding of Input-Output biases, and the role of eye movements. When compared to the reach task, the Landmark task maintains consistent sensory input across task conditions, to the extent that perceptual and response biases are calculated from the exact same data set. A downside of this consistency is the potential for mathematical dependence, particularly when using Bisiach et al.'s (1998) bias quantification method (for a review of this mathematical issue, see Toraldo et al., 2004). It is possible that Input-Output biases were not sufficiently dissociated in my healthy sample for PA to exert its effects. With respect to eye movements, while participants were encouraged to maintain central fixation during the reach task, on the Landmark their eye movements were unrestricted. Given that PA can impact oculomotor activity without altering perceptual judgements (Ferber et al., 2003; Ferber & Murray, 2005), LPA may have induced an Output bias on the Landmark task in the form of a rightward shift in eye movements that simply went unmeasured.

Overall, comparing the methodological issues present in these two tasks reveals that they have complementary advantages and drawbacks. While the speeded reach task's manipulation of response directionality unintendedly manipulates sensory input as well, the speeded reach task does control for eye movements, allowing for a better isolation of (visual) perceptual and premotor biases. The Landmark task, by contrast, has excellent consistency of sensory input across conditions, but does not restrict eye movements so any perceptual or response biases observed could be due to biases in oculomotor activity (see also Ishiai et al., 1998). Ultimately, selection of Input-Output subtyping tasks depends upon what Input-Output dissociation is most germane to the purpose of the research study in question. In the context of the present thesis, I was interested in the broad claim that PA modulates Output processing. Thus, selecting two divergent subtyping tasks like the speeded reach task and the Landmark task allows me to cover more literature and take a broader stance on the nature of Input-Output subtyping and implications for PA.

5.2.3 Neural Correlates

My third conclusion was the need to neural theories and correlates to reflect network models of neglect that have been developed in concert with advances in neuroimaging. Given the behavioural nature of my experimental data, I am unable to fully enact this recommendation. However, this section will draw upon data from past research to compare neural correlates of the speeded reach and Landmark tasks, while the next section will connect my findings to network models of neglect and PA mechanism.

Lesion-symptom mapping studies have linked both directional hypokinesia on the speeded reach task (Sapir et al., 2007) and response biases on the Landmark task (Bisiach, Ricci, Lualdi, et al., 1998; Vossel et al., 2010) to subcortical damage. There is also some correspondence in the perceptual biases of both tasks being linked to frontal damage (Bisiach, Ricci, Lualdi, et al., 1998; Husain et al., 2000; Mattingley et al., 1998). However, there are also numerous discrepancies in neural correlates both between *and* within tasks across various studies (see Tables 2.6-2.8 in Chapter 2 for a summary). Critically, no studies to our knowledge have examined the speeded reach and Landmark tasks in the same group of PwN, which makes it challenging to directly compare their respective neural correlates. Furthermore, it is unclear whether the lesions corresponding to Input-Output biases on the speeded reach and Landmark task are the same brain regions that are engaged during these tasks in healthy adults. While our scoping review did not identify any studies measuring or manipulating neural activity during the speeded reach task in healthy adults, one study on the Landmark task found that rTMS applied to either the right frontal premotor or right posterior parietal area induced a perceptual bias, whereas neither stimulation site induced a response bias (Brighina et al., 2002). Another study found that right parietal single-pulse TMS induced a right-sided perceptual bias on the Landmark task, whereas vertex TMS induced a left-sided response bias that was associated with increased left caudate activity on fMRI (Ricci et al., 2012). Taken together, neural correlate studies to date suggest that both the speeded reach and Landmark tasks likely recruit distributed frontal-parietal-subcortical networks to varying degrees depending on the subtype being displayed. However, to characterize these neural differences, more research is needed measuring and/or manipulating the activity of these networks during both tasks in the same sample of individuals.

5.2.4 Connecting Mechanisms of Assessment and Treatment

My fourth conclusion considered the importance of connecing neurocognitive mechanisms underlying subtyping task performance to those underlying intervention effects. As noted in the previous section, the correspondence of neural mechanisms underlying speeded reach and Landmark task performance in healthy adults is not entirely clear. Furthermore, the neural mechanisms underlying PA are still actively under investigation (Boukrina & Chen, 2021; Rossetti et al., 2019). However, I can speculate on links between my behavioural findings and relevant neurocognitive theories of PA. One aforementioned link is Striemer and Danckert's (2010b) proposal that PA primarily modulates attentional and visuo-motor behaviour subserved by the dorsal visual stream, with relatively minimal influence on visual-perceptual processing subserved by the ventral visual stream. Although Striemer and Danckert's (2010b) dorsal-ventral dissociation theory was developed with reference to PwN, who often have lesions in areas that connect these two processing streams (e.g., IPL, TPJ; see also Lunven & Bartolomeo, 2017), there is considerable evidence that healthy adults are also capable of displaying behavioural dissociations between perception and action (Westwood & Goodale, 2011). In the context of my experiments, since the speeded reach task is designed to measure the initiation and execution of manual movements, it may better engage the dorsal visual stream than the Landmark task, which is more suited to measure explicit perceptual judgments of the ventral stream. Thus, Striemer and Danckert's (2010b) theory seems broadly consistent with my differential PA effects across these two tasks.

However, there are also a couple of issues related to Striemer and Danckert's (2010b) theory that should be acknowledged. One issue is that Striemer and Danckert's (2010b) theory cannot fully account for effects of PA in PwN on some perceptual tasks, such as tasks involving implicit, preferential perceptual judgements (Sarri et al., 2006, 2011, reviewed in Newport & Schenk, 2012), temporal order judgements (Berberovic et al., 2004), and dichotic listening (Jacquin-Courtois et al., 2010). Another issue is that the general concept of fractionating dorsal and ventral processing has been criticized in recent years: in reflecting on decades of research on two-stream visual theory, Rossetti et al. (2017) concluded that perception and action cannot be meaningfully dissociated in most instances and should instead be considered "as a functional ensemble" coordinated by complex interconnected neural networks (p. 130). Taken together, these issues highlight discrepancies between to Striemer and Danckert's (2010b) theory and contemporary research on perception-action cycles and PA effects in neglect.

These issues with the dissociation of PA effects by dorsal and ventral visual streams prompted me to compare my experimental results to a more recent theory of PA's mechanism put forward by Clarke and Crottaz-Herbette (2016). Based on Corbetta and Shulman's (2002, 2011) attention network model of neglect, Clarke and Crottaz-Herbette's (2016) theory provides a neural account of PA's asymmetric effects on visual attention in both PwN and healthy controls. In essence, Clarke and Crottaz-Herbette (2016) proposed that RPA in PwN shifts ventral attention network's (VAN) hemispheric lateralization from the damaged right hemisphere to the intact left hemisphere by increasing the left inferior parietal lobule's (IPL) topographic representation of the left visual field. Clarke and Crottaz-Herbette (2016) described this phenomenon as a "shift in hemispheric dominance within the ventral attentional system (SHD-VAS)" (p. 35). This left-lateralized VAN can now provide input about the left visual field to the dorsal attention network (DAN), resulting in re-balancing of DAN activity and improved detection of stimuli in the left visual field in PwN (see also Crottaz-Herbette et al., 2017). In contrast, RPA has minimal effects in healthy adults because their right VAN is still functionally able to represent the left visual field. However, LPA exaggerates their intact right VAN's hemispheric dominance by further increasing the right IPL's pre-existing topographic representation of the right visual field, which may have downstream unbalancing effects on DAN activity, thus resulting in temporary lateralized dysfunction in spatial attention and visuo-motor behaviours (Clarke et al., 2022). This asymmetry of LPA and RPA effects in the healthy brain is consistent with my finding that only LPA induced a rightward premotor bias on the speeded reach task. Moreover, my observation that this effect was restricted to right-handers resembles the recent finding that the shift in hemispheric dominance of the VAN after PA was more extensive when the right hand was used for PA than when the left hand was used (Farron et al., 2022, albeit this study was using RPA in exclusively right-handed people). However, given that Clarke and Crottaz-Herbette's (2016) work suggests that PA modulates the IPL's representation of visual space, it is unclear why LPA did not also induce a rightward perceptual bias on the speeded reach task, or induce any biases on the Landmark task which presumably relies even more so on visual space representations (Bisiach, Ricci, Lualdi, et al., 1998). One alternative view, albeit not clearly connected to the Input-Output dichotomy, is that PA had a greater impact on speeded reach task performance because this task involved uncued visual targets detected via exogenous orienting, which is subserved by the VAN (Corbetta & Shulman, 2011). In discussing these possible links between my data and these neural theories, I must stress that neither Corbetta and Shulman's (2002, 2011) or Clarke and Crottaz-Herbette's (2016) model drew a firm distinction between Input and Output processing. Thus, it is not surprising that it is challenging to draw a clear connection between these neural models and my Input-Output subtyping task findings.

5.2.5 Interim Conclusions

In summary, this discussion section (5.2) has used my scoping review conclusions to structure a comparative discussion of the speeded reach and Landmark tasks and their capacity to measure PA's effects on Input-Output processing in healthy adults. One resounding conclusion from this section is that the approach of using different subtyping tasks to draw a similar link between PA effects and Output biases is complicated by the inter-task differences in underlying conceptual models, methodological considerations, and (putative) neural mechanisms. This issue of Input-Output subtyping task heterogeneity was well-articulated by Toraldo et al. (2014):

> … each [Input-Output subtyping] task involves a different sub-set of functions of the cognitive architecture; hence what is named, e.g., "input-related neglect" in different techniques, actually reflects damage to different representations or processes. Thus the caveat should be born in mind that a useful classification of

> neglect patients along the input-output dimension can only be carried out with reference to one specific task. (p. 250)

The same caveat holds when studying the link between PA effects and Input versus Output neglect symptoms: because the method of Input-Output dissociation varies by task, so will PA's influence on the Input and Output biases being dissociated. Thus, one would expect the effect of PA on Input-Output biases to be task-specific, which was demonstrated by my experimental data. However, rather than drawing overall thesis conclusions from the behavioural effects of PA on two subtyping tasks alone, the next section will use the broader foundation of my scoping review to expand this discussion to more fruitful links between the Input-Output neglect concept and theories of PA's therapeutic mechanisms.

5.3 Integrating the Input-Output Neglect Concept with Prism Adaptation Mechanism

If the link between PA effects and Output neglect is task-specific and not fully compatible with current views of PA's neural mechanisms, the overarching question of this thesis remains: does the Input-Output neglect concept hold any utility for the study of PA as a neglect treatment? In this section, I assert that rather than examining the differential effects of PA on Input and Output neglect symptoms, a more fruitful application of the Input-Output concept may be to examine how PA affects PwN's ability to integrate Input and Output processing. This theoretical view is not novel. In fact, Rossetti et al.'s (1998) seminal article states:

> The frequent parietal locus of the lesion producing neglect reflects the impairment of coordinate transformation used by the nervous system to represent extra-personal space… adaptation to a visual distortion can provide an efficient way to stimulate neural structures responsible for the transformation of sensorimotor coordinates… (Abstract, p. 166)

Thus, a logical application of the Input-Output neglect concept to PA is to conceptualize PA itself as an Input-Output task that uses visual displacement to manipulate the congruence of visual input with proprioceptive input and motor output. In this conceptualization, PA becomes a means of training the updating of internal representations of the external world via sensorimotor integration. This is a beneficial view for several reasons.

Firstly, conceptualizing PA as an Input-Output task can account for the link between spatial opposition tasks, PA response, and frontal lesions and/or intact temporo-parieto-cerebellar networks (see Chapter 1, Section 1.8, pp. 16-17). Prism adaptation is essentially a 'spatial displacement' version of spatial opposition tasks that manipulates the congruence of input and output in a less dramatic fashion (see p. 382 of Rossetti & Rode, 2002). Thus, it is not surprising that PA's therapeutic benefits have been linked to Output neglect symptoms on a spatial opposition task (Fortis, Chen, et al., 2011; Goedert et al., 2014), since Output neglect on this task is characterized by difficulty moving the line bisection cursor leftward in not only the congruent condition, but also the incongruent condition. Thus, Output neglect is associated with a difficulty executing spatially incompatible movements, which is in turn associated with frontal-subcortical lesions. Prism adaptation may ameliorate PwN's ability to execute such incompatible movements, perhaps by recruiting intact temporo-parietal regions involved in sensorimotor integration (Chapman et al., 2010; Chen et al., 2014; Goedert et al., 2018; Huang & Sereno, 2018; Luauté et al., 2009).

This view resembles that of Pierce and Saj (2019), who asserted that PA trains the spatial remapping processes that are often dysfunctional in neglect (for a seminal review of spatial remapping deficits in neglect, see Pisella & Mattingley, 2004). In brief, spatial remapping is the process that allows for a stable internal representation of the external world despite constantly changing retinal images by remapping the spatial coordinates of the visual environment across saccades (Pierce & Saj, 2019). This process requires integration of sensory input regarding the target(s) location and gaze position with (oculo)motor output regarding the direction and amplitude of past and future saccades. Spatial remapping processes have been localized to the right posterior parietal cortex, which is a common lesion site of neglect (Pisella & Mattingley, 2004). Spatial remapping can be measured using a double-step saccade paradigm whereby participants are presented two sequential visual targets and are asked to rapidly fixate on their two locations after both targets have disappeared (Duhamel et al., 1992; Heide et al., 1995). With respect to PA, Bultitude et al. (2013) demonstrated that LPA can induce a deficit in the spatial remapping of left-sided visual targets in healthy adults. The authors took this result to mean that RPA could potentially alleviate spatial remapping deficits in PwN. Alternatively, PwN may *require* intact spatial remapping abilities to benefit from PA, given that both spatial remapping and PA treatment response has been linked to intact parietal regions (Heide et al., 1995; Saj et al., 2019).

The shift in focus from measuring the separation of Input and Output processing to measuring the integration of Input and Output processing also allows the Input-Output neglect concept to better encompass representational accounts of neglect and their amelioration by PA (Bisiach & Luzzatti, 1978; Rode et al., 1998). Jerison and Barlow (1985) proposed that mammals like monkeys, dolphins, and humans developed a larger cortical surface area (i.e., encephalization) so that they could use sensory input to form internal representations of reality to guide behaviour (i.e., motor output). Thus, it is through the integration of inputs and outputs that internal representations of the external world are constructed and updated. Instrumental to this integration process is the posterior parietal cortex, which contains overlapping topological maps of multisensory inputs (e.g., visual, tactile) and effector-specific Output programs (e.g., reaching, stepping; Huang & Sereno, 2018). As suggested by Jeannerod and Biguer (1987), PwN have a deficit in the transformation of inputs to outputs across different sensory modalities and spatial reference frames (see also Filipowicz et al., 2016, for a description of neglect as a deficit in mental model updating). As long suggested by Redding and Wallace (1996), PA creates a discrepancy in visuo-proprioceptive inputs and motor outputs that is resolved through realignment of spatial reference frames. In PwN, this realignment results in a contralesional shift in their sensorimotor reference frames (i.e., internal representation of peri-personal space) and associated contralesional shift in motor output behaviour (e.g., reaching, eye movements; Redding & Wallace, 2006). These shifts somewhat resemble Crottaz-Herbette et al. (2017) proposal that RPA shifts the topological representation of the left visual field from the right to left VAN, which subsequently works to balance DAN activity and facilitate contralesional visuomotor behaviours. In summary, considering the integration of Input-Output processing allows for stronger parallels between the Input-Output neglect concept and theories of neglect and PA that incorporate internal representation of space.

Lastly, considering PA itself as an Input-Output task supports past work comparing PA's cognitive after-effects with those of other adaptation techniques. For instance, while PA manipulates visual input to produce subsequent motor output reaching errors, force-field adaptation directly manipulates the trajectory of motor output by applying an external force vector to the reaching arm via robot manipulandum apparatus (Shadmehr & Mussa-Lvaldi, 1994). Fleury et al. (2019) suggested that PA's sensorimotor after-effects generalize to more cognitive areas because the reaching errors produced by a shift in visual input are attributed to an internal cause, which stimulates more extensive realignment across internal reference frames; by contrast, the cognitive generalization of force-field adaptation is more limited because reaching errors produced by a force field are attributed to an external cause, and thus adaptation processes are more task-specific (see also Michel et al., 2018). Comparing different adaptation paradigms in this manner parallels the comparisons made in the present thesis between different Input-Output subtyping approaches. Further convergence of these two fields could lead to interesting discoveries.

5.4 THESIS LIMITATIONS

One limitation of the present thesis is its attempt to make claims about the neurocognitive relationships between Input-Output neglect and PA based on behavioural experiments in healthy adults. While it was the writer's intention to collect and include data from PwN in this thesis, this endeavor was precluded by the timing of the COVID-19 global pandemic (2019-2023, present) and associated effects on research activities. It may be premature to criticize the concept of measuring Input and Output processing separately based on data from non-lesioned individuals in which these processes are presumably highly integrated. These processes may be more dissociated in PwN, whose lesions interrupt communication between neural networks (Bartolomeo et al., 2007; Ciaraffa et al., 2013; McIntosh et al., 2004; Striemer & Danckert, 2010a). Furthermore, the neural mechanisms of PA differ between neglect and healthy control populations (Boukrina & Chen, 2021). Thus, before moving away from the Input-Output neglect subtyping approach in the field of PA, more research is needed measuring these subtypes in PwN undergoing PA and linking these behavioural presentations to differences in neural functioning (Brodtmann & Loetscher, 2022; Lunven et al., 2019; Moore et al., 2023; Scheffels et al., 2022; Vaessen et al., 2016). A related generalizability limitation is that I mainly sampled younger adults whose PA effects may or may not generalize to older populations. In addition to increased risk of stroke, aging is associated with changes in visual acuity (Salvi et al., 2006), visuospatial functions (e.g., working memory, Murre et al., 2013; Myerson et al., 1999), and non-spatial abilities (e.g., alerting, Jennings et al., 2007), all of which could modulate PA's effects on Input-Output subtyping tasks. Despite these changes, older adults tend to show equivalent, if not bigger, prism aftereffects than younger adults (Bock & Schneider, 2002; Lazar-Kurz et al., 2023). Overall, any measure of Input-Output subtypes and/or PA effects in PwN requires age-matched normative data to disentangle effects of normal aging from effects of post-stroke neglect. On a broader generalizability scale, my scoping review identified that research on Input-Output neglect subtypes has largely taken place in English-dominant countries (see Figure 2.3 in Chapter 2), and the experiments I have conducted are no exception. Reading habits such as text reading direction interact with measures of visuospatial function (for a review, see Chokron et al., 2011). Furthermore, cross-cultural differences exist in the prioritization of speed versus accuracy on neuropsychological tasks (e.g., the trail-making task, Ojeda et al., 2016), meaning that the relationship between subtyping tasks that focus on speed (e.g., speeded reach task) versus accuracy (e.g., Landmark tasks) may be culturally specific. Given that the increasing burden of post-stroke disability is expected to disproportionately affect low-income countries (Feigin et al., 2021), it is important that theories of post-stroke neurocognitive dysfunction and associated rehabilitative approaches are informed by relevant sociodemographic variables (e.g., linguistic background, cultural values) and systemic issues (e.g., poverty, barriers to health care access).

5.5 Future Directions

One potential application of the present thesis is to apply the scoping review conclusions (see Section 5.1) to the study of other neglect subtyping dimensions, with the logical extension being to further investigate the interaction between Input-Output processing and other neglect subtyping dimensions. This area of study could benefit from the recent advances in virtual or augmented reality technology, which have the potential to simultaneously manipulate multimodal inputs and measure multi-effector outputs across different reference frames and spatial sectors. In terms of neural theories of Input-Output neglect, advancements in neuro-computational modelling could provide a bridge between the psychological concepts discussed in this thesis and the functioning of neural networks; this bridge is already being built in PA research (Petitet et al., 2018), and in countless other areas of clinical and cognitive neuroscience (Astle et al., 2023; Doerig et al., 2023). Importantly, these neuro-computational investigations must be guided by conceptual knowledge best achieved through behavioural study of the observed phenomena of interest (Krakauer et al., 2017).

To advance this thesis' line of work, our ongoing research project will compare subtype performance patterns on the speeded reach and Landmark tasks in PwN and age-matched controls. The PwN will subsequently undergo PA, and we will test whether the speeded reach and Landmark tasks can predict PA-related improvements on conventional and functional measures of neglect. In addition, it would be interesting to further examine the link between spatial opposition tasks and PA response by administering a spatial opposition task repeatedly over the course of PA treatment, and/or by linking spatial opposition task performance in PwN to other cognitive processes, such as inhibitory control or spatial remapping. Another possible future direction is to study the influence of relevant demographic variables (e.g., linguistic background, handedness) on the relationship between Input-Output processing and PA effects.

Finally, as with any clinically relevant research, it is important to consider what stage in the translational pathway is the subject of inquiry. The present thesis operates at the basic mechanistic level, and addresses questions such as, "how does PA influence Input and Output processing?", "why does PA improve neglect symptoms?", or, "why do only certain PwN respond to PA?" However, other essential questions are addressed at later points in the translational pathway, such as "how do we decide who should receive PA?" or, "how, when, and where should PA be administered, and by whom?" These questions require skills in assessment tool selection (e.g., relative psychometrics), implementation science, and knowledge translation (Khalil, 2016). Importantly, this translational pathway is bidirectional, and clinicians and researchers at either end can continue to work together to advance both basic and applied research on spatial neglect and PA.

5.6 Thesis Conclusions

The present thesis examined the Input-Output neglect subtyping dimension and its implications for the study of PA as a neglect treatment. My first thesis study was a scoping review of the terminology, subtyping approaches, and neural correlates and theories of Input and Output neglect (Chapter 2). My next two thesis studies were behavioural experiments that investigated PA's differential effects on Input and Output processing by testing whether PA could induce a temporary Output bias on two different neglect subtyping tasks in healthy adults (Chapter 3/3A, 4). Such a finding would be in line with past work suggesting a link between Output neglect symptoms and PA response (Fortis, Chen, et al., 2011; Goedert et al., 2014; Gutierrez-Herrera et al., 2020; Striemer & Danckert, 2010a).

Overall, the scoping review findings highlighted that broadly classifying neglect symptoms as either Input- or Output-related cannot capture all the complexities of this heterogeneous disorder. However, reviewing the various Input-Output subtyping approaches provided useful conceptual, methodological, neuro-anatomical, and clinical considerations that I used to design and interpret the results of my two experiments. In brief, these experiments demonstrated that (L)PA induced a rightward, neglect-like Output bias on a speeded reach task in right-handers (Chapter 3, task based on Husain et al., 2000; Mattingley et al., 1998; Striemer & Borza, 2017), but PA had no effect on Input-Output biases measured by a horizontal line judgment task (Chapter 4, task based on Bisiach et al., 1998). While my results may suggest that PA mainly acts on visuomotor behaviours governed by the dorsal stream (Striemer & Danckert, 2010b), when viewed through the lens of my scoping review conclusions, it became clear that the link between Output neglect symptoms and PA effects is task-specific and not entirely consistent with recent accounts of perception-action cycles or PA's mechanisms in neglect or control populations (Clarke et al., 2022; Crottaz-Herbette et al., 2017; Rossetti et al., 2017). I then presented the alternative view of conceptualizing PA itself as an Input-Output task manipulating the congruence of visual input with proprioceptive inputs and motor outputs. This conceptualization shifts the focus from measuring dissociations of Input and Output processes, to measuring the ability to integrate these processes. I subsequently review research on spatial opposition tasks, spatial remapping, and other adaptation paradigms that demonstrate the benefits of this alternative application of the Input-Output neglect subtyping dimension. Importantly, further research is needed examining the interface between Input-Output concepts and PA in sociodemographically diverse populations of PwN and age-matched controls. In closing, while separating neglect into Input and Output subtypes may not be too broad an approach to conceptualizing neglect, the range of research on the Input-Output subtyping dimension can inform research on the integration of Input and Output processing that is central to prism adaptation.

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APPENDIX A PUBMED/MEDLINE SEARCH STRING

((“Perceptual Disorders”[MeSH] AND “neglect”) OR "unilateral spatial neglect"[Title/Abstract] OR "unilateral neglect"[Title/Abstract] OR "uni-lateral neglect"[Title/Abstract] OR “contralateral neglect”[Title/Abstract] OR "visuospatial neglect"[Title/Abstract] OR “visuosensory neglect”[Title/Abstract] OR "visuo-spatial neglect"[Title/Abstract] OR "spatial neglect"[Title/Abstract] OR "hemispatial neglect"[Title/Abstract] OR "hemi-spatial neglect"[Title/Abstract] OR “hemineglect”[Title/Abstract] OR “hemi-neglect”[Title/Abstract] OR “hemisensory neglect”[Title/Abstract] OR “left neglect”[Title/Abstract] OR "visual neglect"[Title/Abstract] OR "sensory neglect"[Title/Abstract] OR "motor neglect"[Title/Abstract] OR "input neglect"[Title/Abstract] OR "output neglect"[Title/Abstract] OR "perceptual neglect"[Title/Abstract] OR "premotor neglect"[Title/Abstract] OR "attentional neglect"[Title/Abstract] OR "intentional neglect"[Title/Abstract] OR "directional neglect"[Title/Abstract] OR "response neglect"[Title/Abstract] OR "parietal neglect"[Title/Abstract] OR "frontal neglect"[Title/Abstract] OR "neglect subtype"[Title/Abstract] OR "sensory inattention"[Title/Abstract] OR "visual inattention"[Title/Abstract] OR "motor inattention"[Title/Abstract] OR "directional hypokinesia"[Title/Abstract] OR "pseudoneglect"[Title/Abstract] OR "Landmark task"[Title/Abstract]) AND ((humans[Filter]) AND (english[Filter]))

APPENDIX B DATA ITEMS

Table B1 Data Items Charted in Scoping Review

Category	Data Item	Description
Refs	Additional refs identified	citations from reference list that may be relevant but have not yet been included in the review
Article Details	Title	title of article
	Authors	author list
	Published Year	year article was published
	Published Month	month article was published
	Journal	journal the article was published in
	Volume	volume of article
	Issue	issue of article
	Pages	page range of article
	DOI	DOI of article
	Country of origin	country (or countries) where the study was conducted
Study Characteristics	Objective/research Qs	state the objectives/research questions of the study. This can be a direct quote.
	Hypotheses	state the study's hypotheses, if applicable. This can be a direct quote.
	Design	brief description of study design (see notes tab for more details), including description of intervention if applicable
Participant Characteristics	Healthy, PwN, or both	refers to type of sample. Healthy = healthy adults only, PwN = persons with post-stroke neglect, both = both healthy and stroke patients.
	Recruitment Source(s)	describe where the participants were recruited from (e.g., rehabilitation units, surrounding community, university)
	Inclusion criteria	List criteria for inclusion as a participant in the study
	Exclusion criteria	List criteria that excluded participants from the study
	Clinical/research setting	the setting in which patients were acquired, and/or the study was run (e.g., acute, subacute, chronic; in-patient vs. out-patient)
	Sample size	size of sample (N). If there are patients and healthy controls, list the N for each
	Age	summary data on age of sample(s)
	Sex/gender	summary data on sex/gender distribution of sample(s)
	Education	summary data on education level of sample(s)
	Race/Ethnicity	summary data on race/ethnicity distribution of sample(s). Note that this may be listed by racial groups (e.g., East Asian, Black/African American, White/Caucasian) and/or nationalities (e.g., Italian, Brazilian, American)
	Handedness	summary data on handedness of sample(s)
	Stroke etiology	etiology of strokes in sample (e.g., ischemic, hemorrhagic)
	Side of stroke	distribution of side of stroke in the sample (left, right, bilateral)
	Time since stroke	summary data on time since stroke
	Average lesion size	provide units as well
	Stroke severity	e.g., NIH score
	Neglect severity	summary data of conventional measure indicating severity of neglect, other than the perceptual/premotor measure (e.g., BIT score)
	Additional impairments	Report if any participants had any additional impairments (type and # of participants), e.g., visual field defect, hemiparesis, optic ataxia
Input-Output Subtyping Measure(s)	Name of task	full name of task
	Subtyping terms/definitions	terms and definitions used to describe Input and Output subtypes/biases
	Stimuli/apparatus	describe the stimuli and apparatus of the task - what materials are required?
	Type of response(s) required	type of response(s) required on the task (e.g., yes-no discrimination, forced choice, reaction time, movement time, line bisection), by which hand (always right?); note if response was time limited
	Behavioural indicator of Input bias	describe what task outcome is associated with Input bias
	Behavioural indicator of Output bias	describe what task outcome is associated with Output bias
	Length of task/number of trials	List total time taken to complete the task, and/or total number of trials
	Sample distribution of subtypes/biases	list any information about distribution of subtypes/biases in the sample (e.g., % of participants with each bias; mean bias compared to a control group)
	Reliability	list any information provided regarding reliability of the task (e.g., test-retest reliability, internal consistency, inter-rater)
	Validity	list any information provided regarding validity of the task (e.g., comparison to other neglect measures, association with response to intervention)
	Subtype-intervention findings	describe key findings of intervention influencing biases, biases predicting responses to interventions, etc.
	Other test information	additional comments on task, e.g. feasibility, was it well-tolerated?
Neural correlates	Type of imaging	type of imaging used in the study (e.g., CT, MRI, PET)
	Time since stroke of imaging	e.g., in days, months
	Lesion quantification method	e.g., traced by hand, computerized
	Neural correlates of Input bias	neural areas/networks associated with behavioural indicator of Input bias
	Neural correlates of Output bias	neural areas/networks associated with behavioural indicator of Output bias
	Discussion of neural theories	search body of paper for mention of any neural/cognitive theories of how their neural correlates of the subtypes may inform neural theories of Input-Output neglect
Other	Other notes	any other important notes about the study, if applicable

APPENDIX C FREQUENCY OF INPUT-OUTPUT TERMINOLOGY

Table C1 Number of included articles using each term to describe Input neglect.

Input term	*n*
perceptual	60
attentional	18
perceptual-attentional	14
sensory-attentional	10
input	9
“where”	9
perception	7
sensory	5
visual	5
perceptual-sensory	4
perceptual/attentional	4
representational	4
attention	3
perceptual judgement	3
sensory inattention	3
hemi-inattention	2
hemispatial inattention	2
non-manual	2
spatial attention	2
visual perception	2
attention-representation	1
attentional orienting	1
explicit perceptual	1

Input term (cont’d)	*n*
hemianopia	1
hemiinattention	1
hemisensory attention-representation	1
hemispatial memory	1
misperception	1
opthalmokinetic	1
orienting attention	1
perceptual space representation	1
perceptual/attention	1
perceptual/ representational	1
representation	1
sensory attentional	1
sensory-perceptual	1
sensory-representational	1
size distortion	1
target selection	1
visual attention	1
visual detection	1
visual perceptual	1
visual-spatial	1

Table C2 Number of included articles using each term to describe Output neglect.

Output term	*n*
motor	29
motor-intentional	21
premotor	20
intentional	18
directional hypokinesia	15
response	13
action	10
output	10
“aiming”	9
manual	7
directional motor	4
exploratory-motor	4
visuomotor	4
action-intentional	3
visually guided action	3
hemispatial akinesia	2
hemispatial hypokinesia	2
motor initiation	2
motor-exploratory	2
motor/intentional	2
orienting	2
visuomotor control	2

Output term (cont’d)	*n*
control of action	1
directional	1
directional akinesia	1
directional bradykinesia	1
directional hypometria	1
exploratory	1
exploratory visuo-motor	1
grasping	1
hemiakinesia	1
implicit visuomotor	1
intention	1
melokinetic	1
motor attention	1
motor exploration	1
motor response	1
motoric	1
perception for action	1
premotor-intentional	1
response production	1
unilateral hypokinesia	1
visually guided grasping	1

APPENDIX D ARTICLES IN MULTIPLE SUBTYPING TASK CATEGORIES

Table D1 List of included articles counted in multiple subtyping task categories.

Article	Task Manipulation(s)	Subtyping Task Category 1	Subtyping Task Category 1
Binder et al. (1992)	Verbal line judgment vs. manual line bisection vs. manual cancellation	Modality of output	Goal of manual output
Bisiach et al. (1995)	Mirror reversal task; included cueing condition (i.e., cued to start cancellation from hemispace neglected on previous attempt)	Congruence of input with output	Presence of visual input
Daffner et al. (1990)	blindfolded manual exploration vs. visual (verbally reported) extinction	Presence of visual input	Modality of output
Harvey and Milner (1995)	Manual Landmark vs. manual line bisection; letter cue at left end, right end, both, or neither	Presence of visual input	Goal of manual output
Harvey et al. (2002)	Overhead Technique (i.e., epidiascope technique); pulley device	Congruence of input with output	Goal of manual output
Hughes et al. (2004)	pointing vs. grasping to bisect rod; manual line bisection vs. verbally indicating when the experimenter's pointer was at the midpoint	Goal of manual output	Modality of output
Hughes et al. (2008)	pointing vs. grasping to bisect rod, under binocular vs. monocular vs. occluded viewing	Goal of manual output	Presence of visual input
Liu et al. (1992)	blindfolded manual exploration vs. visual extinction	Presence of visual input	Modality of output
Maeshima et al. (1996)	cancellation tasks and blindfolded manual exploration vs. visual extinction	Presence of visual input	Modality of output
Maeshima, Truman, et al. (1997)	manually moving marbles while blindfolded vs. verbally counting marbles by vision alone	Presence of visual input	Modality of output
Mattingley et al. (1998)	centrally responding to peripheral targets (i.e. simple lateralized detection) vs. lateralized reaching to peripheral targets	Goal of manual output	Direction of manual output

Milner et al. (1992)	verbal Landmark vs. manual line bisection; letter cue at left end, right end, both, or neither	Modality of output	Presence of visual input
Rengachary et al. (2011)	centrally responding to centrally cued peripheral targets (i.e. cued lateralized detection) vs. lateralized reaching to peripheral targets	Goal of manual output	Direction of manual output
Reuter-Lorenz and Posner (1990)	manually bisecting line vs. verbally indicating when the experimenter's pencil was at the midpoint; cueing condition (i.e., naming number cue at left vs. right end of line, vs. no cue)	Modality of output	Presence of visual input
Samuelsson (1990)	manually sliding pencil to midpoint vs. verbally indicating when the experimenter's pencil was at the midpoint; visuo-verbal cueing conditions	Modality of output	Presence of visual input
Schwartz et al. (1999)	video monitoring apparatus (based on Na et al 1998; Schwartz et al. 1997); attentional cue (i.e., read letter at end of line) vs. intentional cue (i.e., touch end of line) before bisecting	Congruence of input with output	Presence of visual input
Vaessen et al. (2016)	Perceptual component (line bisection, text reading) vs. exploratory visuo-motor component (manual cancellation tasks)	Modality of output	Goal of output

APPENDIX E SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 3

Table E1 Mean reach initiation time in milliseconds (standard deviation) on the speeded reach task in right-handers by PA group, time, hand start position, and target side.

PA Group	Time	Left start		Centre Start		Right Start	
		Left target	Right target	Left target	Right target	Left target	Right target
LPA	pre-PA	406 (80)	385 (70)	408 (64)	400 (82)	390 (62)	398 (64)
	post-PA	367 (46)	358 (58)	386 (57)	361 (48)	366 (58)	370 (57)
RPA	pre-PA	403 (79)	385 (75)	413 (85)	395 (71)	401 (82)	402 (78)
	post-PA	368 (66)	358 (59)	376 (58)	370 (108)	364 (60)	374 (132)

Note. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation.

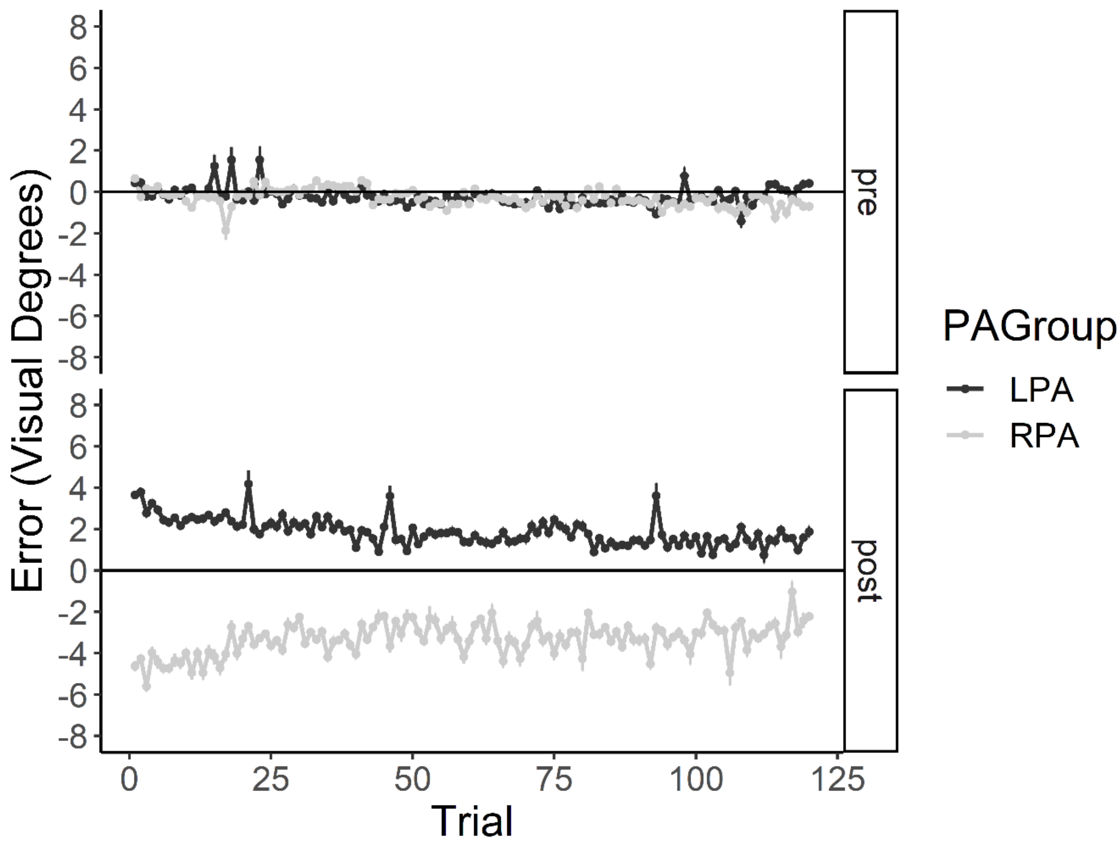

Figure E1 Pointing error size on the speeded reach task in right-handers by PA group, trial, and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

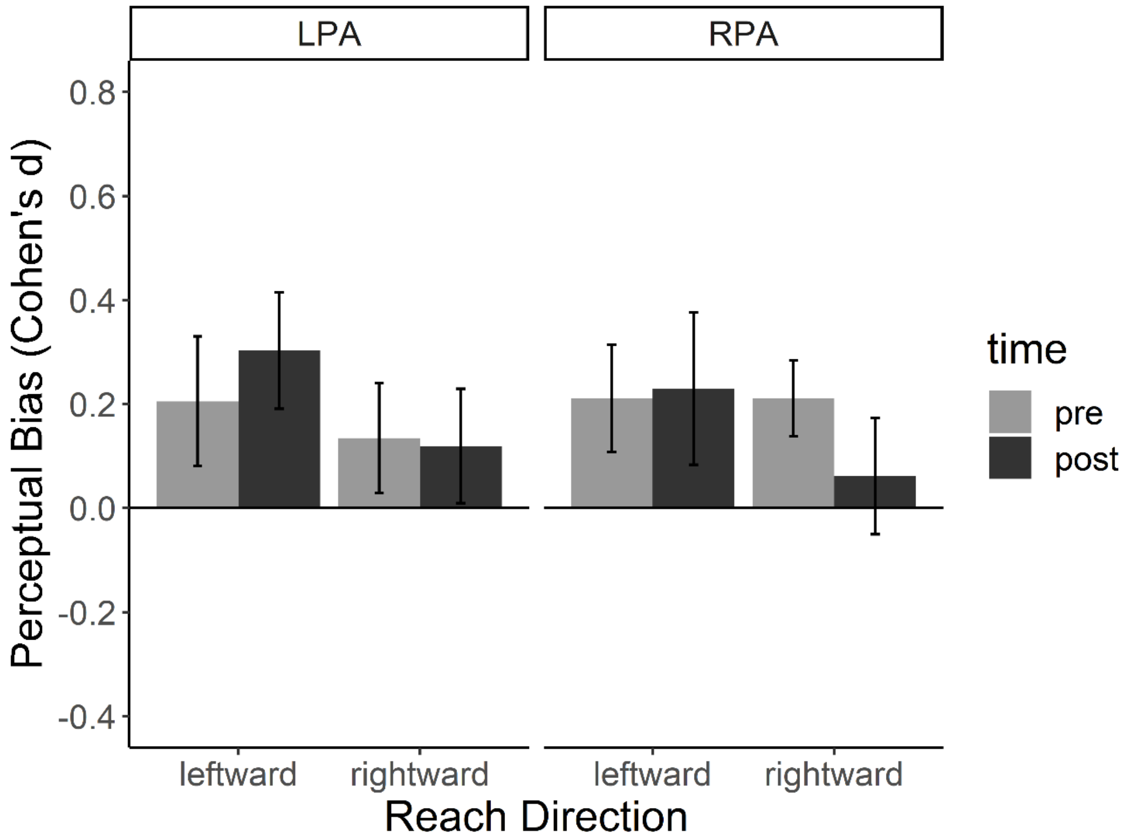

Figure E2 Perceptual bias (Cohen's *d*) on the speeded reach task in right-handers by group, target side, and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. A more positive perceptual bias (Cohen's *d*) means they are faster to initiate reaches to the right target than the left target, for a given reach direction.

APPENDIX F SUPPLEMENTARY TABLES AND FIGURE FOR CHAPTER 3A

Table F1 Mean reach initiation time in milliseconds (standard deviation) on the speeded reach task in left-handers by PA group, time, hand start position, and target side.

PA Group	Time	Left start		Centre Start		Right Start	
		Left target	Right target	Left target	Right target	Left target	Right target
LPA	pre-PA	407 (55)	406 (54)	408 (56)	420 (46)	395 (49)	416 (65)
	post-PA	374 (45)	370 (41)	382 (66)	396 (47)	374 (46)	386 (44)
RPA	pre-PA	403 (80)	406 (84)	404 (81)	417 (81)	389 (72)	413 (92)
	post-PA	378 (69)	371 (71)	382 (82)	395 (79)	371 (74)	377 (72)

Note. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation.

Table F2 Mixed analysis of variance (ANOVA) of hand preference, PA group, target side, hand start position, and time predicting reach initiation time on the speeded reach task.

Effect	df_n	df_d	*F*	*p*	η_p^2
handPref	1	50	0.69	0.41	0.01
PAGroup	1	50	0.002	0.96	<.001
time	**1**	**50**	**79.82**	**<.001**	**0.62**
targetSide	1	50	0.27	0.61	0.005
startPos	**2**	**100**	**12.97**	**<.001**	**0.21**
handPref:PAGroup	1	50	0.03	0.86	<.001
handPref:time	1	50	0.19	0.66	0.004
PAGroup:time	1	50	0.002	0.97	<.001
handPref:targetSide	**1**	**50**	**47.95**	**<.001**	**0.49**
PAGroup:targetSide	1	50	0.04	0.85	<.001
handPref:startPos	2	100	0.76	0.47	0.02
PAGroup:startPos	2	100	0.01	0.99	<.001
time:targetSide	1	50	0.15	0.70	0.003
time:startPos	2	100	1.13	0.33	0.02
targetSide:startPos	**2**	**100**	**24.52**	**<.001**	**0.33**
handPref:PAGroup:time	1	50	0.07	0.79	0.001
handPref:PAGroup:targetSide	1	50	0.03	0.87	<.001
handPref:PAGroup:startPos	2	100	0.72	0.49	0.01
handPref:time:targetSide	**1**	**50**	**10.04**	**0.003**	**0.17**
PAGroup:time:targetSide	1	50	1.32	0.26	0.03
handPref:time:startPos	2	100	0.56	0.57	0.01
PAGroup:time:startPos	2	100	1.01	0.37	0.02
handPref:targetSide:startPos	**2**	**100**	**5.54**	**0.005**	**0.10**
PAGroup:targetSide:startPos	2	100	0.20	0.82	0.004
time:targetSide:startPos	2	100	1.03	0.36	0.02
handPref:PAGroup:time:targetSide	**1**	**50**	**7.83**	**0.007**	**0.14**
handPref:PAGroup:time:startPos	2	100	0.03	0.97	<.001
handPref:PAGroup:targetSide:startPos	2	100	0.13	0.88	0.003
handPref:time:targetSide:startPos	2	100	2.90	0.06	0.06
PAGroup:time:targetSide:startPos	2	100	2.36	0.10	0.05
handPref:PAGroup:time:targetSide:startPos	2	100	1.16	0.32	0.02

Note. Bolded effects are significant at $p < .05$.

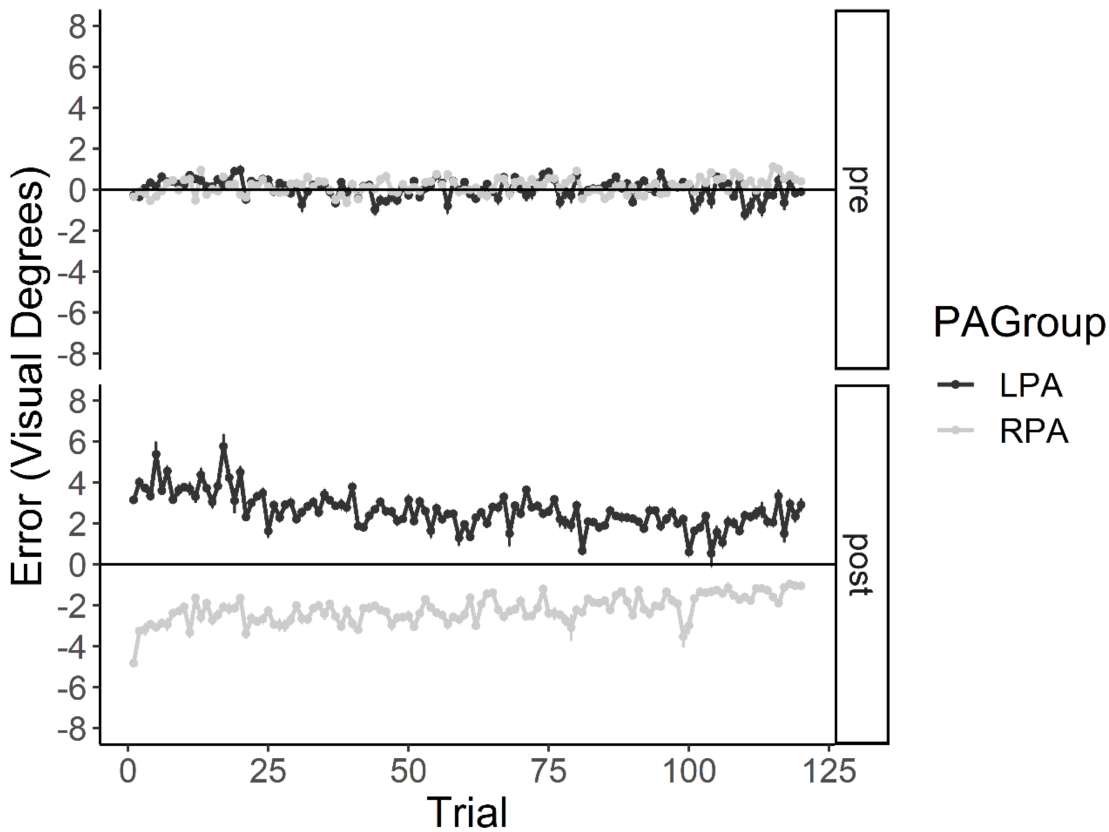

Figure F1 Pointing error size on the speeded reach task in left-handers by PA group, trial, and time. LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Error bars represent standard error of the mean.

APPENDIX G SUPPLEMENTARY FIGURES FOR CHAPTER 4

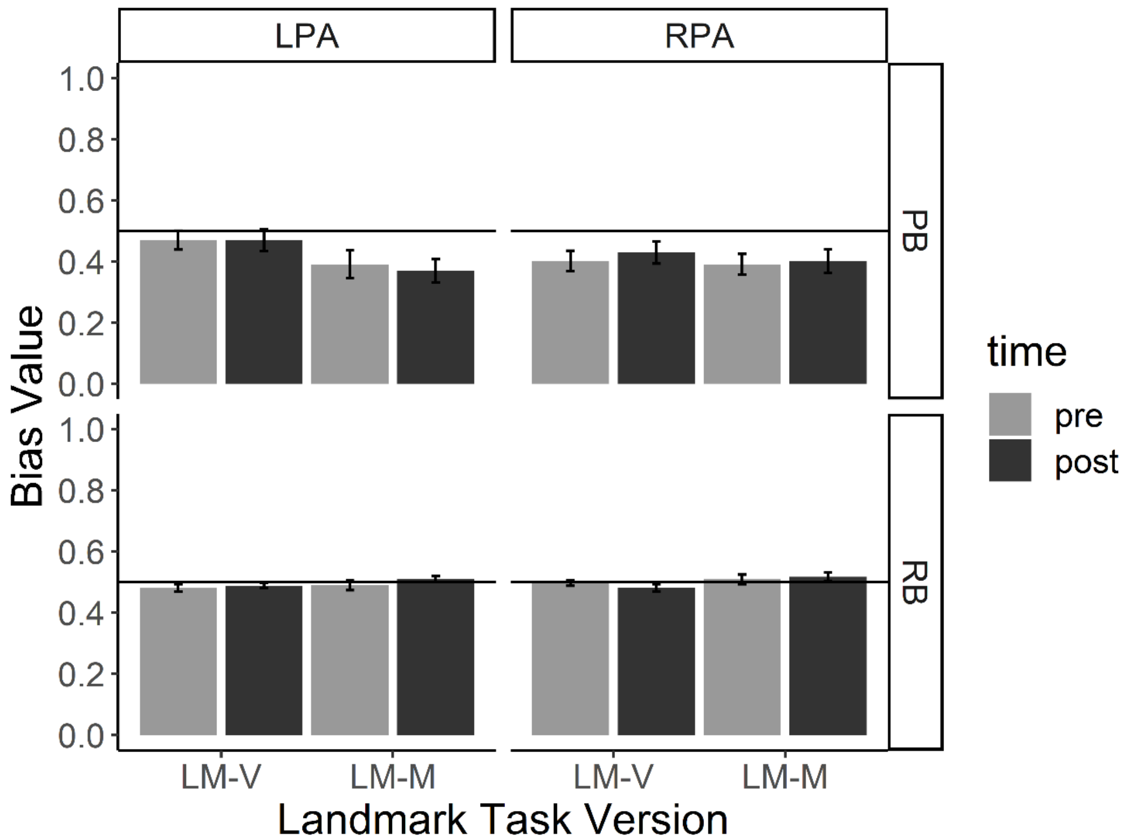

Figure G1 Perceptual and response biases (Bisiach et al., 1998) by Landmark version, PA group, and time. LM-V = Landmark task-verbal version; LM-M = Landmark task-manual version; PB = perceptual bias based on Bisiach et al. (1998); RB = response bias based on Bisiach et al. (1998); LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Horizontal black lines indicate no bias (0.50). Error bars represent standard error of the mean.

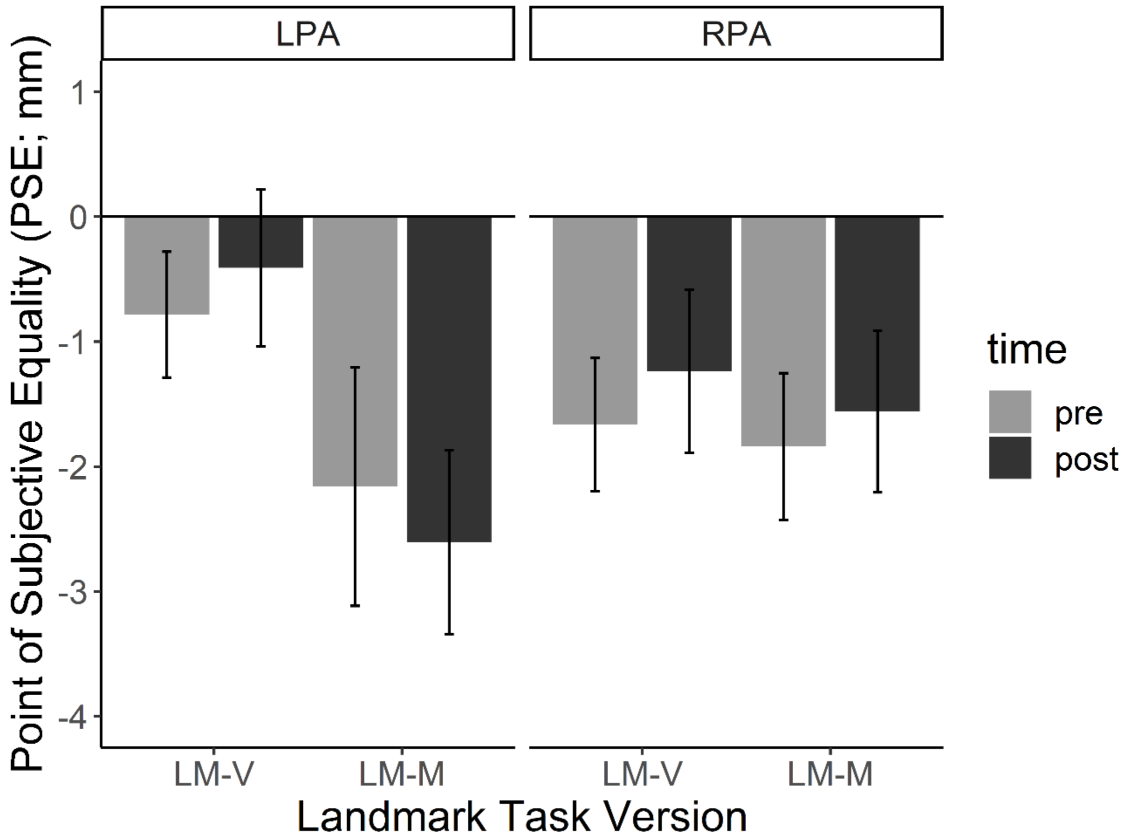

Figure G2 Point of subjective equality (Toraldo et al., 2002) by Landmark version, PA group, and time. LM-V = Landmark task-verbal version; LM-M = Landmark task-manual version; LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Horizontal black lines indicate no bias (0). Error bars represent standard error of the mean.

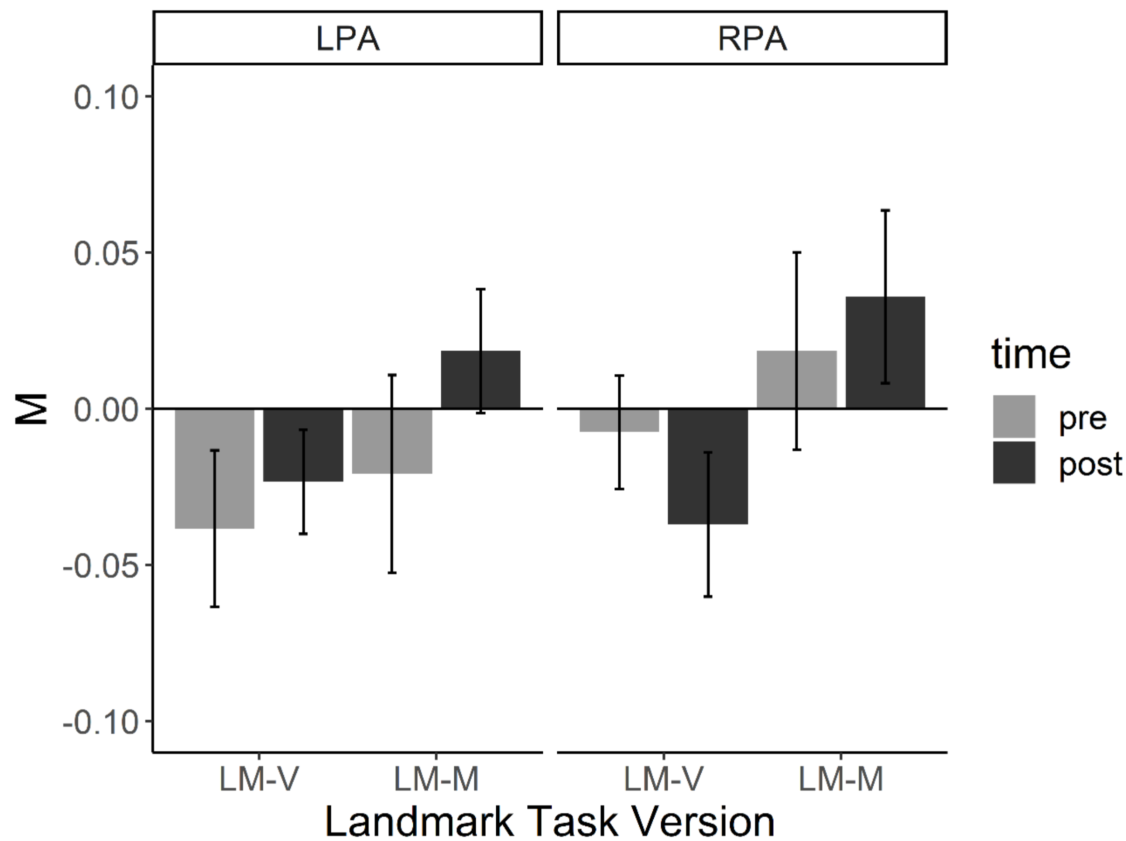

Figure G3 Mean probability of default response (*M*; Toraldo et al., 2004) by Landmark version, PA group, and time. LM-V = Landmark task-verbal version; LM-M = Landmark task-manual version; LPA = left-shifting prism adaptation; RPA = right-shifting prism adaptation. Horizontal black lines indicate no bias (0). Error bars represent standard error of the mean.

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